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THE JOURNAL OF Organic Chemistry®

VOLUME 43, NUMBER 6 MARCH 17, 1978

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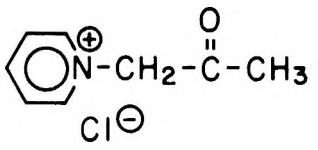

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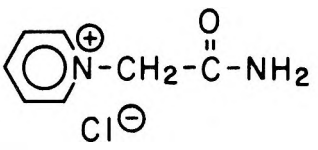

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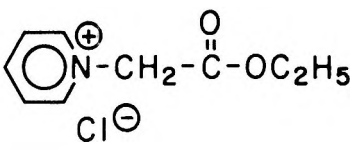

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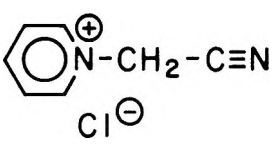

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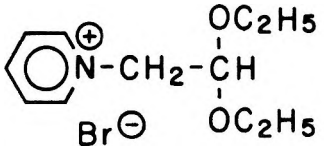

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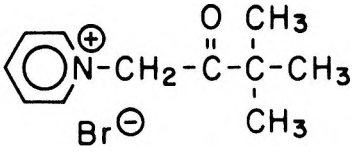

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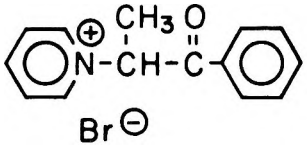

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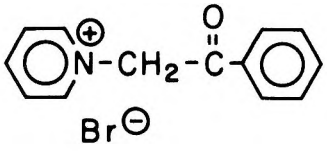

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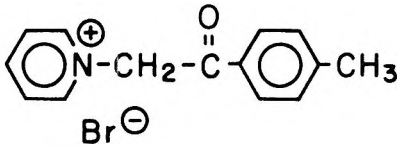

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Absolute Stereochemistry of *cis*-1,2-, *trans*-1,2-, and *cis*-3,4-Dihydrodiol Metabolites of Phenanthrene

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An unequivocal assignment of the absolute stereochemistry of *cis*-1,2- (**5a**) and *cis*-3,4- (**9a**) (bacteria) and *trans*-1,2- (**7a**) (rat) dihydrodiol metabolites of phenanthrene is described. The diacetates of these dihydrodiols are levorotatory. *cis*-1,2-Dihydroxy-1,2-dihydrophenanthrene (**5a**) was converted into (−)-2-acetoxy-1,2,3,4-tetrahydrophenanthrene (**3b**) by catalytic hydrogenation of the double bond and hydrogenolysis of the 1-acetoxyl group. The *S* configuration of C-2 in **3b** was assigned by application of the exciton chirality circular dichroism method to its corresponding benzoate **3c** and by chemical degradation of the methyl ether **3d** to (−)-dimethyl β-methoxyadipate (**4**) of known absolute configuration. The negative sign associated with the longest wavelength Cotton effect for the benzoate **3c** is consistent with the (1*R*,2*S*) configuration for the *cis*-dihydrodiol **5a**. The (1*R*,2*R*) and (3*S*,4*R*) configurations assigned to *trans*-1,2-dihydroxy-1,2-dihydro- (**7a**) and *cis*-3,4-dihydroxy-3,4-diydrophenanthrenes (**9a**), respectively, were obtained by use of the exciton chirality method on the monobenzoate derivatives of the corresponding tetrahydrodiols (**8b** and **8c** from **7a** and **10d** from **9a**). This is the first determination of the absolute stereochemistry of a bay region dihydrodiol.

Certain non-K region *trans*-dihydrodiol metabolites of carcinogenic polycyclic aromatic hydrocarbons (PAH's) such as benzo[*a*]pyrene[2] and benz[*a*]anthracene[3] have recently been shown to be highly carcinogenic and mutagenic on metabolic activation. These results have led to the formulation of the "bay region" theory (cf. **1**) which predicts carcinogenicity for specific PAH metabolites.[4] In this context optically active benzo[*a*]pyrene *trans*-7,8-dihydrodiols and the corresponding 7,8-diol 9,10-epoxides have been prepared and their absolute stereochemistry assigned.[5-7] Interestingly, all three of the metabolically formed *trans*-dihydrodiols of benzo[*a*]-pyrene, at the 4,5, 7,8, and 9,10 positions, are of high optical purity when formed from benzo[*a*]pyrene by rat liver microsomes.[8]

Metabolism of phenanthrene (**1**) is of considerable interest since it is the simplest hydrocarbon that has a "bay region". In addition, phenanthrene is known to be weakly carcinogenic on mouse skin.[9] Previous studies on the metabolism of phenanthrene have shown that it is converted in mammals to *trans*-1,2- (minor), 3,4- (trace), and 9,10- (major) dihydrodiols and in bacteria to *cis*-1,2- (minor) and 3,4- (major) dihydrodiols.[10] Among these metabolites, only the absolute stereochemistry of the (−)-(9*S*,10*S*)-*trans*-9,10-dihydrodiol **2** has been determined.[11] The present study unequivocally assigns absolute stereochemistry of the *cis*-1,2-, *cis*-3,4- and *trans*-1,2-dihydrodiols of phenanthrene by employing both the exciton chirality circular dichroism (CD) method and chemical degradation.

A particularly attractive compound for determining the absolute configurations of both *cis*- and *trans*-1,2-dihydroxy-1,2-dihdyrophenanthrenes would be 2-acetoxy-1,2,3,4-tetrahydrophenanthrene, since it could be readily obtained by catalytic hydrogenolysis of the diacetates of both 1,2-dihydrodiols. An optically active sample of authentic 2-hydroxy-1,2,3,4-tetrahydrophenanthrene was prepared as follows: diastereomeric *l*-menthyloxyacetates of *trans*-1-bromo-2-hydroxy-1,2,3,4-tetrahydrophenanthrene, obtained from 3,4-dihydrophenanthrene, were partially resolved by short-column chromatography.[12] Base treatment ($NaOCH_3$) of a fraction highly enriched in one of the less polar diastereomer ($[\alpha]_D$ −150° ($CHCl_3$)) gave (+)-1,2-epoxy-1,2,3,4-tetrahydrophenanthrene ($[\alpha]_D$ +82° ($CHCl_3$)), which was subsequently reduced by $LiAlH_4$ to (−)-2-hydroxy-1,2,3,4-tetrahydrophenanthrene (**3a**, $[\alpha]_D$ −71° ($CHCl_3$)). The acetate **3b** ($[\alpha]_D$ −50° ($CHCl_3$)) showed positive Cotton effects in its CD spectrum in the ca. 215–245-nm region with $\Delta\epsilon$ +8.5

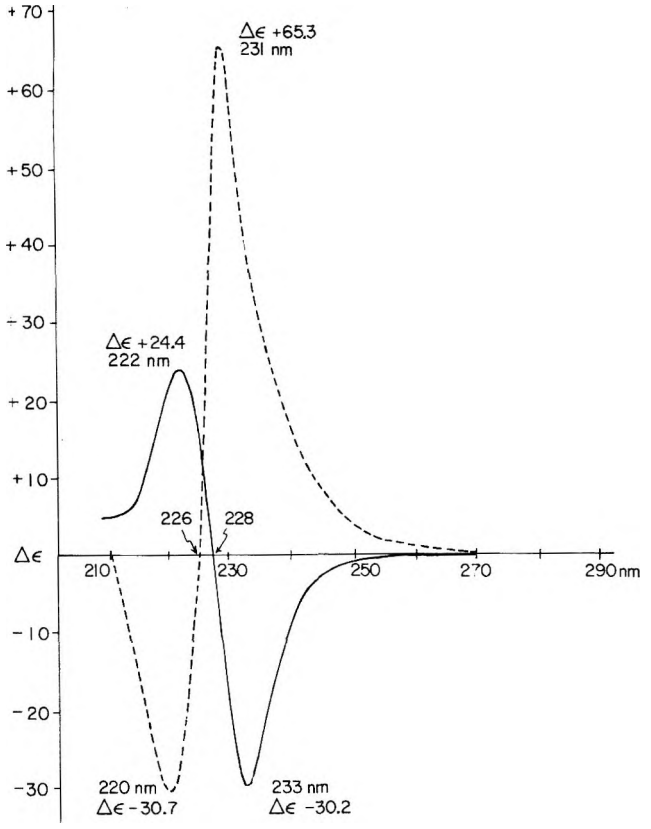


Figure 1. CD spectra of (*S*)-2-benzoyloxy-1,2,3,4-tetrahydrophenanthrene (**3c**) (–) and (3*S*,4*R*)-*cis*-3-hydroxy-4-benzoyloxy-1,2,3,4-tetrahydrophenanthrene (**10d**) (---) in MeOH/dioxane (9:1).

at 242 nm. The absolute configuration of the alcohol **3a** at C-2 was determined as *S* by applying the exciton chirality CD method[13-16] to its benzoyl derivative **3c**; $\Delta\epsilon_{233}$ −30 and $\Delta\epsilon_{222}$ +24, Figure 1. The strong $\pi \rightarrow \pi^*$ chromophores ascribable to the benzoyloxy group at 228 nm ($\epsilon \sim 12\,000$; intramolecular charge-transfer band[18]) and to the 1,2,3,4-tetrahydrophenanthrene moiety at 239 nm ($\epsilon \sim 100\,000$; $^1A \rightarrow {}^1B_b$ band[16]) are shown in Figure 2. The CD spectrum of **3c** shows a symmetric pair of Cotton effects centered at 228 nm (Figure 1) due to exciton splitting. Since the longest wavelength (first) Cotton effect at 233 nm is negative, the 2*S* absolute configuration is required. The cyclohexene ring conformation as well as the quasi-equatorial orientation of the benzoyloxyl group in **3c** were indicated from the NMR spectrum of **3c** (see Experimental Section).

Further evidence for the 2*S* configuration in alcohol **3a** ($[\alpha]_D$ −28° ($CHCl_3$)) was obtained by chemical degradation to (−)-dimethyl β-methoxyadipate (**4**) which is known to have the *S* configuration.[19] Thus, the methyl ether **3d** ($[\alpha]_D$ −37° ($CHCl_3$)) prepared from the alcohol **3a** with CH_3I/NaH was subjected to mild ozonolysis in $CHCl_3$ at −50 °C. Oxidative workup of the resulting ozonide with H_2O_2/HCOOH followed by treatment with diazomethane yielded *S*-(−)-dimethyl β-methoxyadipate (**4**, $[\alpha]_D$ −2.2° ($CHCl_3$)).

The structure of the microbial metabolite *cis*-1,2-dihydroxy-1,2-dihydrophenanthrene (**5a**) isolated as its acetate **5b** ($[\alpha]_D$ −1° ($CHCl_3$)) was determined by conversion into 2-acetoxy-1,2,3,4-tetrahydrophenanthrene. The diacetate **5b** was catalytically reduced (10% Pd–C) first to *cis*-1,2-diacetoxy-1,2,3,4-tetrahydrophenanthrene (**6**, $[\alpha]_D$ −193° (dioxane)) in ethyl acetate and then to 2-acetoxy-1,2,3,4-tetrahydrophenanthrene in acetic acid. This 2-acetoxy-1,2,3,4-tetrahydrophenanthrene showed positive CD peaks in the 215–245-nm region with $\Delta\epsilon_{240}$ +7.4 which allows assignment

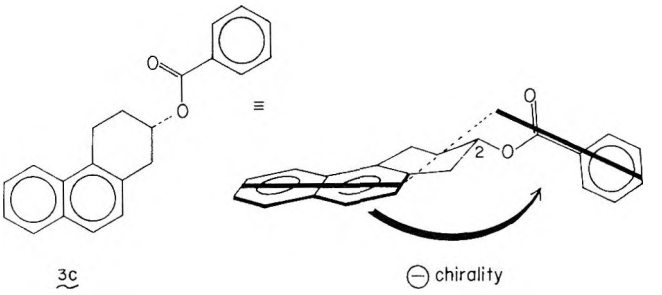
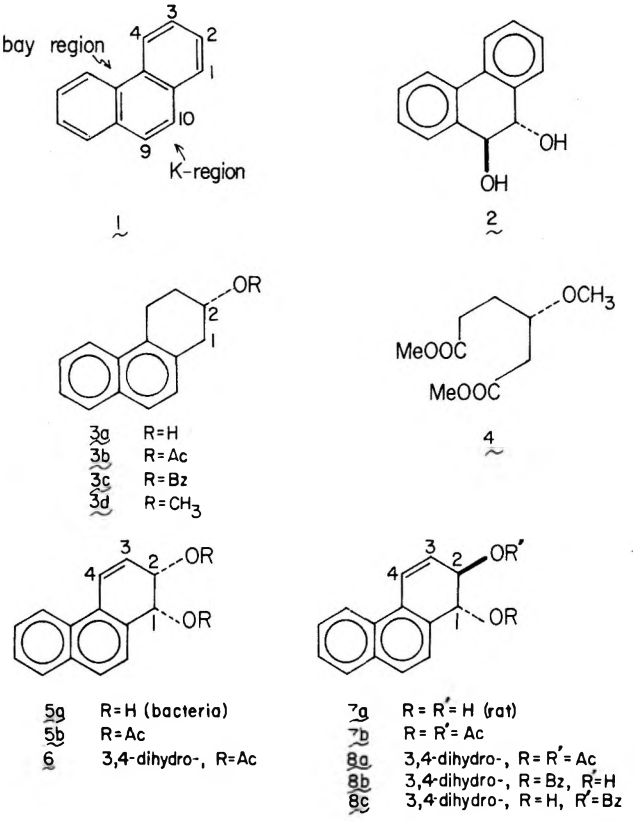


Figure 2. The stereostructure of (*S*)-2-benzoyloxy-1,2,3,4-tetrahydrophenanthrene (**3c**). Bold lines denote the electric transition dipole of the chromophore.

of 1*R*,2*S* stereochemistry to the *cis*-dihydrodiol **5a** and indicates that the bacterial dihydrodiol has reasonably high optical purity. Incubation of racemic phenanthrene 1,2-oxide with liver microsomes from phenobarbital-induced Sprague–Dawley rats (cf. ref 8) provided (−)-*trans*-1,2-dihydroxy-1,2-dihydrophenanthrene (**7a**) which was isolated as its diacetate **7b** ($[\alpha]_D$ −192° (dioxane)). Although reduction of **7b** smoothly produced (−)-*trans*-1,2-diacetoxy-1,2,3,4-tetrahydrophenanthrene (**8a**, $[\alpha]_D$ −39° (dioxane)), attempted hydrogenolysis of the 1-acetoxyl group under a variety of conditions did not cleanly remove the acetoxyl group without substantial reduction of the naphthalene system. Consequently the CD spectra of 1- and 2-monobenzoates (**8b** and **8c**, respectively) of the tetrahydrodiol derived from **8a** were examined. The negative and positive longest wavelength Cotton effects observed at 231 nm for **8b** and **8c**, respectively, require the 1*R*,2*R* configuration for the dihydrodiol **7a** based on the exciton chirality method.[11-14] Furthermore, the Δε values for these Cotton effects indicate that the *trans*-dihydrodiol metabolite **7a** has an ~30% optical purity.



The major bacterial metabolite of phenanthrene, the *cis*-3,4-dihydrodiol **9a** ($[\alpha]_D$ +58° (MeOH)), was isolated as its diacetate **9b** ($[\alpha]_D$ −204° (dioxane)). The above hydrogenation–hydrogenolysis sequence proved to be inadequate in that

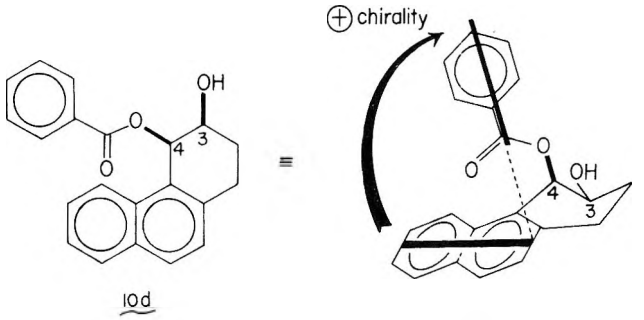
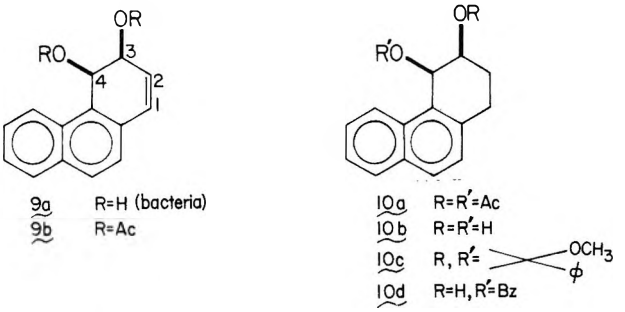
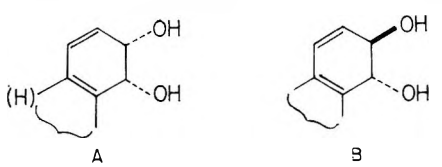


Figure 3. The stereostructure of (3*S*,4*R*)-*cis*-3-hydroxy-4-benzoyloxy-1,2,3,4-tetrahydrophenanthrene (**10d**). Bold lines denote the electric transition dipole of the chromophore. The alternative conformation which forms a *seven*-membered intramolecular hydrogen bond between the 3-OH and the carbonyl oxygen of the 4-benzoyloxy group would provide the same positive chirality.

the intermediate *cis*-3,4-diacetoxy-1,2,3,4-tetrahydrophenanthrene (**10a**) resisted several attempts to hydrogenolyze the acetoxyl group at C-4 under the conditions employed above. Although the exciton chirality CD spectrum of the 3,4-dibenzoate of **10b** should prove complex due to exciton interaction among the three chromophores, a monobenzoate derivative should show a CD spectrum which could be directly analyzed. Thus, treatment of the diol **10b** ($[\alpha]_D$ −21° (dioxane)) with trimethyl orthobenzoate in the presence of benzoic acid provided the benzyloxydioxolane **10c**, which was then hydrolyzed in AcOH/THF/H_2O at room temperature to *cis*-3-hydroxy-4-benzoyloxy-1,2,3,4-tetrahydrophenanthrene (**10d**). A related example of selective hydrolysis to the axial hydroxy ester of the *cis*-α-glycol has been reported.[20] Retention of the configuration at C-3 and C-4 in this conversion was validated by hydrolysis of the benzoate **10d** with mild base back to the original (−)-*cis*-3,4-diol **10b**. Typical exciton coupling was observed in the CD spectrum of the monobenzoate **10d**, $\Delta\epsilon_{231}$ +65.3 and $\Delta\epsilon_{220}$ −30.7 (Figure 1), indicative of the positive chirality between the naphthalene and 4-benzoyloxy chromophores (Figure 3). Therefore, the absolute configuration at C-4 in the benzoate **10d** is *R,ergo*, the 3*S*,4*R* stereochemistry in the orginal dihydrodiol **9a.** This is the first determination of the absolute stereochemistry of a bay-region dihydrodiol.



Notably, the absolute stereochemistry of the bacterial metabolites **5a** (1*R*,2*S*) and **9a** (3*S*,4*R*) from phenanthrene is common to the *cis*-dihydrodiols produced on bacterial metabolism of toluene,[21,22] naphthalene,[23] and anthracene.[24] All five *cis*-dihydrodiols share the common partial structure A, while the configuration in B (*R,R*) is the preferred enantiomer of the *trans*-1,2-dihydrodiols obtained on metabolism



of naphthalene in vivo in mammals or by the action of epoxide hydrase on naphthalene 1,2-oxide.[25] The enantiomeric preference for the urinary excretion of *trans*-1,2-dihydroxy-1,2-dihydroanthracene by mammals is species dependent (cf. ref 24). Microsomal epoxide hydrase from rabbit liver acts on racemic anthracene 1,2-oxide to produce a slight excess of the *R,R* enantiomer (as in B).[26] Administration of phenanthrene to rabbits leads to excretion of an excess of the (−)-*R,R* enantiomer of *trans*-1,2-dihydroxy-1,2-dihydrophenanthrene in the urine.[27] An excess of the same enantiomer was found when racemic phenanthrene 1,2-oxide was hydrated by rat liver microsomal epoxide hydrase in the present study. In vitro conversion of either benzo[*a*]pyrene or benzo[*a*]pyrene 7,8-oxide results in the formation of an excess of the (−)-(7*R*,8*R*)-dihydrodiol.[28] Thus all in vitro experiments which have examined the stereospecificity of epoxide hydrase on non-K-region arene oxides have found that an excess of the *R,R* enantiomer (B) is produced.

Experimental Section

Proton nuclear magnetic resonance spectra were measured in deuteriochloroform on Jeol MH-100 and Varian HA-100 instruments. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard with coupling constants (*J*) in hertz. Chemical ionization (NH_3 gas) and electron-impact mass spectra were run on a Finnigan Model 1015 gas chromatograph/mass spectrometer using the direct-inlet mode. Optical rotations were obtained at 23 °C using a Perkin-Elmer 141 automatic polarimeter, and circular dichroism spectra were recorded on a Cary 16 CD spectrometer. Analytical gas chromatography was carried out using a Pye-Unicam Model 104 instrument and a 2.5% silicon gum rubber column (2.5 m). Preparative GLC separations were carried out using identical column packing (6.3 m) and a modified Varian Autoprep (Model A-700).

Partial Resolution of (−)-2-Hydroxy-1,2,3,4-tetrahydrophenanthrene (3a). The optical resolution of 2-hydroxy-1,2,3,4-tetrahydrophenanthrene was carried out via the bromohydrin *l*-menthyloxyacetates.[10] *l*-Menthyloxyacetyl derivatives of *trans*-1-hydroxy-2-bromo-1,2,3,4-tetrahydrophenanthrene were partially resolved by short silica gel column chromatography and then converted via lithium aluminum hydride reduction of the corresponding epoxides (formed by base treatment of the partially separated diastereomers) to 2-hydroxy-1,2,3,4-tetrahydrophenanthrenes: mass spectrum (CI-NH_3) of (−)-enantiomer **3a** *m/e* 216 (M^+ + 18).

A summary of the optical rotations (all in $CHCl_3$) derived from two separate chromatography fractions is: *trans*-1-*l*-menthyloxyacetoxy-2-bromo-1,2,3,4-tetrahydrophenanthrene ($[\alpha]_D$ −150° or −60°) → 1,2-epoxy-1,2,3,4-tetrahydrophenanthrene ($[\alpha]_D$ +82° or +45°) → **3a** ($[\alpha]_D$ −71° or −28°).

(−)-2-Methoxy-1,2,3,4-tetrahydrophenanthrene (3d). To a stirred suspension of 1.20 g (25 mmol) of 50% sodium hydride (washed with hexane prior to use) in 50 mL of dry benzene at room temperature was added dropwise a solution of **3a** (1.13 g, 5.7 mmol, $[\alpha]_D$ −28° ($CHCl_3$)) in 50 mL of dry benzene under nitrogen. The reaction mixture was refluxed for 1 h and cooled prior to the slow addition with stirring of methyl iodide (20.0 g, 140 mmol). After refluxing for 21 h, the mixture was cooled to room temperature, poured into ice-cooled water, extracted with petroleum ether (bp range 40–60 °C), dried (Na_2CO_3), and concentrated to yield a red-brown oil, which was further purified by distillation to give 0.93 g of pale-yellow oil **3d:** bp 116–118 °C (0.22 mm), $[\alpha]_D$ −37° (c 1.80, $CHCl_3$).

Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 85.10; H, 7.70.

Ozonolysis of 3d. An ozone–oxygen mixture (BOC cryoproducts Mark II ozonizer) was passed for 3 h into a solution of 900 mg of **3d** in 50 mL of a chloroform/methanol mixture (1:1) maintained at a temperature of ca. −50 to −40 °C. Removal of the solvent in vacuo at room temperature produced a colorless oil which was then refluxed with 5 mL of 95% formic acid and 2.5 mL of 30% hydrogen peroxide for 8 h. Concentration of the reaction product under reduced pressure produced a viscous red oil which was dissolved in 20 mL of ethanol and treated with excess diazomethane (generated in situ from 5 g of Diazald and 0.8 g of KOH) in 40 mL of ether. The resultant crude product was analyzed by analytical GLC and was found to consist of three major components in the ratio of 2.9:1.1:1.0. Isolation of the second and third major peaks by preparative GLC and comparison

of these components with authentic samples[20] by GLC retention time, IR, MS, and NMR showed the second peak to be dimethyl β-methoxyadipate (**4**, 4.0 mg, $[\alpha]_D$ −2.2° (c 0.40, $CHCl_3$)) and the third peak to be dimethyl phthalate.

(−)-2-Acetoxy-1,2,3,4-tetrahydrophenanthrene (3b). The optically active alcohol **3a** ($[\alpha]_D$ −71° ($CHCl_3$), 5 mg) was dissolved in 0.30 mL of pyridine and treated with 0.15 mL of acetic anhydride. After 12 h at room temperature, the solvent was evaporated under reduced pressure. The semiliquid residue was purified by preparative TLC developed by CH_2Cl_2 to yield 6 mg of pure acetate **3b:** $[\alpha]_D$ −50° (c 0.262, $CHCl_3$); CD (MeOH) $\Delta\epsilon_{242}$ +8.5; mass spectrum (EI) *m/e* 240 (M^+).

2-Benzoyloxy-1,2,3,4-tetrahydrophenanthrene (3c). To a stirred solution of 9 mg of the alcohol **3a** in 0.3 mL of pyridine was added 0.15 mL of benzoyl chloride at 4 °C. The reaction mixture was kept at room temperature for 16 h, poured into ice-cooled water, and extracted twice with ethyl acetate. The combined organic layer was washed twice with aqueous $CuSO_4$ solution and once with water and dried, and the solvent was evaporated under reduced pressure. The residue thus obtained was purified by preparative silica gel TLC developed by 1% ethyl acetate in benzene to give 7 mg of the benzoate **3c:** mass spectrum (CI-NH_3) *m/e* 320 (M^+ + 18), 180 (M^+ − $C_6H_5CO_2H$); NMR δ 2.34 (m, 2 H, H-3), 3.32 (m, 4 H, H-1 and H-4), 5.58 (m, $\Delta W_{1/2}$ = 18 Hz), and 7.16–8.10 (11 H, aromatic protons).

(−)-*cis*-1,2-Diacetoxy-1,2,3,4-tetrahydrophenanthrene (6). (−)-*cis*-1,2-Diacetoxy-1,2-dihydrophenanthrene (**5b**, 4.1 mg) dissolved in 2 mL of dioxane was reduced catalytically in the presence of 10% Pd–C (10 mg) at room temperature for 40 min. The reaction mixture was diluted with 20 mL of ethyl acetate and the catalyst was removed by filtration. Evaporation of the solvent and purification by preparative TLC gave the tetrahydro derivative **6** (3.3 mg): $[\alpha]_D$ −193° (c 0.167, dioxane); mass spectrum (EI) *m/e* 298 (M^+), 238 (M^+ − AcOH), 196 (M^+ − AcOH − CH_2CO), 179, 178 (M^+ − 2 × AcOH), and 167; NMR δ 5.32 (d, t, H, H-2) and 6.31 (d, d, 1 H, H-1) with $^3J_{1eq,2ax}$ = 3.5 Hz, $J_{1eq,3eq}$ = 1.0 Hz, $^3J_{2ax,3eq}$ = 3.5 Hz, and $^3J_{2ax,3ax}$ = 10.5 Hz.

Hydrogenolysis of 6. Compound **6** (1.1 mg) was dissolved in 1.0 mL of acetic acid and treated with hydrogen at atmospheric pressure in the presence of 5 mg of 10% Pd–C. After 2 h another 5 mg of the catalyst was added to the reaction mixture. After 3 h at room temperature with stirring, the catalyst was removed by filtration and washed with 5 mL of ethyl acetate. The filtrate was diluted with water and extracted three times with ethyl acetate. The combined organic layer was washed twice with saturated aqueous $NaHCO_3$ and once with water and dried (Na_2SO_4), and the solvent was evaporated. Purification by preparative TLC gave pure **3b** (0.29 mg): CD (MeOH) $\Delta\epsilon_{240}$ +7.4.

(−)-*trans*-1,2-Diacetoxy-1,2,3,4-tetrahydrophenanthrene (8a). (−)-*trans*-1,2-Diacetoxy-1,2-dihydrophenanthrene (**7b**, $[\alpha]_D$ −192° (dioxane), 13 mg) dissolved in 6 mL of dioxane was reduced catalytically in the presence of 10% Pd–C (20 mg) at room temperature for 40 min. The reaction mixture was diluted with 40 mL of ethyl acetate and the catalyst was removed by filtration. Evaporation of the solvent and purification by preparative TLC gave the tetrahydro derivative **8a** (11 mg): mp 120–121 °C; $[\alpha]_D$ −39° (c 0.176, dioxane); mass spectrum (CI-NH_3) *m/e* 316 (M^+ + 18), 238 (M^+ − AcOH), 196 (M^+ − AcOH − CH_2CO); NMR δ 1.98 and 2.08 (both s, 3 H, OAc), 2.18 (m, 2 H, H-3), 3.16 (apparent t, 2 H, H-4), 5.27 (m, 1 H, H-2), 6.20 (d, 1 H, H-1), and 7.2–8.0 (6 H, aromatic protons) with $^3J_{1,2}$ = 6.0 Hz.

1-Benzoate (8b) and 2-Benzoate (8c) of (+)-*trans*-1,2-dihydroxy-1,2,3,4-tetrahydrophenanthrene. The diacetate **8a** (9 mg) was dissolved in 0.3 mL of tetrahydrofuran and diluted with 1 mL of methanol. The solution was treated with 0.3 mL of 1N aqueous sodium hydroxide in an ice bath and allowed to warm up to room temperature. After 2 h, the mixture was diluted with ~10 mL of water and extracted four times with 20-mL portions of ethyl acetate. The combined organic layer was washed with water, dried (Na_2SO_4), and evaporated under vacuum to dryness. The solid residue after recrystallization from ethyl acetate afforded pure (+)-*trans*-1,2-dihydroxy-1,2,3,4-tetrahydrophenanthrene (6.5 mg): mp 170–172 °C; $[\alpha]_D$ +10° (c 0.116, dioxane). This diol (5.5 mg) was dissolved in 0.1 mL of dry pyridine and diluted with 1 mL of dry methylene chloride. The solution was treated with 6.1 mg of benzoyl chloride (1.7 mol equiv) at 0 °C and allowed to warm up to room temperature. After 24 h, 20 μL of methanol was added and the solvent was evaporated to dryness under high vacuum. The oily residue was then purified by preparative TLC (developed with cyclohexane/ethyl acetate, 2:1) to yield 1-benzoate **8b** (2.0 mg) and 2-benzoate **8c** (2.2 mg), **8b**: mp 157–158 °C; NMR δ 4.22 (m, 1 H, H-2) and 6.18 (d, 1 H, H-1) with $^3J_{1ax,2ax}$ = 6.5 Hz; CD (MeOH/dioxane, 9:1) $\Delta\epsilon_{231}$ −14.2, $\Delta\epsilon_{226}$ 0, and $\Delta\epsilon_{222}$ +11.0. **8c**: mp 191–193 °C; NMR δ 4.92 (d, 1 H, H-1) and 5.32 (m, 1 H, H-2) with $^3J_{1ax,2ax}$ = 6.0 Hz; CD (MeOH/dioxane, 9:1) $\Delta\epsilon_{231}$ +12.5, $\Delta\epsilon_{227}$ 0, and $\Delta\epsilon_{222}$ −6.8.

(−)-*cis*-3,4-Diacetoxy-1,2,3,4-tetrahydrophenanthrene (10a). (−)-*cis*-3,4-Diacetoxy-3,4-dihydrophenanthrene (**9b**, $[\alpha]_D$ −204° (c 3.03, dioxane), 50 mg) dissolved in 10 mL of dioxane was reduced catalytically (30 mg of 10% Pd-C) at room temperature for 30 min. The mixture was diluted with 50 mL of ethyl acetate and the catalyst removed by filtration. Evaporation of the solvent and purification by preparative TLC gave the tetrahydro diacetate **10a** (40 mg): mp 123–124 °C; $[\alpha]_D$ −214° (c 3.14, dioxane); mass spectrum (CI-NH_3) *m/e* 316 (M^+ + 18); NMR δ 2.07 and 2.10 (both s, 3 H, OAc) 2.3 (m, 2 H, H-2), 3.1 (m, 2 H, H-1), 5.22 (d, t, 1 H, H-3), and 6.93 (d, 1 H, H-4) with $^3J_{2eq,3ax}$ = $^3J_{3ax,4eq}$ = 3.5 Hz and $^3J_{2ax,3ax}$ = 10.5 Hz.

(−)-cis-3,4-Dihydroxy-1,2,3,4-tetrahydrophenanthrene (10b). (−)-*cis*-3,4-Diacetate **10a** (25 mg) was dissolved in 0.5 mL of tetrahydrofuran and diluted with 1.5 mL of methanol. The solution was treated with 0.5 mL of 2 N aqueous sodium hydroxide in an ice bath and allowed to warm up to room temperature, and the mixture was kept at room temperature for 2 h. The reaction mixture was then diluted with ca. 20 mL of water and extracted four times with 40-mL portions of ethyl acetate. The combined organic layer was washed once with 50 mL of water, dried over Na_2SO_4, and evaporated under vacuum. The solid residue was recrystallized from ethyl acetate to yield pure **10b** (18 mg): mp 168–169 °C; mass spectrum (EI) *m/e* 214 (M^+); $[\alpha]_D$ −21° (c 0.578, dioxane); NMR δ 3.96 (m, $\Delta W_{1/2}$ = 22 Hz, 1 H, H-3) and 5.37 (t, 1 H, H-4) with $^3J_{3ax,4eq}$ = $^4J_{2eq,4eq}$ = 3.6 Hz. Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.60; H, 6.87.

***cis*-3-Hydroxy-4-benzoyloxy-1,2,3,4-tetrahydrophenanthrene (10d).** A suspension of 12 mg of (−)-*cis*-3,4-diol **10b** and 5 mg of benzoic acid in 0.5 mL of trimethyl orthobenzoate was heated at 100 °C for 2 h. The course of reaction was followed by silica gel TLC (2% MeOH in CH_2Cl_2). Excess trimethyl orthobenzoate and methyl benzoate formed in the reaction were evaporated under vacuum. The orange-colored oily residue **10c** was then dissolved in 1 mL of tetrahydrofuran and 0.25 mL of water and treated with three drops of acetic acid and one drop of concentrated HCl. After 2 days, the reaction mixture was diluted with 10 mL of H_2O and extracted three times with 15-mL portions of ethyl acetate. The combined organic layer was washed with 40 mL of water, dried over K_2CO_3, and evaporated under vacuum to yield semisolid residue (13 mg). Purification by preparative TLC using 0.5% MeOH in $CHCl_3$ as a developing solvent provided 7 mg of pure **10d:** mass spectrum (CI-NH_3) *m/e* 336 (M^+ + 18), 300 (M^+ − H_2O), 196 (M^+ − C_6H_5COOH − H_2O); NMR δ 2.3 (m, 2 H, H-2), 3.18 (m, 2 H, H-1), 4.33 (d, t, 1 H, H-3), 7.09 (d, 1 H, H-4), and 7.3–8.1 (11 H, aromatic protons) with $^3J_{2eq,3ax}$ = 4.0 Hz, $^3J_{2ax,3ax}$ = 11.5 Hz, and $^3J_{3ax,4eq}$ = 4.0 Hz.

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Registry No.–**3a**, 64036-29-9; **3b**, 64036-30-2; **3c**, 64036-31-3; **3d**, 64036-32-4; **4**, 16859-76-0; **5a**, 64069-86-9; **5b**, 64069-87-0; **6**, 64069-88-1; **7a**, 64069-83-6; **7b**, 64069-84-7; **8a**, 64069-85-8; **8b**, 65484-16-4; **8c**, 65484-17-5; **9a**, 60966-01-0; **9b**, 60917-40-0; **10a**, 64069-89-2; **10b**, 64069-90-5; **10c**, 64036-26-6; **10d**, 64036-27-7; (+)-1,2-epoxy-1,2,3,4-tetrahydrophenanthrene, 64069-91-6; *trans*-1-*l*-menthyloxyacetoxy-2-bromo-1,2,3,4-tetrahydrophenanthrene isomer I, 64036-28-8; *trans*-1-*l*-menthyloxyacetoxy-2-bromo-1,2,3,4-tetrahychophenanthrene isomer II, 64069-92-7; methyl iodide, 74-88-41; benzoyl chloride, 98-88-41.

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Stereoselective Total Synthesis of Racemic Acorone

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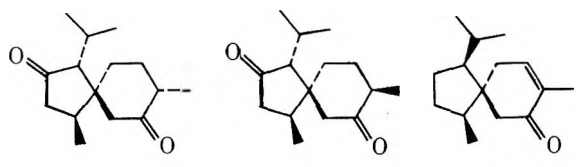
An efficient, stereoselective total synthesis of the acorane sesquiterpenes, (±)-acorone (**1**) and (±)-isoacorone (**2**), has been achieved. The synthetic approach, which utilizes a newly developed procedure for the spiroannulation of a cyclopentenone ring, commences with the alkylation of the pyrrolidine enamine (**10**) of 4-methyl-3-cyclohexene-1-carboxaldehyde with 3-iodo-2-chloropropene. Mercuric ion promoted hydrolysis of the vinyl halide **13** thus produced gave the γ-keto aldehyde **14**, which underwent smooth, base-catalyzed cyclization to give the key intermediate, 8-methylspiro[4.5]deca-1,7-dien-3-one (**15**). Condensation of the enolate generated from compound **15** with acetaldehyde followed by the acid-catalyzed dehydration of the aldols gave a 47:53 mixture of (*E*)- and (*Z*)-1-ethylidene-8-methylspiro[4.5]deca-3,7-dien-2-one (**17a** and **17b**, respectively). After the introduction of the two remaining methyl groups by a facile, one-pot procedure involving two successive treatments of **17a** and **17b** with lithium dimethylcuprate, followed by hydroboration and direct oxidation, a mixture consisting primarily of (±)-acorone (**1**) and (±)-isoacorone (**2**) was obtained. Separation of this mixture by preparative high-pressure liquid chromatography afforded the pure racemic natural products.

The greatest obstacle to the synthesis of the acorane sesquiterpenes such as acorone (**1**), isoacorone (**2**), and acorenone B (**3**) is the stereocontrolled construction of the spirocyclic carbon skeleton. A successful synthesis of these spiro sesquiterpenes depends critically, therefore, upon the generation of a quaternary carbon center which is suitably substituted for the direct annulation to a functionalized spiro[4.5]decane that may be subsequently elaborated to the target natural product. Although several syntheses of acorone (**1**) and isoacorone (**2**) have been reported,[1] the primary synthetic interest has been in acorenone B (**3**).[2] We now wish to report a highly stereoselective synthesis of racemic acorone and racemic isoacorone using a new approach for the spiroannulation of a cyclopentenone ring.[3]



1 **2** **3**

As part of a general synthetic program, we have been interested in developing new synthetic methods for the construction of quaternary carbon atoms which bear dissimilarly functionalized alkyl appendages. We have recently discovered one particularly attractive procedure for the geminal alkylation at a carbonyl carbon atom that involves the direct conversion of ketones into the enamines of the homologous aldehydes.[4] These enamines are useful synthetic intermediates and may be employed without purification in subsequent reactions with electrophiles. For example, by the appropriate choice of electrophiles, this general synthetic procedure, which is depicted in eq 1, may be exploited for the preparation of α-allyldialkyl aldehydes,[4a] 4,4-disubstituted cyclohexenones,[4b] and 4,4-disubstituted cyclopentenones.[4c] When the starting ketone is cyclic, the latter two methods allow for the facile spiroannulation of cyclohexenones and cyclopentenones.

Our initial approach to the synthesis of acorone (**1**), shown in Scheme I, was based upon our new method for the spiroannulation of cyclopentenones and began with the ethylene glycol monoketal of cyclohexane-1,4-dione **4**.[5] Thus, reaction

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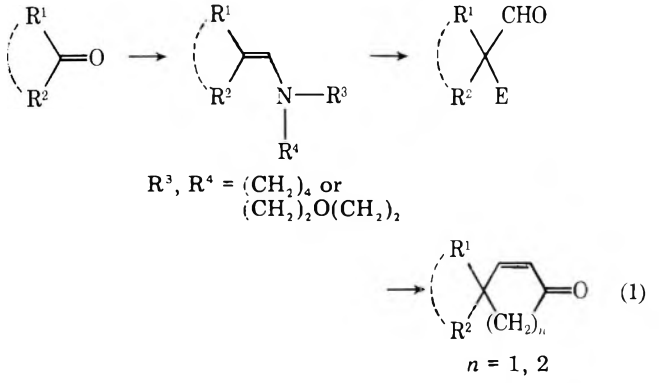


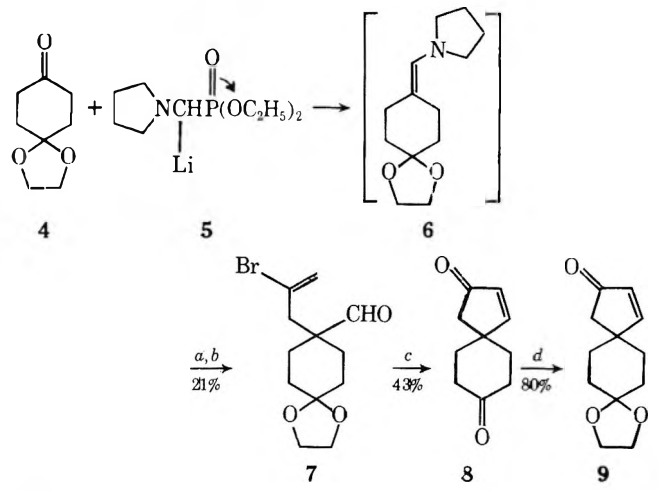
(1)

of 4 with diethyl lithiopyrrolidinomethylphosphonate (5), followed by the direct alkylation of the enamine 6, produced the aldehyde 7, albeit in only 21% overall yield. When this 2-(2-bromo-2-propenyl) aldehyde 7 was treated with concentrated sulfuric acid at 0 °C, cyclization to the cyclopentenone ring proceeded as anticipated, but unavoidable hydrolysis of the ketal also occurred concomitantly to give the spiro enedione 8 in 43% yield. Despite this difficulty, selective ketalization of the saturated carbonyl function was readily achieved producing the monoprotected enedione 9 in 80% yield. Owing to the low yield at the outset of this synthetic sequence, coupled with the problem of ketal hydrolysis in the subsequent cyclization step, an alternate approach to the synthesis of acorone was examined (Scheme II).

Another attractive enamine precursor to a suitably functionalized spiro[4.5]decane ring system is the enamine 10. Unfortunately, all attempts to generate 10 in situ by the reaction of diethyl lithiopyrrolidinomethylphosphonate (5) with 4-methyl-3-cyclohexenone (11)[6] were unsuccessful. However, the reaction of the readily available 4-methyl-3-cyclohexene-1-carboxaldehyde (12)[7] with pyrrolidine in refluxing benzene containing a catalytic amount of *p*-toluenesulfonic acid cleanly provided the desired enamine 10 in 94% yield. When the enamine 10 was treated with 2-chloro-3-iodopropene, followed by aqueous hydrolysis, the alkylated aldehyde 13 was produced in 74% yield.

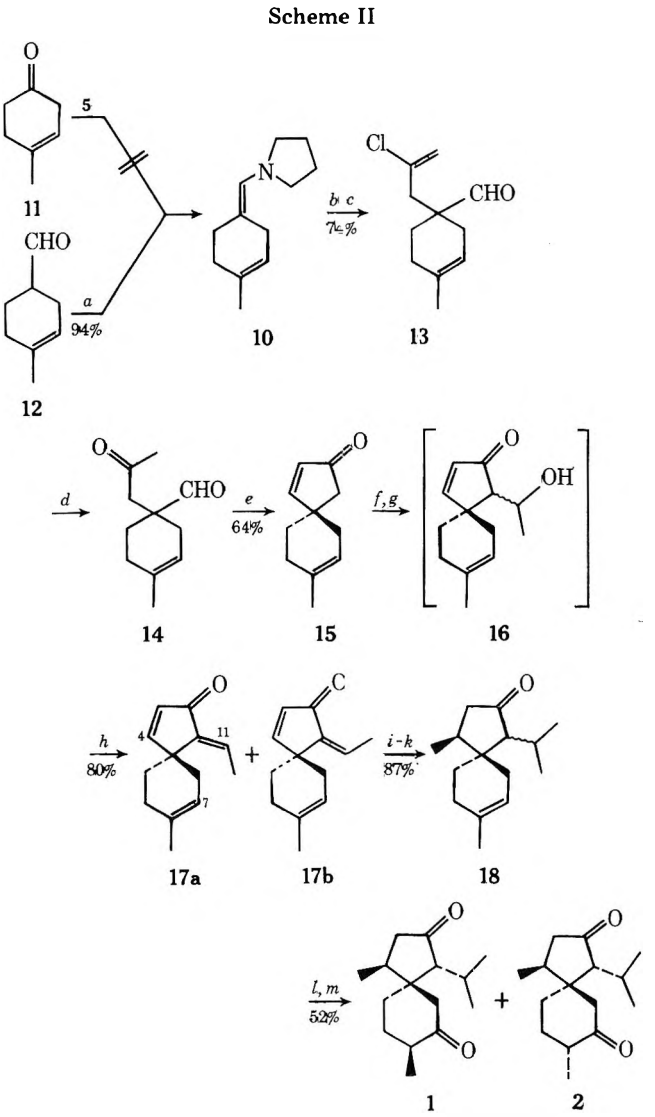
Efforts to promote the cyclization of the vinylchloro aldehyde 13 with concentrated sulfuric acid were rather unsatisfactory because they resulted in the formation of several products, only one of which was the desired spiro[4.5]decadienone 15. Moreover, several other known methods for the hydrolysis of vinyl chlorides[8] proved equally fruitless. We have recently discovered, however, that vinyl chlorides may be

Scheme I



[a] $BrCH_2CHBr{=}CH_2/THF/\Delta$. [b] H_2O. [c] 98% $H_2SO_4/CH_2Cl_2/0$ °C. [d] $HOCH_2CH_2OH/TosOH/C_6H_6/\Delta$.

Scheme II



[a] $(CH_2)_4NH/TosOH/C_6H_6/\Delta$. [b] $ICH_2CHCl{=}CH_2/CH_3CN/\Delta$. [c] H_2O. [d] $Hg(OAc)_2/BF_3{\cdot}Et_2O$/HOAc. [e] 10% KOH/$CH_3OH$. [f] LDA/THF/−30 °C. [g] CH_3CHO/THF/−78 °C. [h] TosOH/C_6H_6/Δ. [i] $(CH_3)_2CuLi/Et_2O/0$ °C. [j] HOAc. [k] $(CH_3)_2CuLi/Et_2O/0$ °C. [l] B_2H_6/THF/25 °C. [m] $Na_2Cr_2O_7/H_2SO_4/H_2O$.

conveniently converted into ketones under very mild conditions using mercuric acetate in the presence of boron trifluoride etherate.[9] For example, hydrolysis of the vinyl chloride 13 to the γ-keto aldehyde 14 was readily achieved with mercuric acetate and boron trifluoride etherate in glacial acetic acid at room temperature. When crude 14 was treated with 10% aqueous potassium hydroxide in methanol, cycloaldolization and dehydration proceeded smoothly to give the key intermediate spiro[4.5]decadienone 15 in 64% overall yield from compound 13.

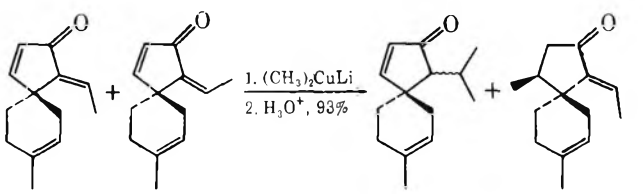
Completion of the construction of the carbon skeleton entailed the stereocontrolled introduction of an isopropyl group at C-1 and a methyl group at C-4. Since we anticipated that the direct isopropylation at C-1 might be attended with considerable difficulty, we elected instead to introduce the isopropyl group by an indirect method. Thus, the reaction of the enolate generated from the ketone 15 with acetaldehyde[10] produced a mixture of uncharacterized compounds presumed to be the directed aldols 16. The subsequent *p*-toluenesulfonic acid catalyzed dehydration proceeded without incident to give an 80% overall yield of a mixture of the diastereomeric *E* and *Z* trienones 17a and 17b in the ratio of 47:53, respectively. This stereochemical assignment was based upon the downfield position of the C-11 vinyl proton of the *E* isomer 17a [δ 6.57

(dq, J = 7.5, 0.8 Hz)] in relation to the C-11 vinyl proton of the Z isomer **17b** [δ 6.03 (q, J = 7.5 Hz)]. Moreover, the C-12 methyl group of **17a** has a high field position [δ 1.90 (d, J = 7.5 Hz)] with respect to the C-12 methyl group of **17b** [δ 2.19 (d, J = 7.5 Hz)]. In agreement with this assignment, the $Eu(fod)_3$ induced shifts of the vinyl proton at C-11 of **17a** are larger (0.11–0.41 ppm) than the corresponding shifts of the C-11 proton of **17b** (0.04–0.13 ppm). The comparison of the relative magnitudes of these shifts implies that the C-11 hydrogen in **17a** is syn to the carbonyl group. A similar comparison of the $Eu(fod)_3$ induced shifts of the C-12 methyl groups in **17a** and **17b** lends further support to this stereochemical assignment.

The next stage of the synthesis required the introduction of the two remaining methyl groups at C-4 and C-11, thereby completing the construction of the carbon skeleton of acorone. We anticipated that this task could be easily accomplished by the sequential addition of lithium dimethylcuprate to both the exo- and endocyclic enone systems of **17a,b,**[11] and a one-pot procedure was especially attractive. Following the addition of the E and Z trienones **17a** and **17b** to a slight excess of lithium dimethylcuprate, an equivalent of glacial acetic acid was added to quench the reaction. When the reaction mixture thus obtained was added directly to an excess of lithium dimethylcuprate, a product mixture consisting primarily (>95%) of the diastereomeric ketones **18**, which were epimeric at C-1, was obtained in 87% yield. Integration of the ^{13}c nmr signals for C-2 at δ 219.03 and 217.67 indicated **18** to be an approximately 1:1 mixture of C-1 epimers. Moreover, careful examination of the ^{13}C NMR spectrum revealed the presence of only one other carbonyl carbon (δ 219.75), albeit in less than 5% of the total products, which might be due to the presence of a C-4 epimer. Although unnecessary for the actual synthesis of acorone, base-catalyzed (methanolic sodium methoxide) epimerization at C-1 of **18** afforded an apparent equilibrium mixture that contained, on the basis of ^{13}C NMR, an 8:1 mixture of C-1 epimers.

This important reaction sequence generates two chiral centers and merits further comment. On the basis of previous reports,[12] the required configuration at the epimerizable center C-1 was known to be greatly favored thermodynamically and presented, therefore, no difficulty. The creation of the other new chiral center at C-4 was less predictable, but a careful examination of Dreiding molecular models suggested that the dimethylcuprate reagent should approach past the Δ^7 double bond, thus adding selectively to the endocyclic enone system from the sterically less hindered direction to give the desired configuration at C-4. The subsequent conversion of **18** into acorone and isoacorone (vide infra) verifies that the introduction of the methyl group at C-4 did indeed proceed with the anticipated stereoselectivity. A similar high degree of stereochemical control in a closely related cuprate addition has also been recently reported by Dolby.[1a]

While it was not crucial to the total synthesis of acorone, we were interested in determining whether there was any regioselectivity in the addition of the first equivalent of lithium dimethylcuprate to the trienones **17a** and **17b.** Consequently, treatment of a 47:53 mixture of the E and Z trienones **17a** and **17b** with a slight excess of lithium dimethylcuprate at 0 °C,[13] followed by quenching the reaction with aqueous acid, gave a mixture of the monoadducts **19** and **20** as the major products in 93% yield (eq 2). Integration of the signals for the protons at C-4 of **19** [δ 7.67 and 7.56 (overlapping d, J = 6 Hz)] and at C-11 of **20** [δ 6.71 (q, J = 7.5 Hz)] clearly showed that **19** and **20** were formed in approximately equal amounts. The stereochemical assignment of the E configuration for the enone **20** was based upon a comparison of the chemical shifts of the vinyl proton at C-11 (δ 6.71) and the C-12 methyl group (δ 1.82) with those observed for compound **17a.** Not only is this



17a **17b** **19** **20** (2)

assignment supported by the $Eu(fod)_3$ induced shifts of the vinyl and methyl protons, but it is also consistent with the NMR data previously reported for this compound.[1a] Apparently, lithium dimethylcuprate adds preferentially to the endocyclic double bond of the E isomer **17a,** but it adds selectively to the exo double bond of the Z isomer **17b.**

Returning to the synthetic task at hand, attention was directed to the conversion of the diastereomeric ketones **18** into acorone. After treating **18** with excess diborane in tetrahydrofuran, followed by oxidation of the intermediate boranes with chromic acid,[14] a mixture of (±)-acorone (**1**) and (±)-isoacorone (**2**), together with several minor unidentified products, was obtained. Separation of the components of the reaction mixture by preparative high-pressure liquid chromatography afforded pure (±)-acorone (**1**) [mp 101.5–102 °C (lit.[1a] 101.5–103.5 °C)] in 25% yield and pure (±)-isoacorone (**2**) (mp 66–67 °C) in 27% yield. Comparison of the IR, NMR, and mass spectra, as well as the GLC and TLC of synthetic racemic acorone and isoacorone, with those of authentic samples[15] confirmed their identity.

Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All boiling points are uncorrected. ^1H NMR spectra were determined on a Varian A-60A or HA-100 spectrometer as solutions in $CDCl_3$. Chemical shifts are reported in δ units downfield from the internal reference, tetramethylsilane (Me_4Si). The ^{13}C NMR spectra were determined on a Bruker WH-90 FT spectrometer, and the chemical shifts are reported in δ units downfield from internal Me_4Si. The infrared spectra (IR) were recorded on a Beckman IR-5A spectrophotometer using chloroform as solvent. Low-resolution mass spectra were obtained on a Du Pont (CEC) 21-491 instrument, and the high-resolution mass spectra were obtained on a Du Pont (CEC) 21-110 instrument. GLC analyses were performed on a Varian Aerograph 2720 equipped with a thermal conductivity detector and a 5 ft × 0.25 in. 1.5% OV-101, Chromosorb HP column unless otherwise noted. Glassware was oven dried prior to use, and all reactions were executed under dry nitrogen. The tetrahydrofuran (THF) was freshly distilled from potassium–benzophenone, and the ether was freshly distilled from sodium–benzophenone. The n-butyllithium–hexane and the methyllithium–ether were purchased from Alfa Inorganics, Danvers, Mass., and titrated prior to use. 2-Chloro-3-iodopropene was prepared in 65% yield by the procedure of Letsinger and Traynham.[16] Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz.

8-(2-Bromo-2-propenyl)-8-formyl-1,4-dioxaspiro[4.5]decane (7). To a well-stirred solution of diethyl pyrrolidinomethylphosphonate (4.0 g, 18.0 mmol) in anhydrous THF (60 mL) at −78 °C was slowly added n-butyllithium–hexane (18.0 mmol). After being stirred at −78 °C for 1 h, a solution of 1,4-dioxaspiro[4.5]decanone (**4**)[5] (2.3 g, 15.0 mmol) in anhydrous THF (5 mL) was added, and the stirring was continued at −78 °C for 4 h and then at room temperature overnight to give a solution of the enamine **6**. 2,3-Dibromopropene (15.0 g, 75.0 mmol) was added, and the mixture was heated at reflux for 48 h. Upon cooling to room temperature, H_2O (30 mL) was added, and the resulting reaction mixture was stirred vigorously at room temperature for 4 h. Saturated brine (50 mL) was then added, and the layers were separated. The aqueous layer was extracted with ether (3 × 75 mL), and the combined organic layers were washed with 1 N HCl and saturated $NaHCO_3$ and dried ($MgSO_4$). After removal of the excess solvent under reduced pressure, vacuum distillation gave 0.91 g (21%) of **7**: bp 128–130 °C (0.05 mm); IR 1625, 1715, 2705 cm^{-1}; NMR δ 9.69 (s, 1 H), 5.56 (m, 2 H), 3.91 (s, 4 H), 2.75 (s, 2 H), 1.50–2.20 (complex, 8 H); mass spectrum m/e 290, 288, 209 (base), 165, 99. The alkylated aldehyde **7** thus obtained was used in the next step without further purification.

Spiro[4.5]dec-1-ene-3,8-dione (8). While a rapid stream of dry

nitrogen was bubbled through concentrated sulfuric acid (3 mL) cooled to 0 °C, compound **7** (0.91 g, 3.15 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise. After completion of the addition, the dark reaction mixture was stirred at 0 °C for 2 h, whereupon it was poured slowly onto crushed ice. The aqueous mixture was extracted with methylene chloride (3 × 70 mL), and the combined organic layers were washed with saturated $NaHCO_3$ and dried ($MgSO_4$). Removal of the excess solvent under reduced pressure, followed by flash distillation [oil bath at 200 °C (0.05 mm)] of the crude material thus obtained, afforded 0.24 g (43%) of **8**: >90% pure by GLC. Preparative GLC (5% Carbowax 20M, firebrick) provided an analytical sample: IR 1595 and 1715 cm^{-1}; NMR δ 7.67 (d, 1 H, J = 6 Hz), 6.16 (d, 1 H, J = 6 Hz), 2.47 (s, 2 H), 1.75–2.70 (complex, 8 H); mass spectrum m/e 164 (base), 94, 79, 66, 55; exact mass (calcd for $C_{10}H_{12}O_2$) 164.0837, found 164.0836.

1,4-Dioxadispiro[4.2.4.2]tetradec-9-en-11-one (9). A mixture of compound **8** (0.12 g, 0.8 mmol) and ethylene glycol (0.15 g, 2.4 mmol) in anhydrous benzene (2 mL) containing a catalytic amount of *p*-toluenesulfonic acid was heated at reflux for 12 h in the presence of Linde 4A molecular sieves (0.5 g). After cooling to room temperature, saturated brine (10 mL) was added, and the layers were separated. The aqueous layer was extracted with ether (3 × 25 mL), and the combined organic layers were washed with saturated $NaHCO_3$ and dried ($MgSO_4$). The excess solvent was evaporated under reduced pressure and the residue flash distilled [oil bath at 200 °C (0.05 mm)] to give 0.13 g (80%) of **9**: >90% pure by GLC; IR 1590 and 1705 cm^{-1}; NMR δ 7.59 (d, 1 H, J = 6 Hz), 6.08 (d, 1 H, J = 6 Hz), 3.97 (s, 4 H), 2.29 (s, 2 H), 1.62–1.90 (complex, 8 H); mass spectrum m/e 208, 164, 99, 86, 55; exact mass (calcd for $C_{12}H_{16}O_3$) 208.1099, found 208.1093.

1-(4-Methyl-3-cyclohexenylidenemethyl)pyrrolidine (10). A solution of 4-methyl-3-cyclohexene-1-carboxaldehyde[7] (**12**) (10.0 g, 0.08 mol) and pyrrolidine (7.2 g, 0.10 mol) in anhydrous benzene (60 mL) containing a catalytic amount of *p*-toluenesulfonic acid was heated at reflux for 8 h with continuous removal of water (Dean-Stark trap). The excess solvent was then evaporated under reduced pressure, and the crude enamine was distilled to give 13.3 g (94%) of **10**: >95% pure by GLC; bp 84–85 °C (0.7 mm); IR 1660 cm^{-1}; NMR δ 5.67 (br s, 1 H), 5.33 (br s, 1 H), 1.50–3.10 (complex, 17 H); mass spectrum m/e 177, 162, 91 (base), 70; exact mass (calcd for $C_{12}H_{19}N$) 177.1517, found 177.1517.

1-(2-Chloro-2-propenyl)-4-methyl-3-cyclohexene-1-carboxaldehyde (13). To a solution of the enamine **10** (8.0 g, 0.045 mol) in anhydrous acetonitrile (100 mL) was added 2-chloro-3-iodopropene (25.0 g, 0.125 mol), and the resulting solution was heated at reflux for 48 h. After evaporation of the excess solvent under reduced pressure, aqueous THF (100 mL, 1:1) was added, and the resulting mixture was stirred vigorously at room temperature for 5 h. Saturated brine (100 mL) was then added, and the layers were separated. The aqueous layer was extracted with ether (5 × 80 mL), and the combined organic layers were washed with 1 N HCl, 5% $Na_2S_2O_3$, and saturated $NaHCO_3$ and dried ($MgSO_4$). Removal of the excess solvent under reduced pressure followed by distillation afforded 6.7 g (74%) of the alkylated aldehyde **13**: bp 74–75 °C (0.2 mm); IR 1640, 1725, 2735 cm^{-1}; NMR δ 9.57 (s, 1 H), 5.37 (br s, 1 H), 5.19 (m, 2 H), 1.50–2.70 (complex, 6 H), 2.60 (m, 2 H), 1.63 (br s, 3 H); mass spectrum m/e 200, 198, 123 (base), 122, 95, 93; exact mass (calcd for $C_{11}H_{15}ClO$) 198.0811, found 198.0805.

1-(2-Oxopropyl)-4-methyl-3-cyclohexene-1-carboxaldehyde (14). To a well-stirred solution of mercuric acetate (4.50 g, 14.0 mmol) and the vinyl halide **13** (1.86 g, 9.3 mmol) in glacial acetic acid (90 mL) was added freshly distilled boron trifluoride etherate (2.60 g, 18.0 mmol). Stirring was continued at room temperature for 12 h, during which time a white precipitate formed. After filtration of the reaction mixture and evaporation of the acetic acid in vacuo, saturated brine (50 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (4 × 75 mL). The combined organic layers were washed with saturated $NaHCO_3$ and saturated brine and then dried ($MgSO_4$). Evaporation of the excess solvent under reduced pressure afforded 1.34 g of crude γ-keto aldehyde **14** which was >95% pure by GLC. An analytical sample was obtained by preparative GLC (5% Carbowax 20M, firebrick): IR 1710 and 2735 cm^{-1}; NMR δ 9.68 (s, 1 H), 5.37 (br s, 1 H), 2.79 (s, 2 H), 2.10 (s, 3 H), 1.50–2.50 (complex, 9 H); mass spectrum m/e 180, 123 (base), 122, 107, 93, 63; exact mass (calcd for $C_{11}H_{16}O_2$) 180.1150, found 180.1153.

8-Methylspiro[4.5]deca-1,7-dien-3-one (15). Crude **14** (1.34 g) from above was dissolved in methanol–10% aqueous KOH (10 mL, 1:1), and the resulting solution was stirred at room temperature for 18 h. After acidification of the reaction mixture with 1 N HCl (10 mL), saturated brine (15 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 × 75 mL). The combined organic layers were washed with saturated $NaHCO_3$ and dried ($MgSO_4$), and the excess solvent was removed under reduced pressure to give, after distillation, 0.96 g (64%) of the spiro dienone **15**: bp 79–80 °C (0.6 mm) [lit.[1a] 59–60 °C (0.15 mm)]. An analytical sample was prepared by preparative GLC (5% Carbowax 20M, firebrick): IR 1595 and 1720 cm^{-1}; NMR δ 7.55 (d, 1 H, J = 6 Hz), 6.00 (d, 1 H, J = 6 Hz), 5.40 (br s, 1 H), 2.10 (s, 2 H), 1.69 (s, 3 H), 1.50–2.50 (complex, 6 H); mass spectrum m/e 162, 95, 68 (base); exact mass (calcd for $C_{11}H_{14}O$) 162.1045, found 162.1041.

(*E*)- and (*Z*)-1-Ethylidene-8-methylspiro[4.5]deca-3,7-dien-2-one (17a,b). To a solution of lithium diisopropylamide [generated from diisopropylamine (0.63 g, 6.3 mmol) in anhydrous THF (10 mL) and *n*-butyllithium (6.3 mmol)] at −78 °C was slowly added a solution of **15** (0.66 g, 4.1 mmol) in anhydrous THF (2 mL). The stirring was continued at −78 °C for 30 min and then at −30 °C for 2 h, whereupon the mixture was again cooled to −78 °C and acetaldehyde (0.84 g, 28.0 mmol) dissolved in anhydrous THF (1 mL) added. After allowing the reaction to proceed at −78 °C for an additional 1.5 h, it was quenched with 10% aqueous acetic acid. The layers were separated, and the aqueous layer was extracted with ether (3 × 40 mL). The combined organic layers were washed with saturated $NaHCO_3$ and dried ($MgSO_4$), and the excess solvent was evaporated under reduced pressure. Flash distillation [oil bath at 180 °C (<0.02 mm)] afforded a mixture of aldol products **16** which was not further characterized. Instead, the crude aldols **16** were dissolved in anhydrous benzene (4 mL) containing a catalytic amount of *p*-toluenesulfonic acid, and the mixture was heated at reflux for 4 h with continuous removal of water (Dean-Stark trap). Saturated brine (20 mL) was added, and the layers were separated. The aqueous layer was extracted with ether (3 × 40 mL), and the combined organic portions were washed with saturated $NaHCO_3$ and dried ($MgSO_4$). Removal of the excess solvent under reduced pressure followed by distillation of the residue gave 0.62 g (80%) of a mixture of *E* and *Z* trienones **17a** and **17b** in a 47:53 ratio (determined by GLC and NMR): bp 75–81 °C (0.03 mm). An analytical sample of each isomer was obtained by preparative GLC (5% Carbowax 20M, firebrick). *E* isomer **17a**: IR 1610, 1660, 1710 cm^{-1}; NMR δ 7.66 (dd, 1 H, J = 6, 0.8 Hz), 6.57 (dq, 1 H, J = 7.5, 0.8 Hz), 6.19 (d, 1 H, J = 6, 0.8 Hz), 5.43 (br s, 1 H), 1.90 (d, 3 H, J = 7.5 Hz), 1.72 (br s, 3 H), 1.50–2.30 (complex, 6 H); mass spectrum m/e 188, 121, 120 (base), 91, 68; exact mass (calcd for $C_{13}H_{16}O$) 188.1201, found 188.1203. *Z* isomer **17b**: IR 1610, 1630, 1710 cm^{-1}; NMR δ 7.43 (d, 1 H, J = 6 Hz), 6.15 (d, 1 H, J = 6 Hz), 6.03 (q, 1 H, J = 7.5 Hz), 5.42 (br s, 1 H), 2.19 (d, 3 H, J = 7.5 Hz), 1.72 (br s, 3 H), 1.50–2.30 (complex, 6 H); mass spectrum m/e 188, 121, 120 (base), 91, 68; exact mass (calcd for $C_{13}H_{16}O$) 188.1201, found 188.1196.

Reaction of Mixture of *E* and *Z* Trienones 17a and 17b with Lithium Dimethylcuprate. To a suspension of CuI (Fischer) (98 mg, 0.5 mmol) in anhydrous ether (2 mL) at 0 °C was added methyllithium (1.0 mmol) and the resulting mixture stirred at 0 °C for an additional 0.5 h. A mixture of compounds **17a** and **17b** (72 mg, 0.4 mmol) dissolved in ether (0.5 mL) was then added dropwise with vigorous stirring, and the greenish yellow mixture was allowed to stir at 0 °C for 2 h. The reaction was quenched by addition of 0.1 N HCl (20 mL) and the mixture filtered through a Celite pad. After the filtrate was saturated with NaCl, the aqueous layer was extracted with ether (3 × 30 mL), and the combined organic layers were washed with saturated $NaHCO_3$ and dried ($MgSO_4$). Removal of the excess solvent under reduced pressure followed by flash distillation of the residue [oil bath at 200 °C (<0.05 mm)] gave 73 mg (93%) of a mixture which consisted primarily of **19** and **20** in an approximately 1:1 ratio: NMR (**19**) δ 7.67 and 7.56 (overlapping d, 0.5 H, J = 6 Hz, $-CH{=}CHCO-$), 5.98 and 5.97 (overlapping d, 0.5 H, J = 6 Hz, $-CH{=}CHCO-$); NMR (**20**) δ 6.71 (q, 0.5 H, J = 7.5 Hz, $CH_3CH{=}C<$), 1.82 (d, 1.5 H, J = 7.5 Hz, $CH_3CH{=}C<$).

1-Isopropyl-4,8-dimethylspiro[4.5]dec-7-en-2-one (18). To a stirred solution of lithium dimethylcuprate (2.5 mmol), prepared at 0 °C as described above, was added dropwise a solution of the *E*/*Z* mixture of trienones **17a** and **17b** (0.36 g, 1.9 mmol) in anhydrous ether (1 mL). The resulting greenish yellow mixture was stirred at 0 °C for another 2 h, at which time a 5% solution of glacial acetic acid in ether (5.0 mmol) was added, and the stirring was continued at room temperature for 30 min. After cooling at 0 °C, the grey mixture was transferred through a cannula to another flask containing lithium dimethylcuprate (5.0 mmol) in ether (25 mL), and the resulting mixture was stirred at 3–5 °C for an additional 20 h. The reaction was quenched by the addition of 1 N HCl (30 mL). The precipitated solids were removed by filtration through a Celite pad, the layers were separated, and the aqueous layer was then saturated with sodium chloride and extracted with ether (3 × 80 mL). The combined organic layers were washed with saturated $NaHCO_3$ and dried ($MgSO_4$), and

the excess solvent was removed under reduced pressure to give 0.41 g of **18** as a light brown oil (>95% pure by GLC). An analysis of the carbonyl region of the ^{13}C NMR spectrum of the crude product revealed it to be a mixture (ca. 1:1) of the C-1 epimers (δ 219.03 and 217.67), together with another minor, unidentified component (<5%) (δ 219.75). Although it was not necessary for the synthesis, an apparent thermodynamic mixture of the C-1 epimers could be obtained by base-catalyzed epimerization. Thus, the crude product obtained above was dissolved in 1 N methanolic sodium methoxide (3 mL) and the solution stirred at room temperature for 5 h. After addition of saturated brine (10 mL), the mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were washed with saturated NH_4Cl and dried ($MgSO_4$). Evaporation of the excess solvent under reduced pressure, followed by distillation of the residue, gave 0.36 g (87%) of **18**, bp 88–89 °C (0.02 mm), which was judged to be an 8:1 mixture of C-1 epimers by ^{13}C NMR. An analytical sample was obtained by preparative GLC (5% Carbowax 20M, firebrick): IR 1740 cm^{-1}; ^1H NMR δ 5.34 (br s, 1 H), 1.71–2.75 (complex, 11 H), 1.63 (br s, 3 H), 1.10 (d, 3 H, J = 7 Hz), 0.96 (d, 3 H, J = 7 Hz), 0.94 (d, 3 H, J = 7 Hz); ^{13}C NMR, C-2 (major diastereomer, ca. 89%), δ 219.03, C-2 (minor diastereomer, ca. 11%) δ 217.67; mass spectrum *m/e* 220, 178, 150, 121 (base), 110, 97, 96, 82, 68; exact mass (calcd for $C_{15}H_{24}O$) 220.1827, found 220.1828.

Acorone (1) and Isoacorone (2). A solution of diborane in THF (3.4 mmol) was added slowly dropwise with vigorous stirring to a solution of the diastereomeric ketones **18** (0.74 g, 3.4 mmol) in anhydrous THF (30 mL) at 0 °C, and the stirring was continued at room temperature for 2 h. To destroy the excess diborane, water (1 mL) was added, and the mixture was stirred at room temperature for an additional 15 min. A solution of chromic acid [prepared by mixing sodium dichromate (2.10 g, 7.6 mmol), 98% H_2SO_4 (1.75 mL, 3.1 mmol), and H_2O (9.3 mL)] was then added with vigorous stirring over the course of 30 min. After completion of the addition, the reaction mixture was heated at reflux for 2 h and then cooled. Saturated brine (40 mL) was added, the layers were separated, and the aqueous layer was thoroughly extracted with ether (6 × 80 mL). The combined organic layers were washed with saturated $NaHCO_3$ and dried ($MgSO_4$). Evaporation of the excess solvent under reduced pressure afforded 0.73 g of a light yellow oil. Analytical GLC and TLC analyses of the crude oil showed it to be a mixture of acorone and isoacorone [ca. 75% by comparison with an authentic sample of neoacorone, which is a mixture of (+)-acorone and (−)-isoacorone], along with several minor unidentified components. Preparative high-pressure liquid chromatography (Waters LC 500) using two Prep PAK columns and ethyl acetate–hexane (1:4) as the eluting solvent and a flow rate of 250 mL/min afforded 0.20 g (27%) of pure (±)-isoacorone (**2**) (6.8 min) and 0.18 g (25%) of pure (±)-acorone (**1**) (10 min). Analytical samples of both (±)-acorone and (±)-isoacorone were obtained by recrystallization from hexane, and these were identical with authentic samples of (+)-acorone and (−)-isoacorone[15] by IR, NMR, MS, GLC, and TLC. (±)-Acorone: mp 101.5–102 °C (lit.[1a] 101.5–103.5 °C); exact mass (calcd for $C_{15}H_{24}O_2$) 236.1776, found 236.1780. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.27; H, 10.33.

(±)-Isoacorone: mp 66–67 °C; exact mass (calcd for $C_{15}H_{24}O_2$) 236.1776, found 236.1777.

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Registry No.—**1**, 61475-94-3; **2**, 61475-97-6; **4**, 4746-97-8; **6**, 64715-23-7; **7**, 64715-24-8; **8**, 64715-25-9; **9**, 64715-26-0; **10**, 64715-27-1; **12**, 7560-64-7; **13**, 64715-28-2; **14**, 61426-19-5; **15**, 61426-14-0; **16**, 64728-47-8; **17a**, 61426-21-9; **17b**, 61426-22-0; **18** (isomer 1), 61475-96-5; **18** (isomer 2), 61426-24-2; **19**, 64715-29-3; **20**, 61475-95-4; diethyl pyrrolidinomethylphosphonate, 51868-96-3; 2,3-dibromopropene, 513-31-5; ethylene glycol, 107-21-1; pyrrolidine, 123-75-1; 2-chloro-3-iodopropene, 39557-31-8.

References and Notes

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New Synthetic Methods. Stereocontrolled Bicycloannulation: an Approach to Gibberellins

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An approach for the stereocontrolled annulation of a bicyclo[3.2.1]nonan-5-one onto a cycloalkanone is delineated. Reaction of 2-(2′-trityloxyethyl)cyclopentanone with diphenylsulfonium cyclopropylide provides the spiro-fused cyclobutanone. Regiocontrolled ring expansion converts the cyclobutanone into a cyclopentanone. This approach serves to create spiro[*n*.4] systems in a stereochemically defined fashion. Sulfinylation, reduction of the β-keto sulfoxide to the β-keto sulfide, and conversion of the trityloxy group to a mesylate allows base-catalyzed cyclization to the desired bicyclo[3.2.1]nonan-5-one. Utilizing the bridgehead sulfur as a control element and Wagner–Meerwein shifts, either stereochemical series of fusion of the bicyclic system is available. Methylenation completed the gibberellin model.

Among the structural types of important natural products that are very common are the bicyclo[3.2.1]octanes fused to another ring. Two examples, gibberellic acid (**1**) and aphidicolin (**2**), illustrate two much sought after important targets that possess this feature. In considering the synthesis of gibberellic acids, the vast majority of methods focus on creating ring D onto a preformed ring C system.[1-4] We report a new approach to the stereocontrolled production of the BCD

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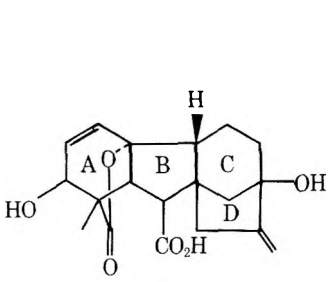

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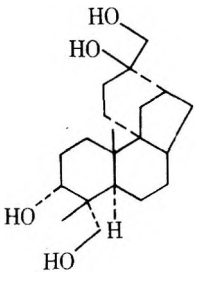
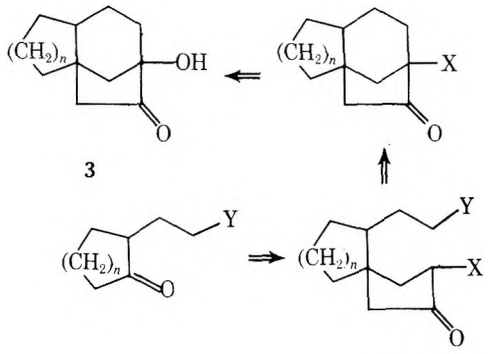


2

fragment which closes ring C to complete the carbon framework. This approach offers one the ability to form either stereochemistry at the BC ring juncture and to manipulate the substitution pattern. Thus, the strategy should be generally applicable and potentially can be extended to the annulation of bicyclo[n.2.1]alkane onto any ketone. Furthermore, this approach illustrates the applicability of the stereocontrolled spiroannulation of cyclobutanones and the versatility of the latter in creating larger cycloalkanones.

In developing an approach to **3**, the problem can factor down to an intramolecular alkylation of a spiro[n.4] system **4**. Thus, a stereocontrolled synthesis of **4** becomes a stereocontrolled synthesis of **3**. The latter simplifies to a spiroalkylation of a five-membered ring onto a cycloalkanone. The importance of spiro[4.5]decanes, for which this methodology will also be applicable, enhances the importance of this approach.



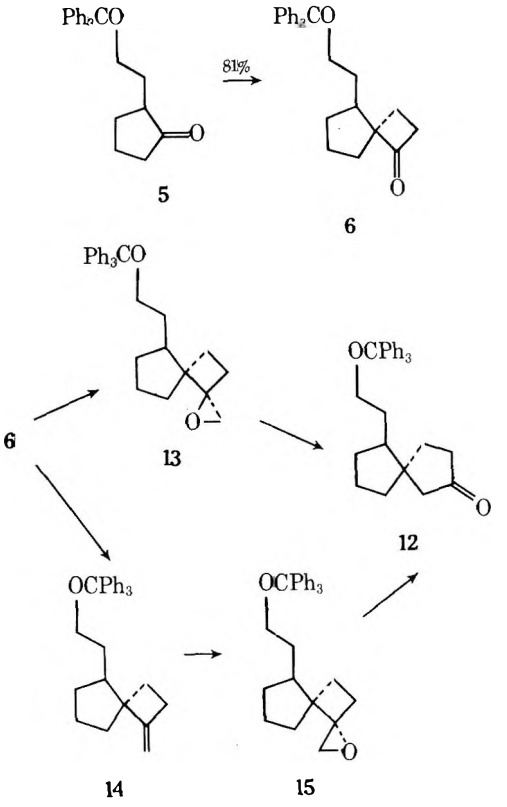
3 4

Results

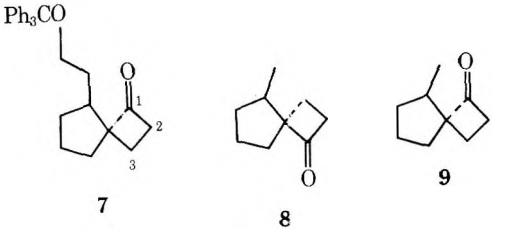
Treatment of 2-(2′-trityloxyethyl)cyclopentanone (**5**) with cyclopropyldiphenylsulfonium fluoborate and potassium hydroxide in Me_2SO, followed by lithium fluoborate in refluxing benzene, gave a single crystalline cyclobutanone, **6**, in 81% yield (see Scheme I). The stereohomogeneity is confirmed by the appearance of only eleven aliphatic carbons in the ^{13}C NMR spectrum and by a clean ^1H NMR spectrum as well as by chromatographic analysis. As far as can be discerned, a single compound results from this spiroannulation. Assignment of stereochemistry follows by analogy to previous examples[5,6] and from the ^{13}C NMR spectrum.[7] Utilizing the type-II stereoreversed rearrangement,[7] a mixture of **6** and its epimer **7** was available. C(3) appears at 3 ppm higher field in **7** (δ 19) compared to **6** (δ 22) as expected for a γ effect. For comparison, the shifts for this carbon in **8** and **9** are δ 22.8 and 20.0, respectively.[7]

With the stereochemistry of the system fixed, attention turns to the ring expansion.[8,9] In pinacol-type ring expansions (via diol, amino alcohol, bromohydrin, etc.), conformational effects can overcome the normal electronic preference for a more substituted carbon to migrate preferentially. Ring expansion via the bromohydrin **10** can lead to either **11** or **12**. Treatment of cyclobutanone **6** with dimethylsulfonium methylide[5b] to give **13**, followed by lithium bromide in benzene

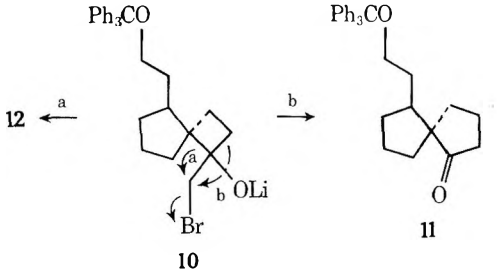
Scheme I



containing 1 equiv of HMPA,[10] produced **12** in 65% yield. Alternatively, conversion of **6** to **15** via MCPBA epoxidation



of the Wittig olefination product **14**, followed by rearrangement, gave **12** in 78% overall yield. The latter procedure, al-



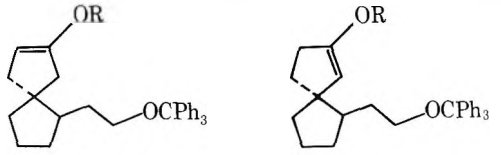
though one step longer, proceeded in higher yield and gave purer product which could be directly crystallized even when crude cyclobutanone was employed. In this sequence, the use of potassium hydride rather than n-butyllithium to generate the Wittig reagent was crucial in avoiding decomposition of starting cyclobutanone, which was apparently catalyzed by the presence of lithium salts.

The stereochemistry of **13** and **15** is based solely upon mechanistic considerations, i.e., least hindered attack of the ylide on **6** and the peracid on **14**, respectively. The former shows the epoxide methylene as an AB pattern with δ_A 2.64, δ_B 2.43, and J = 6 Hz, whereas the latter shows this pattern at δ_A 2.70, δ_B 2.50, and J_{AB} = 5 Hz. The intermediacy of the bromohydrin corresponding to **10** is secured by the isolation of a small amount of this compound when the reaction is taken

to partial completion. The compound showed the methylene group bearing bromine as an AB pattern with δ_A 3.62, δ_B 3.50, and J_{AB} = 15 Hz. Subjection of this compound to lithium carbonate in refluxing benzene containing HMPA led smoothly to the same cyclopentanone, **12.**

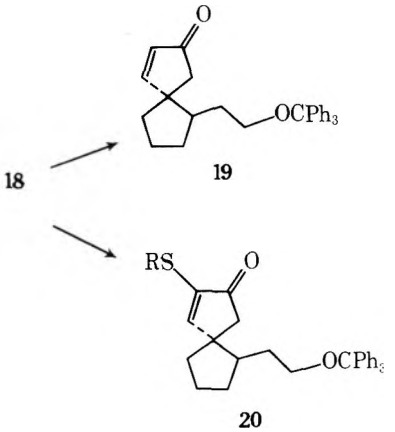
The ring-enlarged cyclopentanone, mp 122 °C, is stereo- and regiochemically homogeneous. The ^{13}C NMR shows only 12 signals for sp^3 carbons. The fact that the spiro carbon shifts from δ 73.2 in **6** to δ 49.8 in **12** indicates that a carbonyl group is no longer adjacent. The NMR spectrum upon addition of 14 mol % of $Eu(dpm)_3$ separates out two methylene groups, one of which is an AB pattern at δ 4.2 and 4.5 with J_{AB} = 17 Hz. This fact indicates that the carbonyl group is flanked by two methylene groups, one of which is adjacent to a quaternary carbon as in **12.** The subsequent chemistry of **12** further confirms this assignment. Thus, by the procedure of spiroannulation and ring expansion, a spiro[4.4]nonyl system was available in 62% overall yield from a cyclopentanone.

Surprisingly, the main problem that was encountered was the regiodifferentiation of the unsymmetrical ketone. Enolate formation under kinetic control gave approximately a 3:2 mixture of the two enolates **16** and **17** (R = Li) as determined by quenching with either trimethylchlorosilane or acetic anhydride.[11] Thermodynamic generation of the enol acetates led to an approximately 1:3 ratio of **16** and **17** (R = Ac). Formylation of **12** equally led to unsatisfactory mixtures of hydroxymethylene derivatives.[12]



16 **17**

The problem was resolved delightfully by use of a more bulky derivatizing agent, methyl *p*-tolylsulfinate,[13,14] which gave a sulfoxide **18** in 91% yield (see Scheme *II*). Because of the complexity of the stereo- and regioisomerism, as well as the coincidence of chemical shifts, direct determination of the regiochemistry was not possible. However, thermal elimination of *p*-toluenesulfenic acid[15] did give an 89% yield of enone **19,** indicating that at least 89% of the sulfinylated compound was the desired regioisomer **18.** Further characterization was achieved by a Pummerer reaction with iodine in methanol[16] or sodium acetate and acetic anhydride[17] to give **20** (R = p-C_7H_7). Interestingly, sulfenylation of the anion of **18** with methylthio methanesulfonate at 0°C led directly to **20** (R = CH_3). Sulfoxide elimination apparently occurred at 0 °C since the intermediate could not be detected.



20

Treatment of the sulfoxide **18** with anhydrous stannous chloride in acetic anhydride and acetonitrile[18] reduced the sulfoxide to the sulfide and replaced the trityl group by acetate to give **21** (R = Ac) in 61% yield. For completion of the tricyclic skeleton, the acetoxy group was converted into a mesylate (**21,** R = Ms)[19] and the latter treated with DBN[20] in DMF–THF to give **22** in 55% overall yield as a crystalline solid, mp 64–65 °C. The structure of **22** is supported by elemental analysis and spectral data. In particular, the regiochemistry of the alkylation is demonstrated by the absence of any proton on the carbon bearing sulfur. The similarity of the ^{13}C NMR data to the corresponding portions of gibberellic acid derivatives **23a** and **23b**[21] further supports the assignments (see Table I). Further characterization was provided by the synthesis of the ketal **25** and the hemithioketal **26,** which showed similar ^{13}C NMR spectra. It is interesting to note that the hemithioketal is a single isomer which is tentatively assigned with sulfur exo. This assignment is based upon the substantial shift for C(8) in the ^{13}C NMR spectrum and the anticipation that the reaction involves at some point trapping of an oxygen stabilized

Scheme II

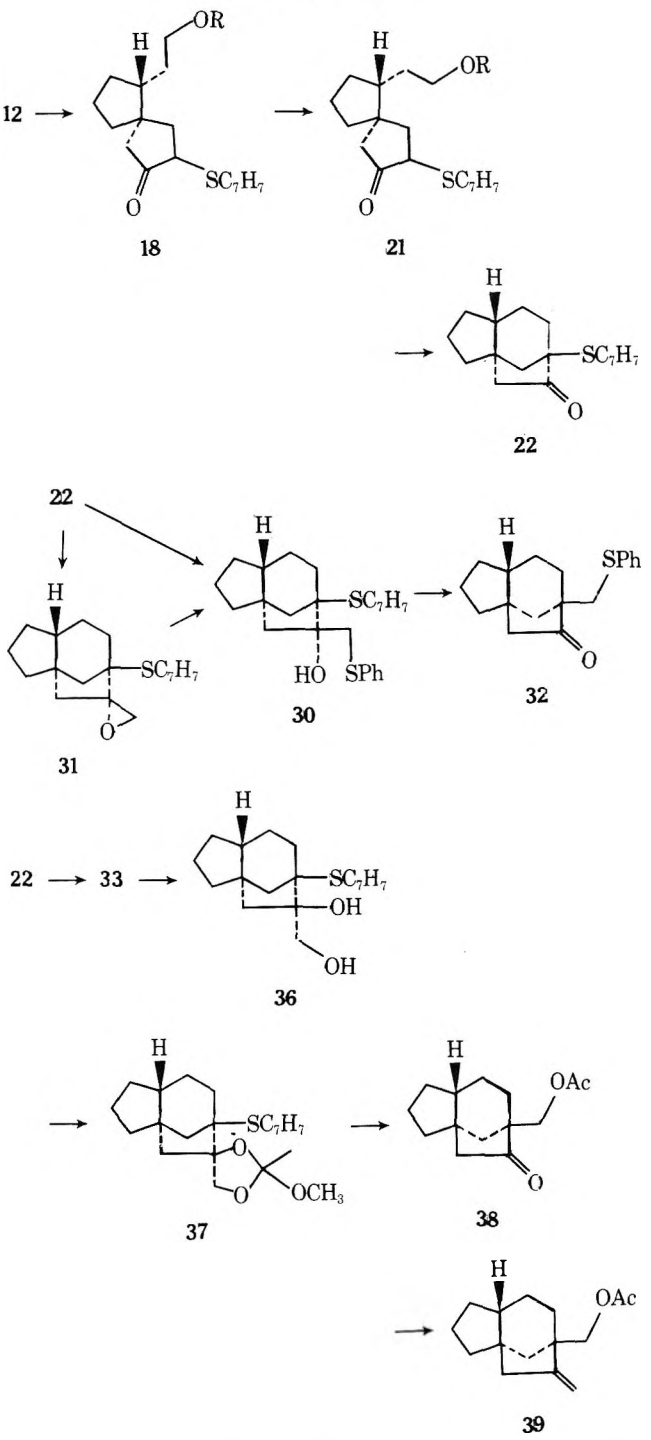
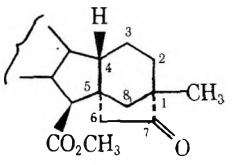
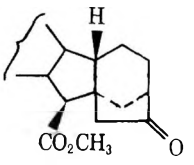


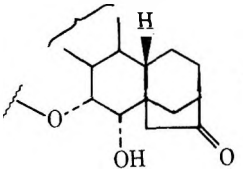
Table I. ^{13}C NMR Data



23a, b



24a, b



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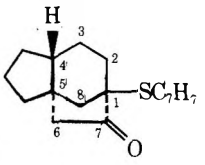

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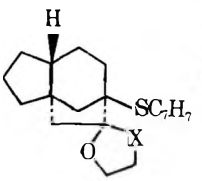
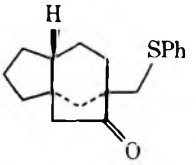


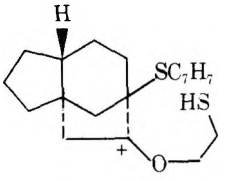
25, 26



32

C atom	23a	23b	24a	24b	I	22	25, X = O	26, X = S	32
1						62.7	62.2	63.8	53.6
2	36.0	35.9	24.9	24.9	26.2	36.6	36.2	37.5	21.7
3	19.9	21.9	16.7	16.9	17.7	21.7	22.0	22.0	22.2
4	54.0 (or 51.0)	50.7 (or 55.2)	54.1	53.4	56.5	46.3	46.3	46.3	50.1
5	51.6	51.3	49.7	51.3	42.8	46.5	46.8	50.5	45.0
6	50.7 (or 47.8)	50.3 (or 47.8)	50.4	50.2	49.8	47.3	49.5	49.5	45.9
7	219.0	218.4	220.1	219.3	221.3	215.3	116.9	96.0	214.3
8	47.8 (or 50.7)	47.8 (or 50.3)	34 5	34.6	31.7	46.1	48.7	53.3	39.3
9						35.2	35.2	35.7	35.2
10						26.0	26.6	27.1	29.1
11						28.5	28.6	28.4	33.6

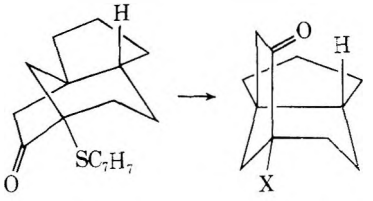
cation **27** by sulfur, which should occur from the exo face. Finally, reduction of **22** to its corresponding alcohol, mp 39–41 °C, showed the methine proton next to the hydroxyl group as



27

a dd (J = 10, 6 Hz) at δ 4.15, indicative of only an adjacent methylene group.

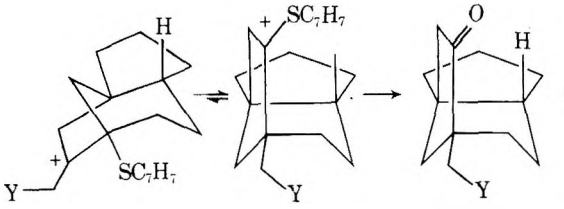
The versatility of the substitution pattern is quite high. For example, desulfurization can, in principle, lead to the parent system—thus constituting a fully stereocontrolled synthesis of substituted bicyclo[3.2.1] systems. Use of Wagner–Meerwein shifts allows modification of the stereochemistry (from that in **28** to, for example, that in **29** as represented by the gibberellins) as well as modification of bridge substitution. The bridgehead sulfur serves as a control element in directing the carbonium ion rearrangements. In fact, the lack of rearrangement in the derivatization reactions mentioned above is noteworthy in this regard. The greater stabilization by oxygen of adjacent positive charge, combined with the necessary conversion of the six-membered ring from a chair to a boat conformation (i.e., **28** → **29**), apparently prevents the



28 **29**

rearrangement. In fact, the facility of the reverse process[22] (i.e., **29** → **28**) in steviols and the facile rearrangement of the CD rings of the gibberellins suggested that a synthon for an oxygen at the bridgehead carbon in **29** (i.e., X ≠ OH) would be most desirable to avoid skeletal rearrangements in a projected synthesis of these plant growth hormones.

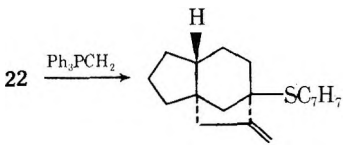
The introduction of a substituted carbon as an unreactive synthon for the hydroxy group in **29**, which by a Baeyer–Villager or carboxy inversion reaction could be converted to the bridgehead hydroxy compound, is outlined in eq 1. Two ap-



(1)

proaches were successful. In the first (see Scheme II), addition of lithiothioanisole[23] to **22** gave **30**. Alternatively, condensation of **22** with dimethyloxosulfonium methylide gave the epoxide **31** which, in turn, was reacted with thiophenol. The hydroxy sulfide appears to be homogeneous, utilizing chromatographic and spectroscopic criteria. The presence of the phenylthio group serves not only as the entry to an oxidized bridgehead substituent but also as a neighboring group to facilitate the generation of the corresponding cation (see eq 1). Exposure of **30** to TosOH in refluxing benzene[24] leads rapidly to inverted ketone **32** in 75% yield in contrast to its behavior with trifluoroacetic acid or stannic chloride. The structure of the ketone is supported by spectroscopic data. IR spectroscopy indicates a five-membered ring ketone (1740 cm^{-1}). NMR shows the loss of the p-tolyl group, a singlet for the methylene group adjacent to sulfur (δ 3.07), and an AB pattern at δ 2.21 and 1.87 (J = 17 Hz) for the methylene group α to the carbonyl group. The ^{13}C NMR spectrum (see Table I) shows sufficient similarities to the corresponding carbons of the gibberellic acid derivatives **24a** and **24b**[25] to confirm their structural correlation. Most noteworthy is the upfield shift experienced at C(2) and C(8) as a function of the ring juncture of the [6,5] system.

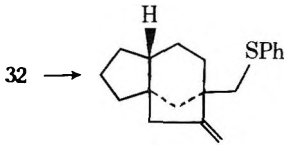
Further support derives from the relative rates of methylenation of **32** compared to **22**. The latter reacts quite nor-



33

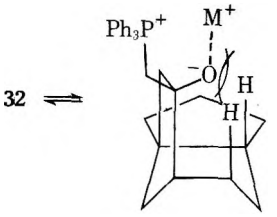
mally to give the methylene derivative **33** at 0 °C; however, under the same conditions **32** is almost inert. For best results,

salt-free phosphorus ylide[26] should be employed, in which case an 81% yield of **34** is obtained after 3 h at reflux in THF. House[27] noted a requirement for the absence of lithium salts



34

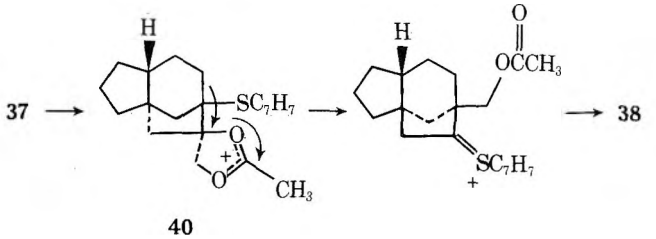
in his synthesis of epiallogibberic acid. One rationalization relates the absence of the lithium salt to the rate of elimination of the intermediate phosphetane or betaine. It can be envisioned that steric crowding in **35** facilitates the reversal reaction in the presence of this salt due to coordination of the



35

salt with the ylide adduct. In the absence of salt, interaction of the oxygen and phosphorus is enhanced and thus facilitates the desired elimination. Such steric crowding is less severe in the ylide adduct of **22,** and thus it behaves normally.

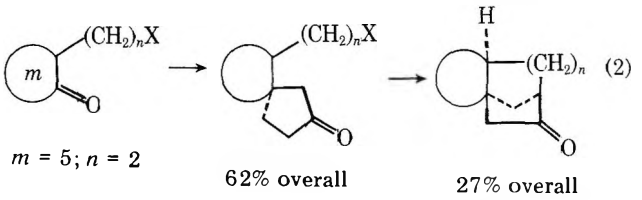
Alternatively, an oxymethyl substituent can be introduced at the bridgehead carbon. Hydroxylation of **33,** available from **22** as outlined above, gives diol **36.** Stereochemistry is assigned on the basis of least hindered attack by the osmium tetraoxide from the exo face. Ortho ester formation with methyl orthoacetate to **37,** followed by dissolving in a 2:1 ratio of carbon tetrachloride–trifluoroacetic acid, gave rearranged ketone **38.** The course of this reaction could be conveniently followed by NMR spectroscopy. Immediately after mixing the absorption for the acetate methyl group shifted from 1.6 to 2.9 and that for the methylene group bearing oxygen from 3.8 to 5.1 (AB, δ 5.08 and 5.15, J = 12 Hz)—indicative of the formation of the acetoxonium ion **40.**[28] Over a period of several hours, a singlet at δ 2.1 and an AB pattern at δ 4.1 (J = 13 Hz) grew in. Quenching the reaction mixture into aqueous hydrochloric acid gave the keto acetate **38** in 57% yield. The IR spectrum showed two carbonyl groups (1743 and 1753 cm^{-1}) and no aryl absorptions. The NMR spectrum confirmed the absence of the p-tolylthio group and the mass spectrum gave a formula of $C_{14}H_{20}O_3$. The similarity of the spectral properties of **38** to those of **32** further supports the structure. Finally, **38** behaved very similarly toward methylenation to give **39** as did **32.** Again similarity of the spectra of **39** to **34** indicates their structural similarity.



40

Conclusions

A straightforward stereocontrolled sequence has been developed for the annulation of a bicyclo[3.2.1] system onto a 2-alkylcycloalkanone by capitalizing upon the spiroannulation of a cyclobutanone (eq 2). In the process, both diastereoisomeric series of the [3.2.1] system were generated without contamination by the alternative isomer. The entire sequence proceeds in high yield and purification need be done at only a few places. In addition, a stereo- and regiocontrolled synthesis of spiro[n.4] ketones is now also available (see eq 2). Since the stereochemistry is established by the cyclobutanone annulation and since either stereoisomer is now available from the same oxaspiropentane,[7] this approach has special merit.



(2)

Furthermore, the products have functionality of sufficient versatility to allow considerable manipulation. For example, bridgehead substitution can vary from hydrogen (by desulfurization of **22** or oxidation and decarboxylation of **32** or **38**) to oxygen (by oxidation and carboxy inversion of **32** or **38**) to carbon (as derived from **32** and **38**). The stereocontrol and chemical flexibility make this sequence of particular use for the preparation of terpenoids such as the kauranes, cedrene, and zizaene, as well as the very complex gibberellins.

Experimental Section

All reactions were run using magnetic stirring under a positive pressure of dry nitrogen at room temperature, unless otherwise indicated. All reaction temperatures were measured externally. All reactions requiring anhydrous conditions were done in glassware flamed under a stream of dry nitrogen. All solvents for anhydrous reactions were distilled as follows: diethyl ether (ether), 1,2-dimethoxyethane (DME), and tetrahydrofuran (THF) from sodium benzophenone ketyl; toluene, benzene, acetonitrile, dimethyl carbonate, dichloromethane, pyridine, dimethyl sulfoxide (Me_2SO), dimethylformamide (DMF), hexane, and hexamethylphosphoric triamide (HMPA) from calcium hydride. Diisopropylamine was distilled from potassium hydroxide. Lithium bromide was pulverized and then dried overnight at 120 °C in a vacuum oven. All other reagents were used as obtained commercially. Drying agents are indicated in the separate experiments and were all anhydrous grade. The term "concentration in vacuo" refers to the removal of the solvents on a Büchi-Brinkman rotoevaporator at water aspirator pressure, followed by the removal of the last traces of solvents with a vacuum pump, except where the product had a boiling point below 100 °C at 0.1 mm.

Purifications are indicated in the text. Kügelrohr distillation refers to the use of the apparatus available from Aldrich Co. connected to a vacuum pump. The term TLC (thin-layer chromatography) is used for microscope slides coated with silica gel PF_{254} (vide infra), by dipping in a slurry of the silica gel in chloroform, and used exclusively for monitoring of a reaction's progress. The term PLC (preparative layer chromatography) refers to purification on 1.5–2.0 mm thick plates of E. Merk and Co. (Darmstadt) silica gel G with PF_{254} spread on glass as an aqueous slurry and activated (after air drying) at 120 °C for 2 h. Typical loadings were up to 80 mg on 20 × 10 cm; 80–200 mg on 20 × 20 cm; and 200–450 mg on 20 × 40 cm plates. Larger amounts were done on appropriate combinations. Eluting solvents are indicated in the text. All plates utilized 17 cm from baseline to maximum elution. Visualization of the bands (spots) on these plates was done with the aid of a UV lamp in conjunction with iodine or spraying with an ethanolic solution of phosphomolybdic acid, followed by heating. The bands were extracted with ether to remove the material.

The term HPLC is used for high (or medium) pressure solid–liquid chromatography and refers to the use of a standard 2.5 (i.d.) × 100 cm column with a precolumn filter of 1.5 (i.d.) × 25 cm dimensions, both of which were packed with the indicated solvent mixture. The system utilized a single stage constant flow pump at approximately 22 mL/min. Sample preparation consisted of filtration of an ether solution through a 1.5-cm cake of W. R. Grace grade 62 silica gel and concentration in vacuo. The sample was dissolved in a minimum

amount of the solvent mixture and injected onto the column. Typically a forerun of 350 mL was taken and discarded, and the outlet was then connected to a Gilson fraction collector to collect 12-mL samples. The solvent systems are such as to give the desired material and R_f on TLC of approximately 0.2. In place of an R_f in these systems, the tube numbers containing the product are given.

Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Boiling points are uncorrected. Infrared spectra were obtained as solutions in the indicated solvent on a Beckman IR-8 or a Perkin-Elmer 267 spectrophotometer and are given in reciprocal centimeters. Proton NMR spectra were determined in the indicated solvent on a Varian A-60A (60 MHz), a Jeolco MH-100 (100 MHz), or a Bruker WH270 (270 MHz); ^{13}C NMR spectra were determined on a Jeolco FX-60 (50 MHz); chemical shifts for both are given in parts per million downfield from tetramethylsilane (Me_4Si). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. Coupling constants are given in hertz. Mass spectra were obtained on an AEI MS-902 high-resolution mass spectrometer at an ionizing current of 100 mA and an ionizing voltage of 70 eV, except for compounds containing trityl ethers (39–40 eV) or benzyl ethers (50 eV) (due to ease of fragmentation), and are reported as m/e (%). Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

Preparation of 2-(2′-Hydroxyethyl)cyclopentanone. In a three-neck 2-L round-bottom flask fitted with a condenser and mechanical stirrer were placed 60 g (0.40 mol) of commercial 2-cyclopentanone carboxylate ester (1:1 methyl–ethyl by NMR), 220 g (1.60 mol, 4.0 equiv) of anhydrous potassium carbonate, and 300 mL of reagent grade acetone. A solution of 68 g (0.48 mol, 1.20 equiv) of 2-bromoethyl acetate in 200 mL of acetone was added over 20 min with vigorous stirring. The mixture was then vigorously refluxed for 21 h, cooled, poured into 1.5 L of a 1:1 mixture of water and saturated aqueous sodium chloride solution, and extracted with 3 × 400 mL of ether. The combined organic layers were dried with sodium sulfate and potassium carbonate and concentrated in vacuo to yield 100 g of a crude yellow oil.

To the crude alkylated mixture was added 1 L of 10% (v/v) aqueous sulfuric acid and this mixture heated at 65 °C until 30 min beyond the cessation of carbon dioxide evolution (4 h). After cooling, the reaction mixture was neutralized carefully with solid sodium carbonate and extracted with 3 × 400 mL of chloroform. The combined organic layers were dried over sodium sulfate and potassium carbonate and concentrated at aspirator pressure with an ice-cold bath to yield 54 g of crude oil. Distillation through a short-path column yielded 36.3 g (0.28 mol, 71%) of the desired alcohol: bp 89–95 °C (16–18 mm) [lit.[29] 126–130 °C (14 mm)];[30] NMR ($CDCl_3$) 1.2–2.5 (9 H, m), 2.5 (variable, 1 H, br s), 3.75 (2 H, t, J = 7 Hz); IR ($CHCl_3$) 3600, 3450, 2990, 2970, 2870, 1735, 1040; MS 128 (5), 111 (5), 110 (20), 109 (15), 100 (10), 99 (100), 98 (8), 97 (17), 95 (10), 85 (25), 84 (40), 83 (80), 82 (15), 81 (25), 67 (40). Anal. Calcd for $C_7H_{12}O_2$: mol wt, 128.0837. Found: mol wt, 128.0838.

Preparation of 2-(2′-Trityloxyethyl)cyclopentanone (5). To a solution of 150 mL each of dry benzene and dry pyridine was added 32 g (0.098 mol, 1.05 equiv) of commercial trityl bromide, and the mixture was stirred until complete dissolution was effected (on some occasions the mixture was warmed slightly to assist dissolution). To this was added the crude alcohol in 50 mL of benzene. This mixture was stirred for 5 days until TLC indicated that no further alcohol was present and that only the desired trityl ether (R_f 0.55) and triphenylcarbinol (R_f 0.6) were present. A small (approximately 0.5 mL) aliquot was removed and partitioned between ether and aqueous 3 N hydrochloric acid. The ether was dried and concentrated at a water aspirator to yield a sample whose NMR showed none of the alcohol (m at δ 3.5–3.8) and only trityl ether (br t, δ 3.0–3.3, in CCl_4). The remainder of the mixture was worked up in a like manner to yield 41 g of crude material. Kügelrohr distillation (90 °C, 0.1 mm) removed the last traces of solvent and 2.5 g of an oligomer derived from 2-(2′-hydroxyethyl)cyclopentanone to yield 34 g (approximately 0.091 mol, approximately 98%) of crude trityl ether as a deep yellow glass. This material was suitable for further transformations with the only discernible impurity being a small amount of triphenylcarbinol, which could be removed only with considerable difficulty by PLC. A 100-mg sample was purified by PLC to yield 95 mg of **5** as a glass. Repeated attempts to crystallize this sample finally yielded crystals from carbon tetrachloride–methanol: mp 77–79 °C; NMR (CCl_4) 1.2–2.3 (9 H, m), 3.10 (2 H, t, J = 7 Hz), 7.0–7.5 (15 H, m); IR (CCl_4) 3090, 3060, 3030, 2970, 2880, 1740, 1490, 1450, 1150, 1090, 1040, 700; MS 370 (~0.001), 260 (15), 259 (13), 245 (5), 244 (40), 243 (100), 184 (5), 183 (35), 182 (9), 167 (5), 166 (5), 165 (20), 155 (9), 154 (12), 128 (6), 127 (85), 112 (5), 111 (55), 109 (7), 105 (40), 84 (4), 83 (11), 77 (10), 55 (9). Anal. Calcd for $C_{26}H_{26}O_2$: C, 84.32; H, 7.02; mol wt, 370.1933. Found: C, 84.24; H, 6.97; mol wt, 370.1944.

Preparation of (4*S,5*R**)-5-(2′-Trityloxyethyl)spiro[3.4]-octan-1-one (6).** To a stirred solution of 370 mg (1.0 mmol) of glassy 2-(2′-trityloxyethyl)cyclopentanone and 360 mg (1.15 mmol, 1.15 equiv) of cyclopropyldiphenylsulfonium fluoborate in 2 mL of Me_2SO (commercial) was added 65 mg (1.16 mmol, 1.16 equiv) of freshly powdered potassium hydroxide in three equal portions at 1-h intervals. The reaction was stirred for 18 h, at which time an additional 65 mg (0.2 mmol, 0.2 equiv) of the sulfonium salt and 15 mg (0.26 mmol, 0.26 equiv) of powdered potassium hydroxide were added all at once, and stirring was continued for 2 h. The reaction mixture was poured into a 1:1 mixture of water and saturated aqueous sodium bicarbonate solution and extracted three times with ether. The combined organic layers were washed twice with water, dried over sodium sulfate and potassium carbonate, and concentrated in vacuo to yield 550 mg of crude oxaspiropentane and diphenyl sulfide: NMR (CCl_4, crude) 0.5–1.0 (m), 1.1–2.1 (m), 2.96 (br t, J = 7 Hz), 7.0–7.5 (m); IR (CCl_4, crude) 3060, 3000, 2960, 2870, 1080, 1070, 1025, 1000.

The crude material was dissolved in 5 mL of dry benzene and 10 mg of anhydrous lithium fluoborate was added. The mixture was refluxed for 1 h, cooled, diluted with ether, washed with water, dried over magnesium sulfate, and concentrated in vacuo to yield 0.6 g of crude oil. Kügelrohr distillation [80 °C (0.1 mm)] evaporated 151 mg (0.81 mmol, 81%) of diphenyl sulfide. Trituration of the crude glass from the pot of the distillation yielded 65 mg (0.158 mmol) of crystalline product, mp 90–95 °C. Purification of the mother liquor by PLC in 2:1 hexane–ether yielded an additional 265 mg (0.646 mmol) of cyclobutanone, mp 92–96 °C, for a total of 330 mg (0.805 mmol, 80.5%). A sample was recrystallized from a concentrated hexane solution to get a sample for analysis: mp 110.5–111.5 °C.

Essentially the same procedure was used on larger scales; however, the starting material was a glass. A 34-g (0.092 mol) sample of glassy **5** in 200 mL of Me_2SO was treated with 40 g (0.127 mmol, 1.4 equiv) of diphenylcyclopropylsulfonium fluoborate and 5.6 g (0.10 mol, 1.1 equiv) of powdered potassium hydroxide in four portions. Additional sulfonium salt (5.0 g, 0.016 mol, 0.17 equiv) and potassium hydroxide (1.0 g, 0.018 mol, 0.2 equiv) were added after 2 days and again after 5 days. After an additional 2 days (7 days total) the reaction was worked up as usual to yield 13.4 g of highly crystalline cyclobutanone, mp 109–111 °C, and a 25.8-g sample, still containing considerable amounts of entrained solvent. By isolation utilizing a 100-mg aliquot, this latter sample contains 45% cyclobutanone for a total yield of 72%. The crude material thus obtained is normally directly employed: NMR (CCl_4) (100 MHz) 1.1–2.2 (11 H, m), 2.66 (2 H, td, J = 8, 4 Hz), 2.90–3.15 (2 H, m), 7.0–7.5 (15 H, m); NMR ($CDCl_3$) (270 MHz) 1.0–2.06 (m), 2.73 (ddd, J = 7, 10, 13 Hz), 2.82 (ddd, J = 18, 9.6, 6.5 Hz), 3.02 (ddd, J = 9.0, 7.0, 6.5 Hz), 3.13 (ddd, J = 9.0, 7.0, 5.5, plus aromatics as an undefined multiple); ^{13}C NMR ($CDCl_3$) 214.41 (s), 143.45 (s), 127.83 (d), 126.86 (d), 126.07 (d), 85.96 (s), 73.23 (s), 62.27 (t), 45.22 (d), 42.38 (t), 35.28 (t), 31.25 (t), 30.90 (t), 22.95 (t), 22.72 (t); IR (CCl_4) 3090, 3060, 3020, 2950, 2870, 1770, 1490, 1445, 1210, 1070, 700; MS 410 (below 0.01%), 259 (1), 244 (23), 244 (100), 242 (4), 241 (4), 228 (3), 215 (2), 183 (4), 167 (8), 166 (4), 165 (20), 151 (7), 99 (3), 95 (8). Anal. Calcd for $C_{29}H_{30}O_2$: C, 84.87; H, 7.31; mol wt, 410.2246. Found: C, 84.82; H, 7.28; mol wt, 410.2233.

Preparation of (5*S,6*R**)-6-(2′-Trityloxyethyl)spiro[4.4]-nonan-2-one (12).** To a slurry of 2.0 g (50 mmol, 2.05 equiv) of potassium hydride (prepared by slurrying the commercial slurry with hexane and pipetting off the liquid, repeating twice, and then removing the residual hexane with a vacuum pump) in 35 mL of THF was added 18.5 g (52 mmol, 2.13 equiv) of methyltriphenylphosphonium bromide in four portions over 15 min. After stirring for 2 h the solution was maintained at 50 °C for 20 min and cooled to 0 °C. To the yellow slurry was added 10.0 g (24.4 mmol) of crystalline **6** in 25 mL of THF over a period of 5–10 min. Vigorous stirring was maintained for 4.5 h, during which time the reaction came to room temperature and showed only one spot at R_f 0.9 (1:1 hexane–ether) corresponding to 1-methylene-5-(2′-trityloxyethyl)spiro[3.4]nonane (**14**) with none of the starting material (R_f 0.6) present. The mixture was poured into 3 vol of water and extracted twice with ether. The ether fractions were combined, washed twice with water, dried over magnesium sulfate, and concentrated in vacuo to yield a semisolid which was tritrated with hexane and filtered through a 3-in. column of Florisil to remove the precipitated triphenylphosphine oxide. The column was washed with 1.5 L of hexane (until no further product came off) and the combined fractions were concentrated in vacuo to yield 9.7 g of crude **14** as a clear, colorless glass. Some samples kept for over 6 months showed crystals in the glass but brief attempts to

recrystallize the sample failed. The purity of this material was such that it could be used for further transformations without additional purification (one spot by TLC, R_f 0.8, 9:1 hexane–ether): NMR (CCl_4) 0.9–2.0 (11 H, m), 2.4 (2 H, br t, J = 8 Hz), 3.0–3.25 (2 H, m), 4.52 (1 H, t, J = 2 Hz), 4.61 (1 H, t, J = 1 Hz), 7.0–7.5 (15 H, m); IR (CCl_4) 3100, 3070, 2950, 2870, 1660, 1070, 875, 705, 695; MS 408 (0.001), 260 (16), 245 (7), 244 (50), 243 (100), 183 (20), 167 (20). 166 (14), 165 (42), 149 (12), 105 (38), 91 (12), 77 (15). Anal. Calcd for $C_{30}H_{32}O$: mol wt, 408.2453. Found: mol wt, 408.2438. To a 0 °C solution of the crude methylenecyclobutane **14** in 35 mL of dichloromethane was added a slurry of 6.75 g (37.5 mmol, 1.54 equiv) of 85% *m*-chloroperbenzoic acid in 40 mL of dichloromethane over 10 min. The resulting solution was stirred for 8 h, during which time it came to room temperature and precipitated a considerable amount of white solid. The reaction showed to be complete by TLC (R_f 0.6) and was diluted with 200 mL of ether, washed with saturated aqueous sodium carbonate solution, dried over sodium sulfate and potassium carbonate, and concentrated in vacuo to yield 10.0 g of 1-epoxymethylene-5-(2′-trityloxyethyl)-spiro[3.4]octane (**15**) as a clear colorless glass. This material again showed itself to be a single spot by TLC and quite clean by NMR and thus was used immediately without further purification: NMR (CCl_4) 0.7–2.4 (13 H, m), 2.50 (1 H, d, J = 5 Hz), 2.70 (1 H, d, J = 5 Hz), 2.9–3.3 (2 H, m), 7.0–7.5 (15 H, m); IR (CCl_4) 3110, 3100, 3070, 2960, 2940, 2870, 1070, 705, 695.

To a solution of the crude epoxide in 50 mL of benzene and 4.5 mL (4.5 g, 25.0 mmol, 1.0 equiv) of dry HMPA was added 2.2 g (25.3 mmol, 1.0 equiv) of anhydrous powdered lithium bromide (dried overnight at 120 °C under 0.5-mm vacuum), at which time the solution became a bright deep yellow. This mixture was immersed in 100 °C oil bath and refluxed for 3 h, at which time TLC showed only a spot at R_f 0.45. The mixture was cooled, diluted with ether, washed three times with water, dried over magnesium sulfate, and concentrated in vacuo to yield a yellow-brown oil, from which was obtained 7.55 g of crystalline **12**, mp 122 °C (hexane). Further purification of the mother liquor by PLC yielded an additional 300 mg of the spiro ketone (R_f 0.5 in 1:1 ether–hexane) (7.85 g total, 18.5 mmol, 76%) and 450 mg (0.89 mmol, 3.6%) of a second material (R_f 0.6), mp 154–157 °C (hexane). From its NMR and IR spectra (see below) this second material was assigned 1-bromomethylene-5-(2′-trityloxyethyl)spiro[3.4]octan-1-ol. Utilizing the 25.8-g sample of the previous crude cyclobutanone (45% pure), **14** was prepared employing 3.90 equiv of triphenylphosphonium methylide and **15** by employing 2.81 equiv of MCPBA to give after rearrangment a 73% yield of **12**: NMR (CCl_4) 1.0–2.25 (15 H, m), 2.9–3.3 (2 H, m), 7.0–7.5 (15 H, m). The addition of 7.3 mg of $Eu(dpm)_3$ (14 mol %) showed a multiplet (2 H) at 5.74–6.0 and an AB pattern [4.2 (1 H, d, J = 18 Hz), 4.5 (1 H, d, J = 17 Hz)] as the only signals significantly shifted downfield. The rest of the spectrum (methylene region) was spread over 1.3–3.5: ^{13}C NMR ($CDCl_3$) 217.7, 143.5, 127.8, 126.9, 126.0, 86.0, 62.5, 49.8, 45.2, 44.0, 38.1, 37.0, 33.4, 31.1, 30.4, 21.3; IR (CCl_4) 3100, 3070, 3050, 2970, 2870, 1745, 1070, 705, 695; MS (70 eV) 425 (0.35), 424 (1), 348 (1), 347 (5), 260 (1.5), 259 (7), 245 (3), 244 (20), 243 (100), 242 (3), 241 (3), 239 (2), 228 (2), 215 (2), 183 (10), 167 (5), 166 (6), 165 (22), 105 (15), 91 (13). 81 (5), 79 (7). Anal. Calcd for $C_{30}H_{32}O_2$: C, 84.85; H, 7.60; mol wt, 424.2402. Found: C, 85.10; H, 7.60; mol wt, 424.2400.

1-Bromomethylene-5-(2′-trityloxyethyl)spiro[3.4]octan-1-ol: NMR ($CDCl_3$) 1.1–2.1 (13 H, m), 2.28 (1 H, br s), 3.12 (2 H, t, J = 6 Hz), 3.50 and 3.62 (2 H, AB, J_{AB} = 15 Hz), 7.0–7.6 (15 H, m); IR (CCl_4) 3550, 3400, 3080, 3050, 3010, 2950, 2870, 1590, 1480, 1445, 1220, 1060, 700; MS 424 (1), 348 (3), 388 (2), 264 (2), 263 (2), 261 (3), 260 (6), 259 (5), 245 (10), 244 (50), 243 (100), 242 (6), 241 (5), 171 (12), 167 (19), 166 (15), 165 (50), 77 (15). No M^+ was observed.

A 350-mg (0.69 mmol) sample of the bromohydrin was mixed with 3 mL of dry benzene, 50 mg (0.67 mmol, 1 equiv) of anhydrous lithium carbonate, and 120 μL (120 mg, 0.67 mmol, 1 equiv) of HMPA, and the solution was refluxed for 12 h. After cooling and workup as above, the crude 320 mg was purified by PLC in 1:1 ether–hexane to yield 200 mg (0.47 mmol) of the desired spiro ketone in addition to 28 mg (0.055 mmol) of recovered bromohydrin for a 68% conversion and 73% yield.

Preparation of 12 via Dimethylsulfonium Methylide. A suspension of 55 mg (1.1 mmol, 2.24 equiv) of a 50% dispersion of sodium hydride in mineral oil in 1 mL of Me_2SO was heated at 70 °C for 1 h and cooled, 1 mL of THF was added, and the solution was further cooled to 0 °C. To this was added 250 mg (1.25 mmol, 2.56 equiv) of trimethylsulfonium iodide in 1.2 mL of Me_2SO, followed 2–3 min later by 200 mg (0.49 mmol) of **6** in 0.5 mL of THF. After 30 min the bath was removed and the reaction allowed to warm to room temperature over 1.5 h. The reaction mixture was then diluted with water and extracted with ether; the organic layer was dried over sodium sulfate and potassium carbonate and concentrated in vacuo to yield 250 mg of a slightly smelly pale yellow glass. This material showed a spot in TLC at the same R_f (0.55 in 3:2 hexane–ether) as the starting cyclobutanone in addition to mineral oil; however, the absence of a carbonyl absorption in the IR showed the compound to be the epoxide. The NMR (CCl_4) was identical with that reported above, with the exception that the AB patterns were at 2.43 (J = 6 Hz) and 2.64 (J = 6 Hz).

This material was treated as above with 50 mg (0.57 mmol, 1.17 equiv) of lithium bromide and 100 μL (100 mg, 0.56 mmol, 1.16 equiv) of HMPA in 3 mL of benzene and refluxed for 12 h. Workup as above and PLC in 1:1 ether–hexane yielded 135 mg (0.32 mmol, 65%, R_f 0.5) of the same spiro ketone as was obtained by the alternate route through the Wittig ylide as described above.

Preparation of (3ξ*,5S*,6R*)-3-(*p*-Tolylsulfinyl)-6-(2′-trityloxyethyl)spiro[4.4]nonan-2-one (18). To a refluxing suspension of 3.30 g (19.6 mmol, 1.1 equiv) of methyl *p*-tolylsulfinate[31] and 1.71 g (35.7 mmol, 2.1 equiv) of a 50% dispersion of sodium hydride in mineral oil in 35 mL of DME was added 7.17 g (16.9 mmol) of **12**. The mixture was maintained at a gentle reflux until the cessation of hydrogen evolution (approximately 45 min) and then cooled, and the excess hydride was destroyed with absolute ethanol. The mixture was then poured into saturated aqueous ammonium chloride and extracted twice with ether; the organic fractions were combined and dried with sodium sulfate. Concentration in vacuo yielded 11.5 g which was purified by HPLC (ether–hexane, 4:6) to yield from tubes 42–72 8.69 g (91.4%) of an off-white foam, typically melting in the range 86–96 °C. No attempt to further purify the mixture of diastereoisomers was made.

Care must be taken with the reflux to see that it does not become too vigorous due to a sudden increase in the rate of evolution of hydrogen after 15–30 min, after which the rate falls off sharply. In addition, this material must be kept cold and/or used immediately to prevent substantial decomposition: NMR (CCl_4) 0.9–2.6 (13 H, m), 2.4 (3 H, s), 2.9–3.3 (3 H, m), 7.0–7.5 (19 H, m); IR (CCl_4) 3080, 3060, 2960, 2895, 1745, 1570, 1490, 1450, 1170, 1090, 1070, 710.

Preparation of (5R*,6R*)-6-(2′-Trityloxyethyl)spiro[4.4]-non-3-en-2-one (19). A solution of 30 mg (0.053 mmol) of sulfoxide **18** in 1 mL of carbon tetrachloride was heated at 60 °C for 7 h. After cooling, the reaction mixture was diluted with ether and washed with saturated aqueous sodium bicarbonate solution. The organic fraction was dried over potassium carbonate and the solvent removed at reduced pressure to yield 33 mg of oil. Purification by PLC yielded 20 mg (89%, R_f 0.5 in 50% ether–hexane) of the desired product: mp 141.5–142.5 °C (methanol–carbon tetrachloride); NMR (CCl_4) 1.0–2.0 (10 H, m), 2.12 (1 H, d, J = 17 Hz), 3.04 (2 H, t, J = 6 Hz), 5.90 (1 H, d, J = 6 Hz), 7.0–7.45 (16 H, m); IR (CCl_4) 3060, 3010, 2940, 2880, 1710, 1580, 1495, 1460, 1080, MS 422 (2), 346 (14), 260 (7), 259 (30), 245 (7), 244 (35), 243 (100), 228 (5), 183 (20), 165 (32), 105 (21), 91 (2), 77 (3). Anal. Calcd for $C_{30}H_{30}O_2$: mol wt, 422.2246. Found: mol wt, 422.2248.

Preparation of (5R*,6R*)-6-(2′-Trityloxyethyl)-3-methylthiospiro[4.4]non-3-en-2-one (20, R = CH_3). To a 0 °C slurry of 54 mg (1.1 mmol, 1.65 equiv) of a 50% dispersion of sodium hydride in mineral oil in 2 mL of DME was added 386 mg (0.67 mmol) of **18** in 2 mL of DME. After 30 min ~130 mg (130 μL, 1.0 mmol, 1.5 equiv) of methylthio methanesulfonate[32] in 150 μL of HMPA was added and stirring continued for 6 h, during which time the reaction came to room temperature. The reaction mixture was diluted with ether, extracted with saturated aqueous sodium bicarbonate solution, dried with sodium sulfate and potassium carbonate, and concentrated in vacuo to yield 400 mg of crude oil. Purification by PLC in 1:1 hexane–ether yielded 148 mg of the methylthio enone (R_f 0.4, 46%) as a glass: NMR (CCl_4) 1.0–2.50 (14 H, m with a singlet at 3.25), 3.04 (2 H, t, J = 7 Hz), 6.50 (1 H, s), 7.0–7.6 (15 H, m); IR (CCl_4) 3110, 3080, 3060, 2940, 2880, 1715, 1490, 1450, 1080, 710; MS 468 (0.1), 264 (2), 259 (4), 244 (45), 243 (100), 228 (10), 226 (13), 183 (16), 167 (17), 165 (50), 153 (13), 139 (13), 105 (22), 91 (13), 77 (10). Anal. Calcd for $C_{31}H_{32}O_2S$: mol wt, 468.2123. Found: mol wt, 468.2104.

Preparation of (3ξ,5S*,6R*)-6-(2′-Acetoxyethyl)-3-(*p*-tolylthio)spiro[4.4]nonan-2-one (21, R = Ac). To a solution of 8.69 g (15.5 mmol) of **18** in 32 mL of acetic anhydride and 125 mL of dry acetonitrile at 0 °C was added 3.46 g (18.4 mmol, 1.2 equiv) of freshly prepared anhydrous stannous chloride. The reaction mixture was stirred for 24 h, during which time it warmed to room temperature. It was then poured into saturated aqueous sodium bicarbonate solution and extracted with ether. The ethereal layer was dried over sodium sulfate and concentrated under reduced pressure. The crude material was triturated three times with 50 mL of hexane; the supernatants were combined and concentrated in vacuo to yield 5.6 g

of crude semisolid. Purification by HPLC yielded 3.24 g (9.4 mmol, 61%) of the desired acetoxy ketone as a pale yellow oil: NMR ($CDCl_3$) 0.9–2.5 (19 H, m with singlets at 2.08 and 2.36), 3.45–3.75 (1 H, m), 4.0–4.25 (2 H, m), 7.16 (2 H, d, J = 8 Hz), 7.45 (2 H, d, J = 8 Hz); IR (CCl_4) 3020, 2960, 2870, 1740, 1480, 1360, 1240, 1030, 905; MS 348 (3), 347 (10), 346 (43), 303 (11), 222 (6), 164 (3), 163 (10), 162 (9), 151 (6), 150 (30), 149 (10), 140 (10), 139 (4), 136 (10), 135 (6), 134 (25), 133 (12), 109 (6), 107 (20), 95 (40), 91 (100), 77 (40), 43 (90). Anal. Calcd for $C_{20}H_{26}O_3S$: mol wt, 346.1603. Found: mol wt, 346.1606.

Preparation of (3aS^*,8aR^*)-6-(p-Tolylthio)-1,2,3,3a,4,-5,6,7,8,8a-decahydro-3a,6-methanoazulen-5-one (22). To a 0 °C solution of 3.04 g (8.8 mmol) of (3ξ,5S^*,6R^*)-6-(2′-acetoxyethyl)-3-(p-tolylthio)spiro[4.4]nonan-2-one in 20 mL of methanol was added 11 mL (11 mmol, 1.25 equiv) of 1 M aqueous potassium hydroxide solution. An additional 90 mL of methanol was added to clarify the solution. After 2 h TLC showed no starting material (R_f 0.6 in 1:1 ether–hexane) and only a new spot at R_f 0.1. The solution was concentrated in vacuo to approximately 50 mL, diluted with brine, and extracted twice with ethyl acetate. The combined organic fractions were dried with sodium sulfate and concentrated at the water aspirator to yield 2.9 g of the crude alcohol (~100%). This material invariably also indicated some decomposition by its odor and, thus, was used immediately due to the apparent instability: NMR ($CDCl_3$) 1.0–2.6 (18 H, m with a s at 2.36), 3.4–3.8 (3 H, m), 7.12 (2 H, d, J = 8 Hz), 7.40 (2 H, d, J = 8 Hz); IR ($CHCl_3$) 3600, 3450, 3000, 2960, 2870, 1740, 1490, 1240, 1050, 910.

The 2.9 g of alcohol was dissolved in 25 mL of dichloromethane and cooled to −30 °C. To this was added 1.6 mL (1.15 g, 11.5 mmol, 1.30 equiv) of triethylamine and then 0.725 mL (1.05 g, 9.25 mmol, 1.05 equiv) of methanesulfonyl chloride dropwise over 5 min. The solution was stirred for 1 h at −30 °C, during which time it developed a substantial amount of a white precipitate. The mixture was diluted with water and extracted with ethyl acetate. The organic fraction was washed with saturated aqueous sodium bicarbonate solution, dried over sodium sulfate, and concentrated in vacuo to yield 3.6 g (~100%) of very clean (NMR), almost colorless oil as a mixture of isomers. Early attempts at purification by PLC gave a low recovery of material. Thus, it was used immediately without further purification: NMR ($CDCl_3$) 1.0–2.5 (16 H, m with a singlet at 2.32), 2.98 (3 H, s), 3.5–3.8 (1 H, overlapping dd in unequal amounts), 4.1–4.4 (2 H, m), 7.08 (2 H, d, J = 8 Hz), 7.36 (2 H, d, J = 8 Hz); IR (CCl_4) 3020, 2950, 2860, 1740, 1490, 1370, 1350, 1080.

The crude mesylate above was dissolved in 125 mL of THF, cooled to 0 °C, and treated with 2.3 g (18.7 mmol, 2.1 equiv) of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), followed by 20 mL of dimethylformamide. The cooling bath was removed, the mixture was stirred for 48 h, at which time TLC showed that only a trace of the starting mesylate (R_f 0.2 in 2:1 ether–hexane) remained, and the reaction was diluted with water and extracted three times with ether. The combined organic fractions were washed with aqueous 3 N hydrochloric acid, water, and saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate, and concentrated in vacuo to yield a yellow oil. Purification by HPLC with 3:1 hexane–ether yielded 1.38 g (4.8 mmol, 55% from 21, R = Ac) from tubes 31–70 of the desired tricyclic ketone, mp 55–57 °C (hexane). While upon further recrystallization the melting point rose to 64–65 °C, the material of the lower melting point was normally quite satisfactory for further work: NMR (CCl_4) 1.0–2.50 (18 H, m with an s at 2.36), 7.08 (2 H, d, J = 8 Hz), 7.36 (2 H, d, J = 8 Hz); ^{13}C NMR ($CDCl_3$) 215.28, 138.82, 136.72, 129.43, 127.22, 62.70, 47.29, 46.51, 46.29, 46.07, 36.62, 35.19, 28.50, 25.96, 21.71, 21.16; IR (CCl_4) 3020, 2970, 2860, 1745, 1490, 1450, 14300, 1050; MS 288 (5), 287 (15), 286 (82), 230 (15), 194 (5), 183 (8), 166 (5), 165 (4), 164 (10), 163 (20), 162 (6), 161 (6), 160 (5), 149 (18), 138 (8), 136 (6), 135 (12), 134 (100), 133 (57), 132 (7), 125 (8), 124 (50), 123 (20), 122 (6), 121 (6), 120 (5), 119 (28), 108 (6), 107 (20), 106 (15), 105 (36), 95 (17), 94 (6), 93 (45), 92 (26), 91 (100), 79 (75), 77 (55), 67 (55), 55 (35). Anal. Calcd for $C_{18}H_{22}OS$: C, 75.52; H, 7.69; S, 11.18; mol wt, 286.1391. Found: C, 75.56; H, 7.77; S, 11.18; mol wt, 286.1392.

Preparation of the Ethylene Glycol Ketal of (3aS^*,8aR^*)-6-(p-Tolylthio)-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulen-5-one (25). To a solution of 60 mg (0.21 mmol) of ketone in 2 mL of benzene was added 0.25 mL of ethylene glycol (dried over 4Å molecular sieves) and 10 mg of p-toluenesulfonic acid. The solution was refluxed with azeotropic removal of water for 5 h, cooled, diluted with ether, washed with water, dried over sodium sulfate, and concentrated in vacuo to yield 80 mg of yellow oil. Purification by PLC yielded 45 mg (0.135 mmol, 65%, R_f 0.7 in 2:1 hexane–ether) of the desired ketal and 5 mg (0.017 mmol, 8%) of the starting ketone, giving a corrected yield of 70%: NMR (CCl_4) 0.9–2.4 (18 H, m with a singlet at 2.32), 3.7–4.2 (4 H, m), 7.0 (2 H, d, J = 8 Hz), 7.32 (2 H, d, J = 8 Hz); ^{13}C NMR ($CDCl_3$) 138.26, 127.08, 129.16, 129.01, 116.93, 65.66, 64.72, 62.18, 49.51, 48.73, 46.87, 46.33, 36.15, 35.17, 28.57, 26.56, 21.97, 21.18; IR (CCl_4) 3060, 3020, 2950, 2870, 1730 (br), 1490, 1450, 1290, 1180, 1170, 1045, 980, 950, 890; MS (40 eV) 332 (6), 331 (22), 330 (100), 286 (2), 244 (5), 243 (19), 223 (8), 208 (12), 207 (80), 179 (15), 155 (10), 91 (15). Anal. Calcd for $C_{20}H_{26}O_2S$: mol wt, 330.1753. Found: mol wt, 330.1661.

Preparation of the 2-Mercaptoethanol Ketal of (3aS^*,8aR^*)-6-(p-Tolylthio)-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulen-5-one (26). To a solution of 65 mg (0.23 mmol) of the ketone in 0.5 mL of ether was added 150 μL (2.1 mmol, 9.5 eq) of distilled 2-mercaptoethanol and 3 drops of freshly distilled colorless boron trifluoride etherate. The mixture was stirred for 2 h, diluted with ether, washed with water and saturated aqueous sodium bicarbonate, and dried with sodium sulfate and potassium carbonate. Concentration in vacuo yielded 85 mg of crude, unpleasant smelling material from which was obtained by PLC in 2:1 hexane–ether 53 mg (0.154 mmol, R_f 0.7, 66%) of the ketal as a colorless odorless oil and 10 mg (0.035 mmol, 15%) of the starting ketone (R_f 0.6). Thus the corrected yield is 80%. From the sharpness of the signals in the NMR and a single set of signals in the ^{13}C NMR, this material is apparently a single isomer, although assignment of which one cannot be made: NMR (CCl_4) 0.9–2.5 (18 H, m with a singlet at 2.34), 2.75–3.2 (2 H, m), 3.80 (1 H, dt, J = 5, 8 Hz), 4.36 (1 H, ddd, J = 3, 5, 9 Hz), 7.00 (2 H, d, J = 8 Hz), 7.32 (2 H, d, J = 8 Hz); ^{13}C NMR 138.21, 137.33, 129.02, 102, 70.06, 63.85, 53.29, 50.45, 49.43, 46.25, 37.60, 35.74, 33.29, 28.36, 27.13, 22.00, 21.17; IR (CCl_4) 3020, 2940, 2860, 1490, 1450, 1260, 1155, 1080, 945, 880; MS (40 eV) 349 (3), 348 (7), 347 (25), 346 (100), 318 (10), 287 (4), 286 (15), 195 (25) 151 (30), 135 (50), 124 (50), 91 (100). Anal. Calcd for $C_{20}H_{26}OS_2$: mol wt, 346.1425. Found: mol wt, 346.1424.

Preparation of (3aS^*,8aR^*)-5-Methylene-6-(p-tolylthio)-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulene (33). To a slurry of 36 mg (0.90 mmol, 3.21 equiv) of potassium hydride in 1.2 mL of THF was added 390 mg (1.09 mmol, 3.89 equiv) of methyltriphenylphosphonium bromide. The bright yellow mixture was stirred for 2 h at room temperature and then for 20 min at 50 °C and cooled to 0 °C, and 80 mg (0.28 mmol) of the ketone in 0.2 mL of THF was added. The mixture was stirred for 5 h, during which time it came to room temperature. After 30 min at 50 °C, the mixture was diluted with ether and washed with water. The organic layer was dried over magnesium sulfate and concentrated in vacuo to yield 120 mg of crude olefin and phosphine oxide. Purification by PLC yielded 70 mg (0.255 mmol, 91%, R_f 0.6 in 1:9 ether–hexane) as a colorless oil: NMR (CCl_4) 0.9–2.2 (14 H, m), 2.2–2.55 (4 H, m), 4.90 (1 H, br s), 5.22 (1 H, br s), 7.0 (2 H, d, J = 8 Hz), 7.32 (2 H, d, J = 8 Hz); IR (CCl_4) 3060, 3020, 2940, 2860, 1490, 1450, 1290, 1190, 1165, 1045, 890, 710; MS 286 (4), 285 (12), 184 (60), 269 (4), 255 (4), 228 (3), 227 (13), 215 (3), 214 (12), 162 (7), 161 (35), 160 (11), 145 (9), 135 (17), 124 (21), 123 (18), 105 (50), 93 (28), 92 (20), 91 (100). Anal. Calcd for $C_{19}H_{24}S$: mol wt, 284.1599. Found: mol wt, 284.1594.

Preparation of (3aS^*,5S^*,8aR^*)-5-Epoxymethylene-6-(p-tolylthio)-1,2,3,3a,4,5,6,7,8,8a,-decahydro-3a,6-methanoazulene (31). A slurry of 58 mg (1.21 mmol, 6.3 equiv) of a 50% sodium hydride dispersion in 0.7 mL of Me_2SO was heated at 70 °C for 40 min, cooled to room temperature, diluted with 0.7 mL of THF, and cooled to 0–5 °C when a solution of 280 mg (1.4 mmol, 7.4 equiv) of trimethylsulfonium iodide in 0.7 mL of Me_2SO was added. Two minutes later a solution of 55 mg (0.19 mmol) of the ketone in 0.25 mL of THF was added and the reaction allowed to warm to room temperature over 2 h. The mixture was then quenched by dilution with water and extraction with ether. The organic layers were dried over sodium sulfate and potassium carbonate and concentrated in vacuo to yield 75 mg of an oil, which was purified by PLC to yield 42 mg (0.14 mmol, 63%) of an epoxide as a colorless oil, R_f 0.7 (2:1 hexane–ether). The crude NMR is very clean and the material can be used without purification, especially since in some preparations new peaks appeared around δ 4.0 after purification: NMR (CCl_4) 1.0–2.4 (18 H, m), 2.62 (1 H, d, J = 6 Hz), 3.30 (1 H, d, J = 6 Hz), 7.04 (2 H, d, J = 8 Hz), 7.28 (2 H, d, J = 8 Hz); IR (CCl_4) 3020, 2960, 2860, 1490, 1450, 1360, 1030; MS 302 (2), 301 (6), 300 (25), 286 (3), 285 (2), 284 (7), 273 (3), 272 (17), 244 (4), 243 (8), 219 (8), 196 (3), 195 (6), 187 (7), 186 (5), 149 (17), 148 (17), 148 (17), 133 (15), 131 (10), 124 (22), 123 (18), 122 (3), 121 (11), 120 (12), 119 (32), 105 (35), 93 (25), 92 (35), 91 (100), 81 (25), 79 (53), 77 (50). Anal. Calcd for $C_{19}H_{24}OS$: mol wt, 300.1548. Found: mol wt, 300.1528.

Preparation of (3aS^*,5S^*,8aR^*)-5-Phenylthiomethyl-6-(p-tolylthio)-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulen-5-ol (30). Via the Epoxymethylene. To a slurry of 26 mg (0.5 mmol, 5.2 equiv) of a 50% sodium hydride dispersion in 0.5 mL of THF was

added 0.10 mL (107 mg, 0.98 mmol, 10 equiv) of thiophenol. After 20 min, 29 mg (0.096 mmol) of **31** in 0.2 mL of THF was added to the white slurry and the mixture stirred overnight, during which time it warmed to room temperature. The mixture was diluted with ether, washed with aqueous 1 M potassium hydroxide solution, dried with sodium sulfate and potassium carbonate, and concentrated in vacuo to yield 40 mg of the crude alcohol. Purification by PLC yielded 30 mg (0.073 mmol, 76%) of the alcohol as a colorless glass: R_f 0.6 in 3:1 hexane–ether; NMR (CCl_4) 0.9–2.6 (18 H, m with a singlet at 2.32), 3.20 (1 H, d, J = 13 Hz), 3.67 (1 H, d, J = 13 Hz), 6.9–7.6 (10 H, m); IR (CCl_4) 3600, 3500, 3050, 3020, 2940, 2860, 1580, 1480, 1475, 1450, 1435, 1120, 1020, 690; MS 412 (1), 411 (2), 410 (7), 313 (3), 312 (13), 299 (6), 288 (4), 287 (16), 286 (21), 285 (18), 283 (12), 244 (2), 243 (8), 242 (27), 226 (5), 213 (4), 191 (7), 177 (12), 149 (23), 147 (7), 145 (10), 135 (20), 133 (12), 131 (12), 124 (48), 123 (36), 121 (20), 120 (15), 110 (12), 109 (12), 108 (5), 107 (18), 106 (10), 105 (30), 91 (100). Anal. Calcd for $C_{25}H_{30}OS_2$: mol wt, 410.1738. Found: mol wt, 410.1730.

Via Lithiothioanisole. To a 0 °C solution of 211 mg (200 μL, 1.70 mmol, 2.34 equiv) of thioanisole and 220 mg (1.96 mmol, 2.70 equiv) of 1,4-diazabicyclo[2.2.2]nonane in 2 mL of THF was added 1 mL (1.4 mmol, 1.9 equiv) of 1.4 N n-butyllithium solution in hexane, and the mixture was stirred for 1.5 h. To this was added over 5 min 208 mg (0.727 mmol) of **22** in 0.5 mL of THF. The reaction mixture was allowed to warm to room temperature over 3 h, diluted with ether, washed with water, dried with potassium carbonate, and concentrated in vacuo to yield 280 mg of crude alcohol. Purification by PLC in 4:1 hexane–ether yielded 208 mg (0.51 mmol, 71%) of the phenylthiomethyl alcohol (R_f 0.4) and 35 mg (0.12 mmol, 17%) of the starting ketone (R_f 0.3). Thus the yield is 85%, allowing for recovered starting material.

Preparation of (3aR*,8aR*)-6-Phenylthiomethyl-1,2,3,3a,4,5,6,7,8,8a-decahaydro-3a,6-methanoazulen-5-one (32). To a solution of 40 mg (0.1 mmol) of alcohol **30** in 0.5 mL of benzene was added 40 mg (0.22 mmol, 2.2 equiv) of p-toluenesulfonic acid monohydrate and the solution heated to 75 °C. After 15 min, TLC showed some starting material (R_f 0.06 in 3:1 hexane–ether) in addition to product (R_f 0.5). After an additional 15 min the solution was diluted with ether, washed with 1 M aqueous potassium hydroxide solution, dried with sodium sulfate and potassium carbonate, and concentrated in vacuo to yield 32 mg of the crude keto phenyl sulfide. Purification by PLC yielded 21 mg (0.76 mmol, 76%) of the desired product: NMR (CCl_4) 0.8–2.4 with AB at δ 2.21 and 1.87 (J = 17 Hz, 15 H, m), 3.07 (2 H, br s), 6.95–7.40 (5 H, m); ^{13}C NMR ($CDCl_3$) 214.31, 137.24, 129.13, 125.8, 53.55, 50.13, 45.87, 45.05, 40.02, 39.25, 35.16, 33.62, 29.15, 22.25, 21.70; IR (CCl_4) 3080, 2960, 2940, 2840, 1740, 1580, 1540, 1480, 1080, 1020; MS 288 (7), 287 (23), 286 (95), 258 (8), 243 (9), 195 (5), 186 (6), 178 (10), 177 (70), 149 (29), 136 (13), 135 (100), 134 (21), 133 (25), 122 (22), 121 (22), 110 (26), 109 (18), 107 (26), 105 (34), 93 (34), 91 (42), 81 (26), 79 (37), 77 (33). Anal. Calcd for $C_{18}H_{22}OS$: mol wt, 286.1391. Found: mol wt, 286.1395.

Preparation of a "Salt Free" Solution of Triphenylphosphonium Methylide. To a slurry of 45 mg (1.1 mmol) of potassium hydride in 1 mL of THF was added 450 mg (1.25 mmol, 1.13 equiv) of methyltriphenylphosphonium bromide, and the mixture was stirred for 2 h at 25 °C and 30 min at 50 °C. The bright yellow slurry was cooled and added to 0.5 mL of benzene in a centrifuge tube capped with a septum. The slurry was centrifuged to give a bright yellow solution which was used without further handling.

Preparation of (3aR*,8aR*)-5-Methylene-6-phenylthiomethyl-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulene (34). To 0.5 mL of the salt free phosphonium methylide solution above (~0.3 mmol, 8.3 equiv) was added 10 mg (0.036 mmol) of ketone **32** in 0.25 mL of THF, and the solution was heated to 80 °C for 3 h, at which time TLC showed only the desired methylene compound (R_f 0.9, 3:1 hexane–ether). The solution was diluted with ether and washed with water, dried with sodium sulfate and potassium carbonate, and concentrated in vacuo. A carbon tetrachloride solution of the crude olefin was filtered through Florisil and concentrated in vacuo to yield 15 mg of crude olefin. Purification by PLC yielded 8 mg (0.029 mmol, 81%) of the desired methylene compound: NMR (CCl_4) 1.0–2.7 (15 H, m), 3.10 (2 H, br s), 4.85 (1 H, br s), 4.95 (1 H, br s), 7.0–7.45 (5 H, m); IR (CCl_4) 3000, 2960, 2920, 2870, 1475, 1435, 1360, 1030; MS 285 (3), 284 (15), 190 (25), 177 (12), 175 (10), 165 (8), 162 (10), 161 (100), 133 (19), 124 (12), 105 (16), 91 (39), 81 (14), 79 (19), 77 (23). Anal. Calcd for $C_{19}H_{24}S$: mol wt, 284.1609. Found: 284.1609.

Preparation of (3aS*,5R*,8aR*)-5-Hydroxymethyl-6-(p-tolylthio)-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulen-5-ol (36). To a solution of 160 mg (0.56 mmol) of **33** in 2 mL of pyridine was added 180 mg (0.71 mmol, 1.26 equiv) of osmium tetraoxide. The solution became black within 3 min. After 3 h, 3 g (30 mmol, 42 equiv) of solid sodium bisulfite was added and the mixture stirred for 3 h, after which time it was partitioned between ethyl acetate and water. The ethyl acetate was dried with sodium sulfate and concentrated in vacuo to yield 200 mg of a colorless diol as an oil. Purification by PLC in 4:1 dichloromethane–ether yielded 4 mg (0.014 mmol, 2.5%, R_f 0.9) of the starting olefin and 164 mg (0.54 mmol, 97%) of the desired diol as a clear colorless oil: NMR (CCl_4) 0.8–2.0 (14 H, m), 2.3–2.45 (4 H, m with singlet at 2.36), 3.0 (1 H, br s), 3.38 (2 H, br s), 7.08 (2 H, d, J = 8 Hz), 7.36 (2 H, d, J = 8 Hz); IR (CCl_4) 3480, 3450, 3020, 2950, 2870, 1490, 1450, 1340, 1290, 1210, 1060; MS 320 (5), 319 (10), 318 (30), 288 (3), 287 (4), 286 (4), 284 (24), 279 (6), 243 (19), 195 (6), 177 (12), 167 (10), 149 (24), 132 (23), 124 (35), 121 (100), 95 (21), 92 (40), 91 (50). Anal. Calcd for $C_{19}H_{26}O_2S$: mol wt, 318.1653. Found: mol wt, 318.1665.

Preparation of (3aR*,8aR*)-6-Acetoxymethyl-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulen-5-one (38). To a solution of 114 mg (0.36 mmol) of **36** and 0.25 mL of trimethyl orthoacetate in 1 mL of benzene was added 2 mg of p-toluenesulfonic acid monohydrate and the mixture stirred overnight. The mixture was diluted with ether, washed with saturated aqueous sodium bicarbonate solution, dried with sodium sulfate and potassium carbonate, and concentrated in vacuo to yield 125 mg of the crude orthoacetate **37** as a colorless oil: NMR (CCl_4, crude) 0.8–2.1 (m with a sharp singlet at 1.60), 2.3–2.6 (m with a singlet at 2.36); IR (CCl_4, crude) 2960, 2860, 1740 (weak), 1490, 1450, 1380, 1250, 1150, 1040, 860.

This sample was dissolved in 200 μL of carbon tetrachloride, placed in a 5-mm NMR tube, and cooled to −40 °C to freeze the sample. To this was added 100 μL of trifluoroacetic acid at −40 °C and the mixture shaken until homogeneous while warming to 25 °C. The progress of the reaction was monitored by periodic NMR investigation to observe the immediate disappearance of the δ1.67 methyl signal to be replaced by one at δ 2.9. The reaction was followed by the gradual disappearance of the δ 2.9 signal and its replacement by a typical acetate methyl signal at ~2.0. After 12 h the δ 2.9 signal was ~5% of its initial intensity, and the reaction mixture was poured into 5 mL of 3 N aqueous hydrochloric acid and stirred for 30 min. The aqueous mixture was extracted with ether. The organic fraction was dried with potassium carbonate and concentrated in vacuo to yield 65 mg of crude pale yellow oil. Purification by PLC with 2:1 hexane–ether yielded 50 mg (R_f 0.35) of a mixture of the desired rearranged keto acetate and the monoacetate of the starting diol in a ratio (NMR) of 2:1. Kügelrohr distillation [120 °C (0.07 mm)] separated the keto acetate from the nonvolatile hydroxy acetate, 40 mg (0.17 mmol, 48% conversion, 57% yield), and 20 mg of the hydroxy acetate (0.044 mmol, 17%).

Keto acetate 38: NMR (CCl_4) 1.3–2.4 (18 H, m with a singlet at 1.98), 3.98 (2 H, br s); IR (CCl_4) 2960, 2870, 1753, 1743, 1450, 1380, 1360, 1240, 1035; MS 236 (2), 218 (10), 193 (3), 177 (12), 176 (92), 175 (10), 174 (40), 156 (35), 135 (23), 134 (95), 133 (46), 132 (50), 119 (29), 105 (20), 43 (100). Anal. Calcd for $C_{14}H_{20}O_3$: mol wt, 236.1412. Found: mol wt, 236.1416.

(3aS*,5R*,8aR*)-5-(Acetoxymethyl)-6-(p-tolylthio)-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulen-5-ol: NMR (CCl_4) 1.3–2.5 (21 H, m with singlets at 2.06 and 2.36), 3.1 (1 H, br s), 3.90 (1 H, d, J = 12 Hz), 4.20 (1 H, d, J = 12 Hz), 7.1 (2 H, d, J = 8 Hz), 7.4 (2 H, d, J = 8 Hz); IR (CCl_4) 3480, 3060, 3020, 2950, 2860, 1742, 1490, 1450, 1380, 1360, 1225, 1040, MS 362 (5), 361 (17), 360 (74), 300 (3), 287 (7), 246 (6), 244 (17), 143 (100), 195 (2), 186 (5), 178 (12), 177 (85), 166 (4), 165 (35), 159 (24), 149 (25), 138 (38), 133 (19), 124 (82), 123 (27), 120 (15), 109 (5), 107 (13), 105 (17), 97 (7), 95 (24), 93 (23), 92 (15), 91 (89), 77 (24), 43 (80).

Preparation of (3aR*,8aR*)-6-Acetoxymethyl-5-methylene-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulene (39). To 0.5 mL (~0.3 mmol, 10 equiv) of the salt free phosphonium methylide solution was added 7 mg (0.03 mmol) of ketone **38** in 0.25 mL of THF. The solution was heated at 80 °C for 3 h until no further starting ketone (R_f 0.4 in 3:1 hexane–ether) was present and only acetoxy methylene (R_f 0.7) and hydroxy methylene (R_f 0.35, from reaction to cleave the acetate) were evident. The solution was cooled, diluted with ether, washed with water, dried with sodium sulfate, and concentrated with a water aspirator. The crude material was filtered through a small amount of Florisil with 50 mL of carbon tetrachloride. The filtrate was concentrated to yield 20 mg of crude olefin. Due to the partial hydrolysis of the acetate, the crude olefin mixture was treated with 0.25 mL each of acetic anhydride and pyridine for 8 h, diluted with ether, and washed with aqueous 3 N hydrochloric acid, followed by saturated aqueous sodium bicarbonate solution. The organic layer was dried with sodium sulfate and concentrated with

a water aspirator to yield 18 mg of the crude acetoxy olefin. Purification in 10:1 hexane–ether by PLC gave 4 mg of the desired olefin (R_f 0.4) (~50%): NMR (CCl_4) 0.9–2.6 (18 H, m with a singlet at 2.00), 4.0 (2 H, br s), 4.80 (1 H, br s), 4.90 (1 H, br s); IR (CCl_4) 2930, 2860, 1740, 1450, 1370, 1360, 1230, 1030; MS 235 (3), 234 (10), 192 (10), 175 (12), 174 (80), 161 (20), 159 (28), 146 (36), 145 (36), 133 (30), 132 (78), 131 (42), 119 (39), 118 (30), 117 (24), 107 (15), 106 (24), 105 (40), 43 (100). Anal. Calcd for $C_{15}H_{22}O_2$: mol wt, 234.1620. Found: mol wt, 234.1618.

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Registry No.—**5,** 64715-45-3; **6,** 64715-46-4; **12,** 64715-47-5; **13,** 64715-48-6; **14,** 64715-49-7; **15,** 64753-45-3; **18** (isomer I), 64715-50-0; **18** (isomer II), 64753-46-4; **19,** 64715-51-1; **20** (R = CH_3), 64715-52-2; **21** (R = Ac), 64715-53-3; **21** (R = H), 64715-54-4; **21** (R = Ms, isomer I), 64715-55-5; **21** (R = Ms, isomer II), 647-47-5; **22,** 64715-56-6; **25,** 64715-34-0; **26,** 64715-35-1; **30,** 64715-36-2; **31,** 64715-37-3; **32,** 64715-38-4; **33,** 64715-39-5; **34,** 64715-40-8; **36,** 64715-41-9; **37,** 64740-23-4; **38,** 64715-42-0; **39,** 64715-43-1; 2-(2′-hydroxyethyl)cyclopentanone, 24804-46-4; 2-cyclopentanone methyl carboxylate, 10472-24-9; 2-cyclopentanone ethyl carboxylate, 611-10-9; 2-bromoethyl acetate, 927-68-4; trityl bromide, 596-43-0; cyclopropyldiphenylsulfonium tetrafluoroborate, 33462-81-6; methyltriphenylphosphonium bromide, 1779-49-3; 1-bromomethylene-5-(2′-trityloxyethyl)spiro[3.4]octan-1-ol, 64740-19-8; trimethylsulfonium iodide, 2181-42-2; methyl *p*-tolylsulfinate, 672-78-6; acetic anhydride, 108-24-7; methanesulfonyl chloride, 124-63-0; ethylene glycol, 107-21-1; 2-mercaptoethanol, 60-24-2; thiophenol, 108-98-5; thioanisole, 100-68-5; trimethyl orthoacetate, 1445-45-0; (3a*S**,5*R**,8a*R**)-5-(acetoxymethyl)-6-(*p*-tolylthio)-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulen-5-ol, 64715-44-2.

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Unsymmetrically Tris-Bridged [2.2.2]Cyclophane.[1] Syntheses of [2.2.2](1,2,4)(1,3,5)- and [2.2.2](1,2,4)(1,2,5)Cyclophanes[2]

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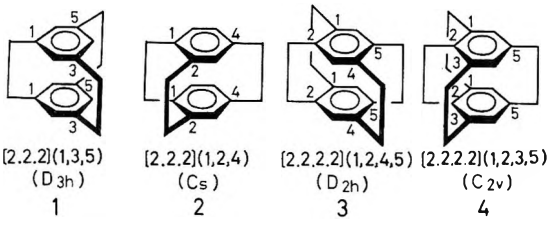
As the first members of [2.2.2]cyclophanes whose two benzene rings are unsymmetrically held together with three ethano bridges, [2.2.2](1,2,4)(1,3,5)cyclophane (C_1 symmetry) (**6**) and [2.2.2](1,2,4)(1,2,5)cyclophane (C_2 symmetry) (**7**) were synthesized and their unusually strained and skew structures were supported by their UV and NMR spectra.

As members of cyclophanes whose two benzene rings are held together with more than two ethano bridges, there have been prepared [2.2.2](1,3,5)- (D_{3h} symmetry) (**1**),[3] [2.2.2]-(1,2,4)- (C_s symmetry) (**2**),[4] [2.2.2.2](1,2,4,5)- (D_{2h} symmetry) (**3**),[5] and [2.2.2.2](1,2,3,5)cyclophanes (C_{2v} symmetry) (**4**).[6]

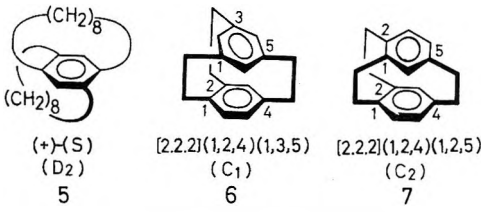
Chart I



Conspicuous features in these compounds are their deformed benzene rings and strong transannular π-electron interaction caused by intense interfacial crowding of the two aromatic rings.

We have been interested in the synthetic studies of high symmetry chiral(gyrochiral)[7] molecules,[8] and previous papers from our laboratory described the syntheses of various gyrochiral compounds with twisted π-electron systems: e.g., (+)-(*S*)-[8][8]paracyclophane[9] (D_2 symmetry) (**5**), (−)-(*R,R,R,R*)-[6]chochin[10] (D_2 symmetry) and (±)-*trans*-bicyclo[10.8.0]eicos-1(12)-ene[11] (C_2 symmetry). In [8][8]paracyclophane (**5**), the central benzene ring is dissymmetrically twisted by two octamethylene groups bridging two para positions, and the (+) Cotton effect at 240–360 nm reveals its skew structure.

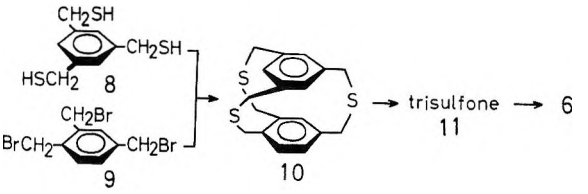
Chart II



An obvious extension of our interests in these dissymmetrically twisted cyclophanes led us to investigate the syntheses of [2.2.2]cyclophanes which have two benzene rings dissymmetrically held together with three ethano bridges, and this contribution is concerned with syntheses of [2.2.2](1,2,4)-(1,3,5)cyclophane (C_1 symmetry) (**6**) and [2.2.2](1,2,4)-(1,2,5)cyclophane (C_2 symmetry) (**7**).

Synthesis of [2.2.2](1,2,4)(1,3,5)Cyclophane (6). Guided by Cram's observation[12] that carbonyl groups attached to one deck of a [2.2]paracyclophane exert a strong influence directing electrophilic substitution to the pseudo-geminal position of the opposite deck, the syntheses of [2.2.2]cyclophane **2** and [2.2.2.2]cyclophanes **3** and **4** have been achieved all starting from [2.2]paracyclophane precursors. This eventually led to the formation of achiral cyclophanes with a mirror plane which passes between two aromatic rings bisecting the molecules. Boekelheide's starting material in his elegant synthesis of [2.2.2](1,3,5)cyclophane (**1**)[3] was 1,3,5-tris(bromomethyl)-benzene whose D_{3h} symmetry again inevitably gives rise to the formation of the achiral cyclophane **1**.

Scheme I



In our synthesis of unsymmetrical [2.2.2](1,2,4)(1,3,5)cyclophane (**6**), 1,3,5-tris(mercaptomethyl)benzene (**8**) was condensed with 1,2,4-tris(bromomethyl)benzene (**9**) following Vögtle's procedure[13] (Scheme I).[14] Whereas **8** possess two homotopic faces around the benzene ring, **9** has two enantiotropic faces which determine the chirality of the condensation product, trithia[3.3.3](1,2,4)(1,3,5)cyclophane (**10**). Refluxing an ethanolic solution of **8** and **9** with sodium hydroxide for 13 h completed the condensation reaction, affording a 74% yield[15] of **10**, mp 200–201 °C. After fruitless attempts for expulsion of sulfur by irradiation of a solution of **10** in triethyl phosphite,[16] the trisulfone **11** was prepared from the corresponding trisulfide **10** in quantitative yield following Vögtle's procedure.[13] Pyrolysis of the trisulfone **11** under conditions (0.1 mmHg, 520 °C) similar to those described by Staab[17] for sulfone pyrolysis led to the formation of [2.2.2](1,2,4)-(1,3,5)cyclophane (**6**) in 6% yield.[18]

Resinifying rather rapidly on standing at room temperature, the unsymmetrically tris-bridged cyclophane **6** was found to be very labile, and attempts to isomerize it into symmetrical [2.2.2](1,3,5)cyclophane (**1**) with aluminum chloride or trifluoroacetic acid failed, giving invariably a polymer as the product. This chemical instability undoubtedly reflects the extraordinarily strained structure **6** which is also responsible to the long-wavelength absorption band exhibited at 300 nm (Table I). The unsymmetrical structure of **6** reveals itself in its ^{13}C NMR spectrum[19] which shows six peaks at δ 35.3–39.2 for the methylene groups and 12 peaks at δ 128.2–148.1 for the aromatic carbon atoms. The ^1H NMR spectrum (Figure 1) contained other interesting features. The aromatic protons exhibited peaks at δ 5–7, and a meta-decoupling procedure assigned three peaks at δ 5.04 (t), 6.32 (t), and 6.80 (m) to the protons on the (1,3,5) deck. A molecular model of **6** indicated that, among these three aromatic protons on the (1,3,5) deck, H_f suffers the highest shielding from the opposite (1,2,4) deck followed by H_e and H_d, and this automatically assigned the peaks δ 5.04, 6.32, and 6.80 to H_f, H_e, and H_d, respectively. Among the remaining peaks corresponding to the aromatic

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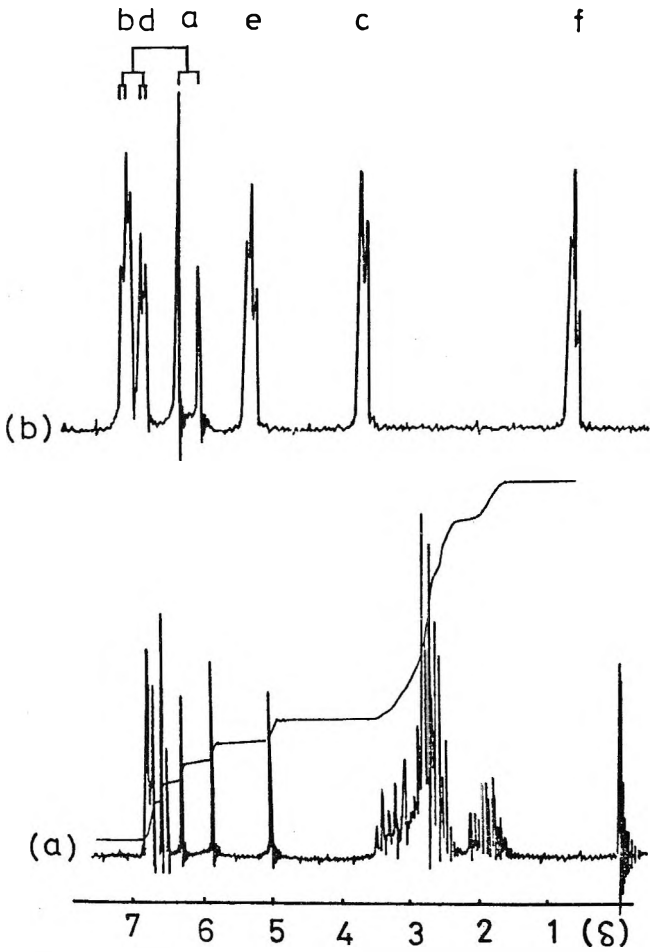


Figure 1. (a) 100-MHz NMR spectrum of [2.2.2](1,2,4)(1,3,5)cyclophane (**6**) in CCl_4. (b) An expanded spectrum (×2) of the aromatic protons.

Table I. Ultraviolet Absorption Data in Isooctane

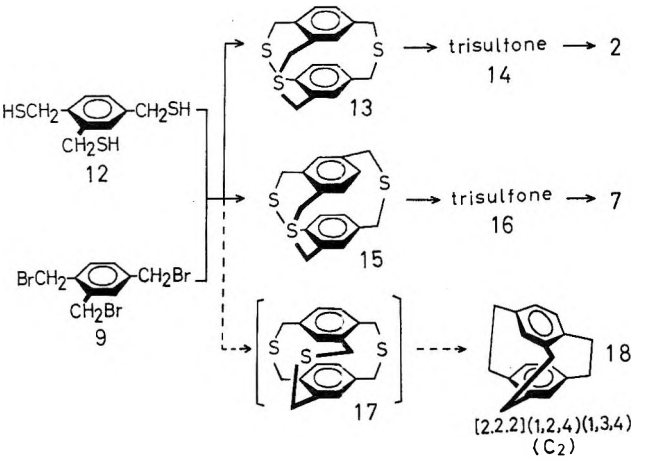
Compd	λ_{max}, nm (ϵ)
6	235 sh (10 030), 300 (380)
7	234.5 sh (10 010), 285.5 (640), 293.5 (530)
2	225 (12 300), 291 (450), 304 sh (250)

protons on the (1,2,4) deck, the peak at δ 5.88 (d) was assigned to H_c again on the basis of meta coupling with H_b, and this was supported by an inspection of the molecular model which indicates H_c suffers the highest shielding from the opposite (1,3,5) deck. Although overlapping with the H_d peak made the downfield AB quartet (J_{ab} = 8 Hz) difficult to discern, meta coupling with H_c assigned the downfield signal δ 6.82 to H_b.

Synthesis of [2.2.2](1,2,4)(1,2,5)Cyclophane (7) (Scheme II).[14] Although symmetrical trithia[3.3.3](1,2,4)cyclophane (C_s symmetry) (**13**) is an obvious candidate for the possible condensation products between 1,2,4-tris(mercaptomethyl)-benzene (C_s symmetry) (**12**) and 1,2,4-tris(bromomethyl)-benzene (C_s symmetry) (**9**), molecular models indicate that one can also expect the formation of trithia[3.3.3](1,2,4)-(1,2,5)cyclophane (**15**) and trithia[3.3.3](1,2,4)(1,3,4)cyclophane (**17**) both having C_2 symmetry.

The condensation reaction was carried out following the procedure described for the preparation of **10**, and column chromatography of the reaction product afforded two trisulfides in 39 and 14% yields, respectively. The major product **13** was converted into the trisulfone **14** whose pyrolysis gave a 12% yield of [2.2.2](1,2,4)cyclophane (**2**),[4] mp 167–168 °C,

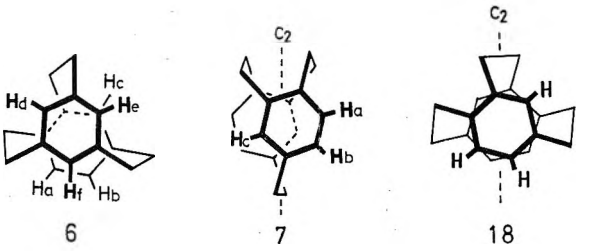
Scheme II



and this established the structure of the major trisulfide as **13**. The trisulfone **16** prepared from the minor product **15** was pyrolyzed to give a 5% yield of colorless platelets, mp 90–91 °C. In contrast to **6**, the dissymmetric cyclophane **7** was found to be more stable, apparently reflecting a less intense interfacial crowding, as the molecular model of **7** indicates. The ultraviolet spectrum of **7** shows absorption maxima at 285.5 (ϵ 640) and 293.5 nm (ϵ 530) (Table I), supporting again the less severely skewed structure of cyclophane **7**.

Structural evidences for the structure of **7** mainly came from its NMR spectum. In its ^{13}C NMR spectrum[19] the cyclophane **7** gives three peaks for the methylene carbon atoms in the δ 35.4–37.4 region, whereas the aromatic carbon atoms give rise to six peaks in δ 127.8–139.5 region. This simple spectrum is indicative of C_2 symmetry in **7** which was further supported by its ^1H NMR spectrum (Figure 2). As C_2 symmetry demands, **7** exhibited a rather simple pattern in its ^1H NMR spectrum; a doublet at δ 5.32 for two aromatic protons and a quartet (δ 6.79, 6.78, J_{ab} = 8 Hz) are downfield for four aromatic protons. Since the aromatic proton H_c is shielded by the opposite benzene ring, the upfield doublet at δ 5.32 can be safely assigned to this proton.[20] The remarkable upfield shift of the aromatic proton H_c clearly indicates a skewed geometry **7** than a less skewed one **18** (Chart III).

Chart III



Searches were made for the presence of another [2.2.2]-cyclophane **18** in the pyrolysate of trisulfone obtained from the crude condensation product between **12** and **9**, but its gas chromatography revealed only the presence of **2** and **7** in a ratio of 3:1 without a trace of the expected cyclophane **18** with C_2 symmetry.

Experimental Section

Melting and boiling points are uncorrected. Infrared spectral data were measured from a Hitachi EPI-S2 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained from a JNM-MH-100 and a JNM-FX-100 spectrometer, respectively. UV spectra were recorded on a Hitachi EPS-3T spectrometer. Mass spectral data were measured on a Hitachi RMS-4 spectrometer. Elemental analyses were performed by a Yanagimoto CHN-Corder Type II.

1,2,4-Tris(bromomethyl)benzene (9). A solution of 1,2,4-tri-

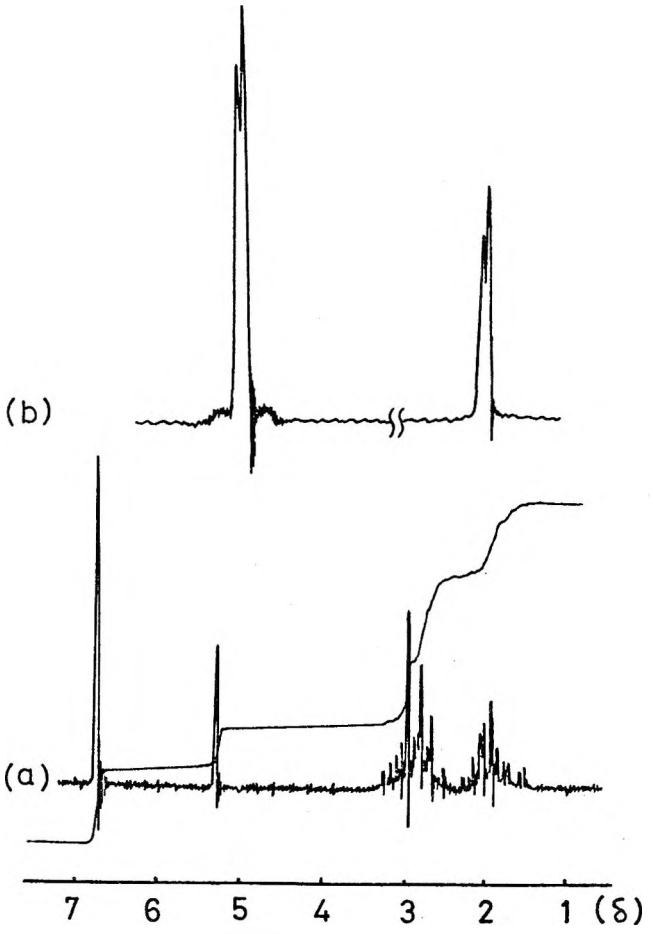


Figure 2. (a) 60-MHz NMR spectrum of [2.2.2](1,2,4)(1,2,5)cyclophane (7) in CCl_4. (b) An expanded spectrum (×5) of the aromatic protons.

carbomethoxybenzene[21] (50 g, 0.2 mol) in dry tetrahydrofuran (200 mL) was added to a suspension of $LiAlH_4$ (16 g, 0.42 mol) in dry tetrahydrofuran (400 mL). The mixture was refluxed with stirring for 8 h, and the excess reducing agent was decomposed with water (40 mL). After the insoluble aluminum hydroxide was removed from the reaction mixture, the filtrate was concentrated under vacuum. The concentrate was distilled to give 1,2,4-tris(hydroxymethyl)benzene (25 g, 72%), bp 200–203 °C (1.5 mm), which was converted to the bromide **9**. To a stirred solution of the alcohol (92 g, 0.55 mol) in dry ether (1.5 L) was added dropwise a solution of phosphorus tribromide (180 g, 0.66 mol) in dry ether (400 mL) at room temperature. After the reaction mixture was stirred for 4 h at room temperature, water (400 mL) was slowly added. The organic phase was washed with dilute sodium bicarbonate solution and then with water and then dried. Removal of the ether afforded a solid which was recrystallized from methanol to yield **9** (122 g, 62%), mp 64–65 °C; MS *m/e* 356 (M^+).

Anal. Calcd for $C_9H_9Br_3$: C, 30.29; H, 2.55; Br, 67.17. Found: C, 30.56; H, 2.56; Br, 66.89.

2,11,20-Trithia[3.3.3](1,2,4)(1,3,5)cyclophane (10). To stirred and refluxed ethanol (2.2 L) were simultaneously added, in a period of 6 h, a solution of 1,2,4-tris(bromomethyl)benzene (**9**) (9.3 g, 0.026 mol) in ethanol (300 mL) and a solution of 1,3,5-tris(mercaptomethyl)benzene (**8**)[13] (5.6 g, 0.026 mol) in 80% ethanol (300 mL) containing sodium hydroxide (4.8 g, 0.12 mol). After being refluxed for 13 h, the mixture was concentrated in vacuum and the residue was extracted with boiling benzene. Removal of the solvent afforded a solid which was recrystallized from benzene to give **10** (19 g, 74%): mp 200–201 °C; IR (KBr) 2970, 2880, 2860, 1602, 1596, 1478, 1443, 1425, 1407, 1217, 1203, 1150, 1123, 1070, 918, 905, 891, 869, 810, 721, 702 cm^{-1}; NMR ($CDCl_3$) δ 3.09–4.08 (m, 12 H), 5.79 (s, 1 H), 6.40–7.21 (m, 5 H); UV (isooctane) λ_{max} 255 nm (ε 5020); MS *m/e* 330 (M^+).

Anal. Calcd for $C_{18}H_{18}S_3$: C, 65.41; H, 5.49; S, 29.10. Found: C, 65.38; H, 5.48; S, 28.91.

2,11,20-Trithia[3.3.3](1,2,4)(1,3,5)cyclophane Trisulfone (11). To a solution of **10** (1.4 g, 4.2 mmol) in benzene (400 mL) and acetic acid (250 mL) was added 35% hydrogen peroxide (6.3 g, 64.8 mmol). After the mixture was refluxed with stirring for 7 h, the resulting crystallines were collected by filtration, washed with ether, and dried: 1.75 g (98%); mp >300 °C; IR (KBr) 2960, 2880, 2860, 1600, 1496, 1475, 1456, 1413, 1400, 1320, 1291, 1277, 1122, 1110, 910, 853, 714, 692 cm^{-1}; MS *m/e* 426 (M^+).

Anal. Calcd for $C_{18}H_{18}S_3O_6$: C, 50.68; H, 4.25; S, 22.55. Found: C, 50.99; H, 4.28; S, 22.38.

[2.2.2](1,2,4)(1,3,5)Cyclophane (6). Following Staab's procedure,[17] the trisulfone (**11**) (1.2 g, 2.8 mmol) was pyrolyzed at 520 °C under vacuum (0.1 mm) using a nitrogen bleed, and the pyrolysate was subjected to alumina column chromatography. Elution with hexane gave **6** (40 mg, 6%), which when recrystallized from pentane gave: mp 87–88 °C; IR (KBr) 1970, 2950, 2880, 2820, 1572, 1475, 1437, 1426, 1395, 1188. 1177, 1150, 1078, 914, 886, 827, 797, 746, 725, 712, 654 cm^{-1}; UV (isooctane) λ_{max} 235 (sh), 300 nm (ε 10030, 380); ^1H NMR (CCl_4) δ 1.64–3.52 (m, 12 H), 5.04 (t, 1 H), 5.88 (d, 1 H), 6.32 (t, 1 H), 6.60, 6.82 (AB quartet, J_{ab} = 8 Hz, 2 H), 6.80 (m, 1 H); ^{13}C NMR ($CDCl_3$)[19] δ 35.3, 35.8, 36.7, 38.4, 38.6, 39.2, 128.2, 131.3, 132.5, 132.7, 135.9, 136.3, 136.7, 136.9, 139.5, 144.3, 147.5. 148.1; MS *m/e* 234 (M^+).

Anal. Calcd for $C_{18}H_{18}$: C, 92.26; H. 7.74. Found: C, 92.26; H, 7.73.

1,2,4-Tris(mercaptomethyl)benzene (12). A mixture of **9** (66 g, 0.185 mol), thiourea (49 g, 0.644 mol), and 95% ethanol (900 mL) was refluxed with stirring for 13 h. The resulting trisisothiuronium salt was collected by filtration and dissolved in 6% sodium hydroxide solution (1.6 L). After refluxing under nitrogen for 8 h, the solution was allowed to cool and was then acidified with 6 N hydrochloric acid (200 mL). The resulting product was extracted with ether, and the ether extract was washed with water and then dried. After removal of the solvent, distillation of the residue gave 12 (29 g, 72%): bp 164–166 °C (0.1 mm), $n^{26}D$ 1.6627; IR (film) 2550 cm^{-1} (ν_{sh}); MS *m/e* 216 (M^+).

Anal. Calcd for $C_9H_{12}S_3$: C, 49.95; H, 5.59. Found: C, 50.13; H, 5.50.

2,11,20-Trithia[3.3.3](1,2,4)cyclophane (13) and 2,11,20-Trithia[3.3.3](1,2,4)(1,2,5)cyclophane (15). The method described for the preparation of **10** was followed for the condensation of 1,2,4-tris(bromomethyl)benzene (**9**) (11.5 g, 0.032 mol) and 1,2,4-tris(mercaptomethyl)benzene (**12**) (7 g, 0.032 mol). After an insoluble polymer was removed from the reaction mixture, the filtrate was concentrated to dryness under vacuum and the residue was chromatographed on neutral alumina. Elution with hexane–benzene yielded trithia[3.3.3](1,2,4)cyclophane (**13**) followed by trithia[3.3.3]-(1,2,4)(1,2,5)cyclophane (**15**). Compound **13** was recrystallized from chloroform: 4.2 g (39%); mp >300 °C; IR (KBr) 2960, 2870, 2850, 1595, 1482, 1415, 1219, 1148, 1138, 1078, 923, 895, 846, 830, 806, 788, 752, 703, 651 cm^{-1}; UV (isooctane) λ_{max} 271 (ε 3130); NMR ($CDCl_3$) δ 3.43–4.79 (m, 12 H), 6.85, 7.10 (AB quartet, J_{ab} = 8 Hz, 4 H), 7.13 (d, 2 H); MS *m/e* 330 (M^+).

Anal. Calcd for $C_{18}H_{18}S_3$: C, 65.41; H, 5.49; S, 29.10. Found: C, 65.50; H, 5.53; S, 29.02.

The compound **15** was recrystallized from benzene: 1.5 g (14%); mp >300 °C; IR (KBr) 2970, 2880, 2860, 1596, 1483, 1440, 1409, 1213, 952, 912, 893, 834, 816, 777, 756, 718, 700, 672 cm^{-1}; UV (isooctane) λ_{max} 256 (ε 5920); NMR ($CDCl_3$) δ 3.25–4.87 (m, 12 H), 5.98 (s, 2 H), 7.15 (s, 4 H); MS *m/e* 330 (M^+).

Anal. Calcd for $C_{18}H_{18}S_3$: C, 65.41; H, 5.49; S, 29.10. Found: C, 65.49; H, 5.56; S, 28.97.

2,11,20-Trithia[3.3.3](1,2,4)cyclophane Trisulfone (14). The trisulfone **14** was prepared from **13** (4.0 g) in a quantitative yield (5.1 g) by the same method described for the preparation of **11**: mp >300 °C; IR (KBr) 2940, 2840, 1610, 1490, 1415, 1313, 1288, 1257, 1108, 906, 877, 857 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}S_3O_6$: C, 50.68; H, 4.25; S, 22.55. Found: C, 50.93; H, 4.31; S, 22.39.

[2.2.2](1,2,4)Cyclophane (2). The pyrolysis of **14** (1.5 g) was carried out by the same method described for the preparation of **6**. The pyrolysis product was recrystallized from benzene to give 2:4 0.1 g (12%); mp 167–168 °C.

2,11,20-Trithia[3.3.3](1,2,4)(1,2,5)cyclophane Trisulfone (16). The trisulfone **16** was prepared from **15** (1.4 g) in a quantitative yield (1.8 g): mp >300 °C; IR (KBr) 2940, 2850, 1610, 1415, 1390, 1318, 1290, 1108, 909, 855 cm^{-1}.

Anal: Calcd for $C_{18}H_{18}S_3O_6$: C, 50.68; H, 4.25; S, 22.55. Found: C, 50.41; H, 4.28; S, 22.69.

[2.2.2](1,2,4)(1,2,5)Cyclophane (7). The trisulfone **16** (2.0 g) was pyrolyzed by the same procedure described for the preparation of **6**. The pyrolysis product was chromatographed on neutral alumina. Elution with hexane produced **7** (55 mg, 5%), which when recrystallized from pentane gave: mp 90–91 °C; IR (KBr) 2960, 2930, 2820, 1575, 1480, 1434, 1426, 1402, 1192, 1166, 1150, 1120, 993, 910, 886, 802,

752, 740, 733, 706 cm^{-1}; UV (isooctane) λ_{max} 234.5 (sh), 285.5, 293.5 (ϵ 10 010, 640, 530); ^1H NMR (CCl_4) δ 1.60–2.30 (m, 4 H), 2.52–3.28 (m, 8 H), 5.32 (d, 2 H), 6.78, 6.79 (AB quartet, J_{ab} = 8 Hz, 4 H); ^{13}C NMR ($CDCl_3$)[19] δ 35.4, 35.7, 37.4, 127.8, 129.1, 134.5, 139.3, 139.4, 139.5; MS *m/e* 234 (M^+).

Anal. Calcd for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.19; H, 7.80.

Registry No.—**2**, 58002-98-5; **6**, 63877-75-8; **7**, 64884,24,8; **8**, 38460-57-0; **9**, 61124-37-6; **10**, 63877-74-7; **11**, 64316-88-7; **12**, 64924-60-3; **13**, 64884-26-0; **14**, 64884-27-1; **15**, 64976-19-8; **16**, 64924-60-3; 1,2,4-tricarbomethoxybenzene, 2459-10-1; 1,2,4-tris(hydroxymethyl)benzene, 25147-76-7; phosphorus tribromide, 7789-60-8; thiourea, 62-56-6.

References and Notes

(1) Presented in part at the 36th Annual Meeting of the Chemical Society of Japan, Osaka, Japan, April 1, 1977, abstracts II, p 580, and a preliminary report of the synthesis of [2.2.2](1,2,4)(1,3,5)cyclophane has been published: M. Nakazaki, K. Yamamoto, and Y. Miura, *J. Chem. Soc., Chem. Commun.*, 206 (1977).
(2) The nomenclature used is that proposed by F. Vögtle and P. Neumann, *Tetrahedron*, **26**, 5847 (1970).
(3) V. Boekelheide and R. A. Hollins, *J. Am. Chem. Soc.*, **93**, 3512 (1970); *ibid.*, **95**, 3201 (1973).
(4) D. J. Cram and E. A. Truesdale, *J. Am. Chem. Soc.*, **95**, 5825 (1973).
(5) V. Boekelheide and R. Gray, *Angew. Chem. Int. Ed. Engl.*, **14**, 107 (1975).
(6) W. Gilb, K. Menke, and H. Hopf, *Angew. Chem., Int. Ed. Engl.*, **16**, 191 (1977).
(7) M. Nakazaki, K. Naemura, and H. Yoshihara, *Bull. Chem. Soc. Jpn.*, **48**, 3278 (1975).
(8) M. Nakazaki, "Syntheses and Stereochemistry of Twisted Organic Compounds", Invited Lecture at 30th National Meeting of the Chemical Society of Japan, Osaka, April 1974, abstracts V, p 1.
(9) M. Nakazaki, K. Yamamoto, and M. Itoh, *J. Chem. Soc., Chem. Commun.*, 433 (1972); M. Nakazaki and K. Yamamoto, *Chem. Lett.*, 1051 (1974).
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(11) M. Nakazaki, K. Yamamoto, and J. Yanagi, *J. Chem. Soc., Chem. Commun.*, 346 (1977); J. A. Marshall and M. Lewellyn, *J. Am. Chem. Soc.*, **99**, 3508 (1977).
(12) H. J. Reich and D. J. Cram, *J. Am. Chem. Soc.*, **91**, 3505, 3527 (1969).
(13) F. Vögtle, *Justus Liebigs Ann. Chem.*, **735**, 193 (1970).
(14) The structural formula of **6**, **7**, **10**, **15**, **17**, and **18**, respectively, represent one of their possible enantiomers.
(15) Vögtle has shown that the condensation of 1,3,5-tris(bromomethyl)benzene with 1,3,5-tris(mercaptomethyl)benzene (**8**) proceeded with only 5.3% yield.[13]
(16) J. Bruhin and W. Jenny, *Tetrahedron Lett.*, 1215 (1973); V. Boekelheide, I. D. Reingold, and M. Tuttle, *J. Chem. Soc., Chem. Commun.*, 406 (1973).
(17) M. Haenel and H. A. Staab, *Tetrahedron Lett.*, 3585 (1970); *Chem. Ber.*, **106**, 2190 (1973).
(18) [2.2.2](1,3,5)Cyclophane (**1**) has been reported to be prepared by pyrolysis of the corresponding trisulfone in a 20% yield.[3]
(19) Chemical shifts are expressed in parts per million relative to Me_4Si.
(20) The heavily shielded proton in [2.2]metaparacyclophane is exhibited at δ 5.24; D. J. Cram, R. C. Helgeson, D. Lock, and L. A. Singer, *J. Am. Chem. Soc.*, **88**, 1324 (1966).
(21) 1,2,4-Tricarbomethoxybenzene, bp 171–173 °C (0.1mm), was prepared by the esterification of 1,2,4-benzenetricarboxylic acid with methanol containing sulfuric acid.

Rearrangement of 2-Cyano-3-(1-methylcyclopentyl)indenone to 4a-Methyl-9-oxo-10-cyano-1,2,3,4,4a,9-hexahydrophenanthrene[1a]

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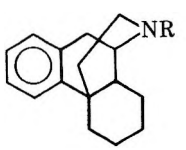
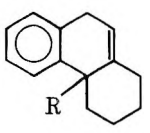
The possibility of preparing partially saturated phenanthrenes with 2-aminoethyl side chains at the 4a position, key precursors in the synthesis of the pharmacologically important morphinan ring system, by a complex carbonium ion rearrangement of the title compounds was explored. Thus, treatment of 1-methylcyclopentanecarbonitrile (**1**) with phenyllithium followed by malononitrile quench gave α-cyano-β-(1-methylcyclopentyl)cinnamonitrile (**2**), which on treatment with sulfuric acid gave a low yield of 3-(1-methylcyclopentyl)-2-cyanoindenone (**3**). Treatment of **3** with sulfuric acid gave 4a-methyl-9-oxo-10-cyano-1,2,3,4,4a,9-hexahydrophenanthrene (**4**) by a rearrangement involving migration of a cyclopentyl carbon followed by a phenyl migration. The structure expected by the reverse sequence of migrations, 2′-methyl-3′-cyanospiro[cyclopentane-1,1′(4′*H*)-naphthalene]-4′-one (**5**), was eliminated as a possible structure of the product by unambiguous synthesis of its Michael cyanide adduct **6** from a known compound (the parent enone of **5**) and comparison of **6** with the Michael cyanide adduct of **4**, with which it was not identical. Attempted cyclization of compounds analogous to **2** with side chains larger than methyl (methoxymethyl, phenyl, and benzyl) was not successful.

The morphinan ring system (**1**) is contained in a number of drugs being studied for use as narcotic antagonists or nonaddictive analgetics. The synthesis of this ring system from partially saturated phenanthrenes with an angular side chain such as **2** (R = $CH_2CH_2NH_2$) has now been studied in some detail.[2–6] The known rearrangement of 3-*tert*-butyl-2-cyanoindenone to give 2-cyano-3,4,4-trimethyl-1-oxo-1,4-dihydronaphthalene,[7] which has a quaternary carbon atom, suggested the possibility of preparing compounds of type **2** by carbonium ion rearrangement of suitably substituted indenones.[8a]



1



2

The use of ylidenemalononitriles as precursors to indenones has recently been reviewed.[8a] An example[7] is the cyclization of pivalophenylidenemalononitrile to 2-cyano-3-*tert*-butylindenone, which probably involves as an intermediate an iminium species, the stability of which prevents further acid rearrangement. The ylidenes may be prepared from ketones by condensation with malononitrile, or, alternatively, by malononitrile quench of the imine salts formed by the addition of organometallic reagents to nitriles, e.g., phenyl Grignard to pivalonitrile. The latter method is especially advantageous when the required ketone would be hindered.[8b]

If two of the methyl groups of the *tert*-butyl group were linked by a two-carbon bridge, as in **3** (Scheme I), the reaction would be a possible example of a double ring expansion approach to the phenanthrene ring system. The tertiary carbo-

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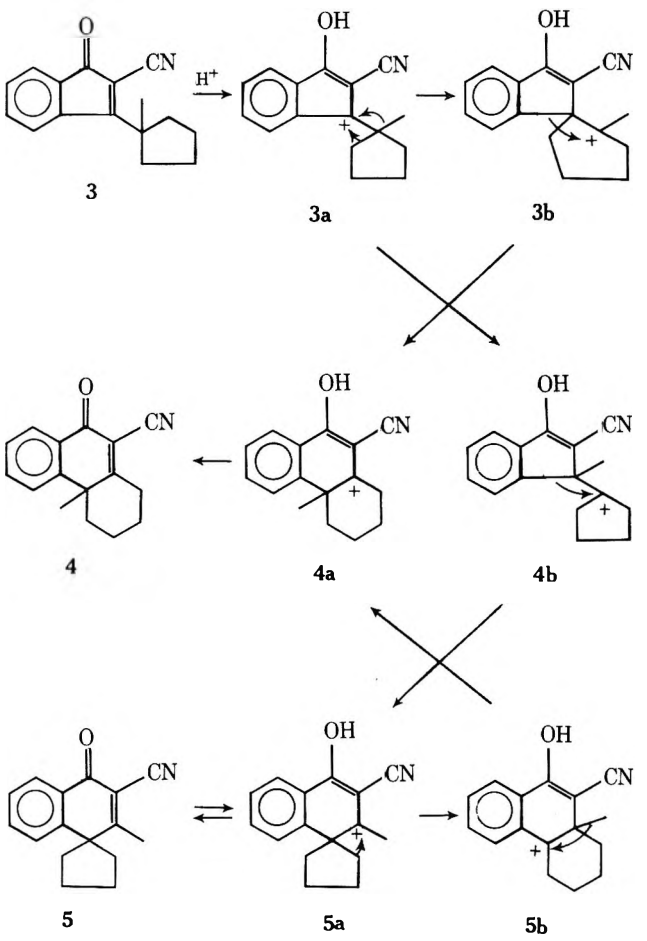
Scheme I



nium ion **3a** would be expected to undergo ring enlargement to a second tertiary carbonium ion **3b**. A second ring enlargement involving a phenyl migration would produce the protonated hydrophenanthrene structure **4a**, which by loss of a proton would give 4a-methyl-9-oxo-10-cyano-1,2,3,4,4a,9-hexahydrophenanthrene (**4**). An alternative rearrangement of **3** involving migration of the methyl group in preference to a ring carbon to give the spiro compound **5** may also be possible (Scheme I). In this case, methyl migration in carbonium ion **3a** followed by ring enlargement of the resulting carbonium ion **4b** would lead to the spiro carbonium ion **5a**, which could lose a porton to produce 2′-methyl-3′-cyanospiro[cyclopentane-1,1′(4′*H*)-naphthalen]-4′-one (**5**). Alternatively, **5a** could undergo ring enlargement to the protonated hydrophenanthrene **5b**, which by methyl migration would ultimately give the desired product **4**. Thus, compound **4** could theoretically arise by either path. However, the rearrangements **3a** → **4b** → **5** shown in Scheme I would not be expected since it is known[9] that α-methylcyclopentyl phenyl ketone rearranges quantitatively in concentrated perchloric acid to give 2-methyl-2-phenylcyclohexanone, the product arising from initial migration of a ring carbon rather than the methyl group. The rearrangement substrate **3** in Scheme I is a vinylogue of α-methylcyclopentyl phenyl ketone.

Compound **3** was prepared from 1-methylcyclopentanecarbonitrile. A recent method[10] for the preparation of 1-substituted compounds of this type using a primary nitrile, 1-chloro-4-bromobutane as the alkylating agent, and lithium diethylamide as the base in hexamethylphosphoramide was rejected due to the high cost of the alkylating agent. An earlier paper[11] describing a similar reaction with the economical 1,4-dibromobutane and sodamide reported low yields. We found that good yields of 1-methylcyclopentanecarbonitrile could be obtained by treating propionitrile with 1,4-dibromobutane and lithium diisopropylamide in tetrahydrofuran, provided the reaction was carried out at low temperatures. The structure was supported by infrared, NMR, and mass spectra, but the compound was not obtained in analytically pure form owing to traces of halide which tended to codistill. Attempted hydration[12] to the corresponding amide was not successful.

Table I. Comparison of Chemical and Physical Data of Rearrangement Substrate 3 with Product 4 and 2-Cyano-3,4,4-trimethyl-1-oxo-1,4-dihydronaphthalene

Compd	3	4	Model compd[a]
Color	Bright yellow	White	White
Mp, °C	137–138	90–91	164–165
MW (*m/e*)	237	237	
IR (KBr), μm			
C=O	5.85	6.07	6.02[b]
CN	4.54	4.51	4.44[c]
NMR, δ			
Me	1.57	1.53	1.61, 2.50
$(CH_2)_4$	1.0–3.0	1.7–2.6	
Anal. Calcd for $C_{16}H_{15}NO$:	Found:	Found:	
C, 80.98	81.04	80.88	*d*
H, 6.37	6.09	6.57	
N, 5.90	6.15	6.19	

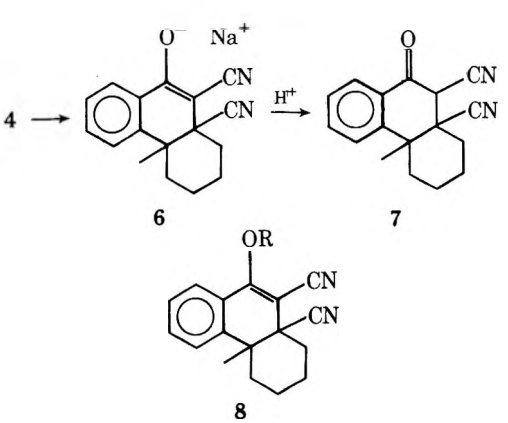
[a] E. Campaigne and D. Maulding, *J. Org. Chem.*, **28**, 1391 (1963). [b] Calculated from the published value of 1662 cm^{-1}. [c] Calculated from the published value of 2250 cm^{-1}. [d] Satisfactory elemental analyses (within 0.3%) were obtained.

Treatment of 1-methylcyclopentanecarbonitrile with phenyllithium and malononitrile[8b] gave α-cyano-β-(1-methylcyclopentyl)cinnamonitrile, which on treatment with concentrated sulfuric acid cyclized in low yield to give the target indenone **3**. The remainder of the product mixture was water-soluble sulfonated material.[13]

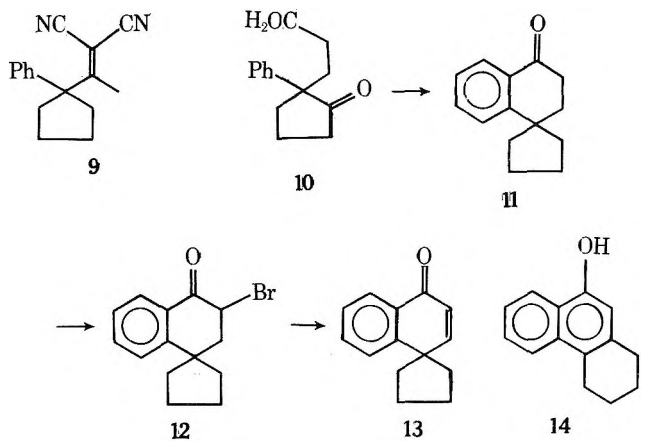
The rearrangement was carried out in good yield by treating the indenone **3** with concentrated sulfuric acid.[7] Comparison of the infrared and NMR spectra of the product with the spectra of 2-cyano-3,4,4-trimethyl-1-oxo-1,4-dihydronaphthalene suggested that it was the desired hexahydrophenanthrene **4**. The substrate, product, and model compound are compared in Table I.

Compound **4** was further characterized by conversion to derivatives. These reactions are outlined in Scheme II. Treatment of **4** with sodium cyanide in aqueous *tert*-butyl alcohol gave a product which on dilution with water remained in the aqueous layer even after extraction with ether, suggesting it to be the salt **6**. Acidification gave the dinitrile **7** in equilibrium (about 1:1 by NMR in deuteriochloroform) with its enol **8** (R = H). Kulp et al.[14] have previously reported

Scheme II



Scheme III



similar keto–enol equilibria in 2-cyanocyclohexanones, but only 6,6-disubstituted cases were included in that study. The product is surprisingly acidic, being readily soluble in 5% aqueous sodium bicarbonate with gentle warming. The enol ether 8 (R = CH_3) was prepared by treating 7 with potassium *tert*-butoxide and methyl iodide. Attempted condensation of 7 with hydrazine resulted in retro-Michael loss of hydrogen cyanide to regenerate the enone 4 in low yield amid a complex mixture of products. An attempted alternate synthesis of 4 by cyclization of the known[15] 2-methyl-2-phenylcyclohexylidenemalononitrile failed.

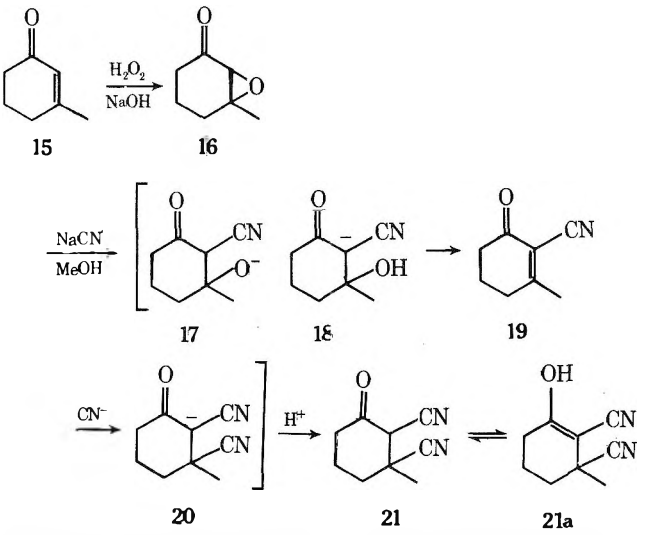
Although the structure of the acid rearrangement product of 3 was confirmed by spectra and properties of derivatives as 4, it was desirable to compare the properties of 4 with its isomer 5, an unambiguous synthesis of which was needed. An obvious approach, the cyclization of the ylidenemalononitrile 9 (Scheme III), was unsuccessful. This is in marked contrast to the behavior of the analogous compound with two methyl groups instead of a cyclopentane ring, which was successfully converted to the ketone.[7] The required ylidene 9 was made by the usual route[8b] from 1-phenylcyclopentanecarbonitrile, which in turn is available by dialkylation of phenylacetonitrile using a two-phase system.[16]

Arnold and co-workers[17] purportedly prepared the enone 13 (Scheme III) as a substrate for the dienone–phenol rearrangement, which under the conditions of the reaction gave the acetate of 14 as the product. Curiously, they did not characterize 13 at all except to obtain an elemental analysis of an oil.

This work was duplicated without difficulty up to the preparation of the bromo ketone 12, but in our hands the enone 13 always rearranged sometime before distillation could be completed, usually observable by the sudden generation of intense heat in the receiving flask and conversion of the distillate to 14. This sudden reaction is probably caused by decomposition of residual collidine hydrobromide, formed in the dehydrobromination of 12, giving gaseous hydrogen bromide which is absorbed in the distillate, and shows the sensitivity of 13 to traces of acid. This problem was circumvented by carrying out the dehydrobromination of 12 by a more recently developed method[18] using a suspension of lithium carbonate and lithium bromide in dimethylformamide. When this was done, pure enone 13 could be isolated, and the yield was somewhat better. It is in fact a solid, mp 32–34 °C, showing carbonyl absorption in the infrared spectrum at 6.00 μm and giving vinyl hydrogen signals (doublet, J = 10 Hz) in the NMR spectrum at δ 6.19 and 6.90. Interestingly, all eight cyclopentyl hydrogens are equivalent, appearing as s sharp singlet (60 MHz) at δ 2.00.

The required starting material, 2-phenylcyclopentanone, was prepared by Arnold[17] from 2-chlorocyclopentanone and phenyl Grignard. A more recent method[19] involving performic acid oxidation of 1-phenylcyclopentene followed by heating was, however, more efficient and reliable.

Scheme IV



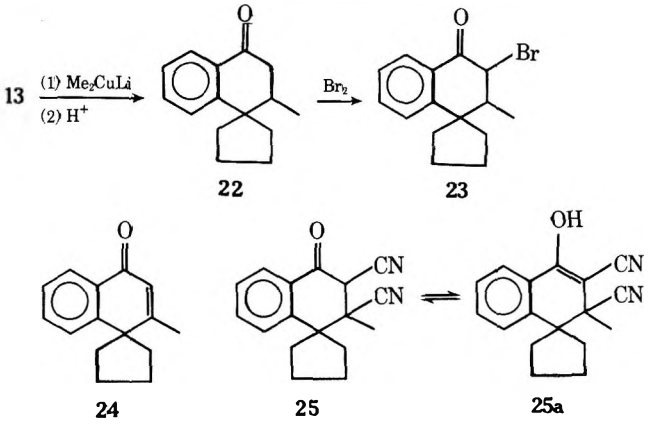
The conversion of 13 to 5 requires placement of a methyl group at the β position and a cyano group at the α position with retention of the double bond. Introduction of the methyl group at the β position by conjugate addition of lithium dimethyl copper to the enone 13 followed by regeneration of the double bond is feasible, but introduction of the cyano group at the α position seemed difficult. We therefore decided to use the enone 15 as a model substrate. Specifically, we were interested in determining whether epoxidation followed by cleavage of the epoxide ring by cyanide would lead to the keto nitrile 19 (Scheme IV).

Treatment of 15[20] with alkaline hydrogen peroxide gave the known[21] epoxide 16. When this epoxide was allowed to react with methanolic cyanide the product obtained (after acidification) was the dinitrile 21, in equilibrium with its enol 21a. The yield of this dinitrile approximately doubled if excess cyanide was used instead of 1 equiv. (Methanolysis is the competing reaction.) Thus, it is best to use at least 2 equiv of cyanide and convert all of the epoxide to dinitrile. These results can be rationalized (Scheme IV) by assuming initial reaction of cyanide at the 2 carbon to give the intermediate 17, which undergoes proton transfer owing to the presence of the acidic hydrogen now between the carbonyl and cyano groups. This new intermediate (18) suffers retro-Michael loss of hydroxide to give the desired enone nitrile 19. However, this compound, apparently an avid Michael acceptor, reacts with more cyanide ion to give 20, which an acidification gives the product.

The dinitrile 21 is strongly acidic, being easily extractable into 5% aqueous sodium bicarbonate. Crystals obtained from benzene gave an infrared spectrum (potassium bromide) that showed mostly keto form present, but an NMR spectrum (deuteriochloroform and acetone-d_6) showed it to be about 70% enolized. There are two diastereoisomers of the ketone 21. The NMR spectrum shows two broadened singlets, one at δ 4.00 and the other (about one-fourth as large) at δ 4.21, for a total of 0.3 hydrogen. We are unable to tell which signal arises from which isomer. Efforts to reverse the second cyanide addition by refluxing the dinitrile in the presence of acetic acid and triethylamine in alcohol were unsuccessful. Treatment with excess hydroxide followed by acidification was also unsuccessful. In both cases the starting material was recovered.

Treatment of 13 with lithium dimethyl copper gave the saturated methylated ketone 22 (Scheme V), which in a separate step was brominated to give 23. Dehydrobromination

Scheme V



gave the methylated enone **24**, which, in contrast to **13**, was so stable to acid that it could be recovered unchanged after being dissolved in 96% sulfuric acid. This marked difference in behavior is no doubt due to the inability of **24** to aromatize by rearrangement and indicates the rearrangement of **5** to **4** (Scheme I) is unlikely. This result was not surprising since the 3,4,4-trimethyl enone is known to be stable to acid also.[22] By coincidence, all eleven alkyl hydrogens in **24** were equivalent in the NMR (60 MHz) spectrum.

The conversion of **24** to **25** is exactly analogous to the conversion of **15** to **21** (Scheme IV). The intermediate epoxide was not isolated, but infrared spectroscopy did show a shift in the carbonyl stretch from 6.07 μm in **24** to 5.93 μm, indicating that the olefinic bond had indeed reacted.

The spiro dinitrile **25** could then be compared to the compound believed to be the hydrophenanthrene dinitrile **7** obtained by Michael addition of cyanide to **4** (Scheme II). The fingerprint regions of the infrared spectra of the two compounds were quite different, although the functional group regions were nearly identical. Comparison of the properties of the two compounds (Table II) clearly shows their nonidentity. Owing to the presence of one enol tautomer and cis and trans forms of the keto tautomer, there are three different shifts observed for the methyl group in **25**. In acetone-d_6 the compound was more than 50% enolized (by NMR). Compound **7** shows a spike in the NMR spectrum at δ 1.58 of uncertain origin. There exists the possibility that both cis and trans forms of this compound are present also, but the spike is not quite as sharp as the main peak and may merely be an alkyl signal of the ring.

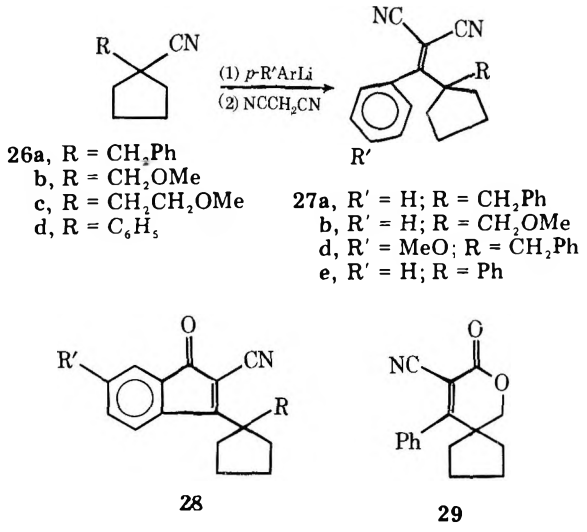
With the utility of an appropriately substituted indenone as a precursor to a hexahydrophenanthrene with an angular methyl group established, an attempt was made to extend this study to the preparation of compounds of structure **28** (Scheme VI), where the R group was larger than methyl. For such a study a variety of 1-substituted cyclopentanecarbonitriles (**26**) was required. These could most conveniently be made by alkylation of cyclopentanecarbonitrile itself.

Table II. Comparison of Chemical and Physical Data of 7 and 25

Compd	7	25
Color	White	White
MP,[a] °C	162.0–163.5	169–170
IR (KBr), μm		
C=O	5.91	5.89
CN	4.55	4.54
NMR (acetone-d_6), δ		
Me	1.71	1.52
	1.58 (spike)	1.55
		1.59
Alkyl	1.3–2.9	0.5–2.2
MW (*m/e*)	264	264
Anal. Calcd for $C_{17}H_{16}N_2O$:	Found:	Found:
C, 77.25	76.92	77.25
H, 6.10	6.03	6.15
N, 10.60	10.37	10.44

[a] The melting point of the mixture is depressed.

Scheme VI



Alkylation of this nitrile with lithium diisopropylamide and benzyl chloride, methyl chloromethyl ether, or 2-methoxyethyl chloride in tetrahydrofuran (Scheme VI) gave the desired compounds **26** in moderate yield with recovery of unchanged nitrile accounting for the balance of starting material. Satisfactory elemental analyses were obtained for the new compounds **26b** and **26c**. Compound **26a** had been previously prepared[31] from 3-phenylpropionitrile and 1,4-dibromobutane in the presence of sodamide.

Treatment of **26a** and **26b** with aryllithium reagents followed by malononitrile quench gave the expected[8b] compounds **27** in good yields, but an analytically pure sample of **26c** failed to react with phenyllithium even under conditions more vigorous than those usually used, e.g., in refluxing tetrahydrofuran. Compound **27e** was prepared from the corresponding 1-phenylcyclopentanecarbonitrile, described earlier.

Cyclization of the compounds **27a–e** using all acid catalysts known to be effective in this reaction[8] failed in every case. The lactone **29** was obtained in low yield when **27b** was treated with acid. This lactone formation from an ether is formally similar to an acid cyclization observed with ylidenemalononitriles bearing an aromatic ether oxygen.[32]

Since we were unable to obtain indenones of type **28**, other than R = methyl, we have not been able to determine whether 4a-substituted hydrophenanthrenes, with groups other than methyl at the 4a position, can be obtained by this route.

Experimental Section

Melting points were obtained on a Mel-Temp capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 137 infrared spectrometer. NMR spectra were obtained on a Varian Associates EM-360 instrument using tetramethylsilane as an internal standard. Magnesium sulfate was used as the drying agent except where otherwise indicated. Elemental analyses were performed by Midwest Microlab, Indianapolis, Indiana.

2-Phenylcyclopentanone was prepared from 1-phenylcyclopentene[19] by treatment with performic acid[19] followed by heating. The yield was 46% as a colorless liquid which was unstable on prolonged storage, bp 105–107 °C (2.2 mm) [lit.[19] bp 115–116 °C (3 mm)].

1-Phenylcyclopentanecarbonitrile. Phenylacetonitrile (0.1 mol, 11.7 g) and 0.1 mol (12.7 g) of 1,4-dichlorobutane were stirred together with 0.5 g of benzyltriethylammonium chloride briefly. Then 30 mL of 50% sodium hydroxide was added, and the mixture was stirred vigorously at 80 °C overnight. After cooling, the mixture was diluted with water and extracted with ether, and the ether layer was washed with water and brine, dried, and evaporated. The residue was distilled to give 10.1 g (59%) of product as a colorless liquid, bp 110 °C (2 mm), in agreement with the literature[16] value.

Cyclopentanecarbonitrile. Ethyl 1-cyanocyclopentanecarboxylate was prepared by alkylating ethyl cyanoacetate, substituting 1,4-dibromobutane for 1,4-dichlorobutane (*Caution!* cooling) in the published procedure,[33] which permitted a decrease in the reaction time to 24 h and gave equivalent yields. A solution of 50 g (0.3 mol) of ethyl 1-cyanocyclopentanecarboxylate and 14.7 g (0.3 mol) of NaCN in 200 mL of Me_2SO was heated at 170 °C for 2 h under reflux. The black reaction mixture was allowed to cool, diluted with three volumes of water, and extracted thoroughly with ether. The ether layers were combined, dried, and evaporated. The residue was distilled, and the fraction boiling at the literature[28] boiling point (168 °C) was collected to give 21.4 g (75%) of cyclopentanecarbonitrile as a colorless liquid which was pure by GC.

2-Methyl-2-phenylcyclohexylidenemalononitrile was prepared from 2-methyl-2-phenylcyclohexanone[14] and malononitrile by a previously published procedure.[15] The yield of 36% was duplicated, bp 155–157 °C (0.5 mm) [lit.[15] bp 150–151 °C (0.1 mm)].

1-Methylcyclopentanecarbonitrile. A solution of lithium diisopropylamide was prepared by stirring 5.6 g (0.8 mol) of lithium wire with 62.8 g (0.4 mol) of bromobenzene in 250 mL of ether with cooling for 30–45 min and then adding 40.4 g (0.4 mol) of diisopropylamine cautiously. This solution was poured slowly into a mechanically stirred solution of 22 g (0.4 mol) of propionitrile and 86.4 g (0.4 mol) of 1,4-dibromobutane in 200 mL of ether in a dry ice bath. The mixture was stirred for 1 h at dry ice temperature, for 1 h at room temperature, then cooled to dry ice temperature again, and a solution of base prepared similarly to that above was added. The mixture was stirred for 3 h in the dry ice bath and then allowed to stand overnight. The solution was quenched carefully with water, washed with water and brine, dried, and evaporated. The residue was distilled, and the fraction boiling at 59–77 °C (20 mm) was collected, giving 27.4 g (63%) of 1-methylcyclopentanecarbonitrile, 94% pure by GC; IR (film) 3.40, 4.50, little absorption beyond 7 μm; NMR (CCl_4) δ 1.40 (s, 3 H, Me), 1.5–2.3 (m, 8 H, cyclopentyl).

Anal. Calcd for $C_7H_{11}N$: 109. Found: *m/e* 109. This sample was used directly in the next step.

α-Cyano-β-(1-methylcyclopentyl)cinnamonitrile. A solution of phenyllithium was prepared by stirring 4.2 g (0.6 mol) of lithium wire with 47.1 g (0.3 mol) of bromobenzene in 200 mL of ether with cooling for 30 min. The solution was cooled to dry ice temperature, and crude 1-methylcyclopentanecarbonitrile (30 g, 0.3 mol) was added and stirred for 20 min, followed by 41 g (0.6 mol) of malononitrile added all at once quickly. The mixture was allowed to warm to room temperature and then was quenched with water, washed thoroughly with water and brine, dried, and evaporated.[8t] Recrystallization from methanol gave 16.5 g (26%) of white crystals, mp 57–58 °C; IR 3.30, 3.40, 4.53, 6.05, 6.35, 6.72, 13.40, 14.25 μm; NMR ($CDCl_3$) δ 1.2–2.3 (m, 11 H, aliphatic with methyl signal protruding at δ 1.64), 7.10–7.50 (m, 5 H, aryl).

Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85; MW 236. Found: C, 81.55; H, 6.62; N, 11.61; *m/e* 236.

2-Cyano-3-(1-methylcyclopentyl)indenone (3). α-Cyano-β-(1-methylcyclopentyl)cinnamonitrile (16 g, 68 mmol) was stirred in 120 mL of concentrated sulfuric acid at 50 °C for 15 min,[8] poured into 500 mL of ice, collected, washed with water, and recrystallized from methanol to afford 6.13 g (38%) of yellow cyrstals, mp 137–138 °C; IR (KBr) 3.45, 4.54, 5.85, 6.27, 6.42, 6.90 μm; NMR ($CDCl_3$) δ 1.57 (s, 3 H, Me), 1.7–2.6 (m, 8 H, cyclopentyl), 7.62 (s, 4 H, aryl).

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90; MW 237. Found: C, 81.04; H, 6.09; N, 6.15; *m/e* 237.

4a-Methyl-9-oxo-10-cyano-1,2,3,4,4a,9-hexahydrophenanthrene (4). A solution of **3** (7.0 g, 30 mmol) in 70 mL of concentrated sulfuric acid was stirred at room temperature for 1 h,[7] poured over ice, extracted with ether, filtered, and the residue triturated with ether, which was combined with the ether extracts. The combined ether extracts were washed with water, 5% $NaHCO_3$, and brine, dried, and evpaorated. Recrystallization of the residue (4.50 g, 65%) from cyclohexane gave white crystals, mp 90–91 °C; IR (KBr) 3.42, 4.51, 6.07, 6.24, 6.38 sh, 6.90 μm; NMR ($CDCl_3$) δ 1.0–3.0 (m, 11 H, aliphatic with methyl signal protruding at δ 1.53), 7.2–7.8 (m, 3 H, aryl), 8.31 (d, J = 7 Hz, 1 H, aryl *peri*- to C=O). It was found that traces of acid present during recrystallization caused decomposition, and it was necessary to wash the crude product several times before recrystallization was carried out.

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90; MW 237. Found: C, 80.88; H, 6.57; N, 6.19; *m/e* 237.

4a-Methyl-9-oxo-10,10a-dicyano-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (7). A mixture of 80 mL of *tert*-butyl alcohol, 20 mL of water, 4.6 g (20 mmol) of **4** and excess (1.5 g) sodium cyanide was refluxed overnight.[23] Most of the solvent was then evaporated, and the residue was cooled, acidified with acetic acid, and extracted quickly with ether. The ether layers were washed with water and brine, dried, and evaporated. Recrystallization of the residue with cyclohexane and a little chloroform resulted in a gummy oil that deposited on cooling, which on addition of a few drops of chloroform with stirring gave 4.61 g (90%) of a fine white powder, mp 162.0–163.5 °C; IR (KBr) 3.1 brd, 3.45, 4.55 s, 5.91 w, 6.15 s, 6.40, 6.77 μm; NMR ($CDCl_3$) δ 1.5–2.5 (m, 11 H, alkyl), 4.67 (s, 0.5 H, H adjacent to C=O), 5.35 (low and rounded, 0.5 H, enolic) 7.5–8.5 (m, 4 H, aryl).

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60; MW 264. Found: C, 76.92; H, 6.03; N, 10.37; *m/e* 264.

Retro-Michael Reaction of 7 to 4. A solution of 1.04 g (4 mmol) of **7** and excess (2.00 g) hydrazine hydrate in 60 mL of ethanol was heated to reflux. Then a small drop of acetic acid was added, and the reflux was continued overnight. The ether extract of the cooled solution was washed with brine, dried with K_2CO_3, and evaporated. The residue was purified by column chromatography (silica gel, chloroform) to give 0.50 g (49%) of **4** as the first material off with spectra and melting point similar to those given above.

4a-Methyl-9-methoxy-10,10a-dicyano-1,2,3,4,4a,10a-hexahydrophenanthrene (8). To a solution of 1.04 g (4 mmol) of **7** in 50 mL of Me_2SO was added excess (1.6 g) methyl iodide and 0.008 mL (0.96 g) of potassium *tert*-butoxide. After stirring overnight at room temperature, the mixture was diluted with three volumes of water and extracted with ether. The ether extracts were washed with water and brine, dried, and evaporated. Recrystallization of the residue from methanol gave 0.59 g (54%) of white crystals, mp 118.5–119.0 °C; IR (KBr) 3.44, 4.56, 6.20, 6.41 μm; NMR ($CDCl_3$) δ 1.2–2.5 (m, 11 H, alkyl), 4.31 (s, 3 H, MeO), 7.3–8.1 (m, 4 H, aryl).

Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.37; H, 6.52; N, 10.06; MW 278. Found: C, 77.47; H, 6.62; N, 10.35; *m/e* 278.

α-Cyano-β-(1-phenylcyclopentyl)crotononitrile (9). In 20 mL of THF cooled to −78 °C was placed 0.02 mol (11.8 mL of 1.7 M solution) of methyllithium followed by 3.42 g (20 mmol) of 1-phenylcyclopentanecarbonitrile. After stirring for 20 min at room temperature, the mixture was cooled again and excess (2.7 g) malononitrile was added all at once quickly. After the usual workup[8b] the residue was distilled to give 2.15 g (46%) of a colorless, viscous oil, bp 134–136 °C (0.07 mm); IR 3.40, 4.51 s, 6.32, 6.71, 13.50, 14.30 μm; NMR ($CDCl_3$) δ 1.2–2.9 (m, 11 H, alkyl with methyl singlet protruding at δ 2.26), 7.40 (s, 5 H, aryl).

Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85; MW 236. Found: C, 81.11; H, 6.94; N, 11.92; *m/e* 236.

Spiro[cyclopentane-1,1′(2′*H*,3′*H*,4′*H*)-naphthalen]-4′-one (11). This material was prepared from 2-phenylcyclopentanone as previously reported[17] without isolation of the intermediate **10** or its reduction product. The overall yield was 40%, obtained as a colorless, neutral liquid, bp 149–150 °C (3 mm) [lit.[17] bp 131–132 °C (2 mm)]; IR 3.41, 5.92, 6.25, 6.80 μm; NMR (CCl_4) δ 1.82 (m, 10 H, alkyl), 2.56 (distorted t, 2 H, J = 6 Hz, α-CH_2), 7.30 (m, 3 H, aryl), 7.93 (m, 1 H, *peri*-).

3′-Bromospiro[cyclopentane-1,1′(2′*H*,3′*H*,4′*H*)-naphthalen]-4′-one (12). Treatment of **11** in carbon tetrachloride with bromine vapor in a nitrogen stream[17] gave this compund in nearly quantitative yield, obtained as white crystals from methanol (*irritant!*), mp 54.0–54.5 °C (lit.[17] mp 54–55 °C); NMR ($CDCl_3$) δ 1.90 (m, 8 H, cyclopentyl), 2.60 (d, 2 H, J = 9 Hz, CH_2), 5.09 (t, 1 H, J = 9 Hz, α-H),

7.2–7.7 (m, 3 H, aryl), 8.12 (m, 1 H, *peri*-).

Spiro[cyclopentane-1,1′(4′*H*)-naphthalen]-4′-one (13). To a solution of 5.60 g (20 mmol) of **12** in 100 mL of DMF was added 16 g of lithium bromide and 10 g of lithium carbonate.[18] The resulting suspension was stirred at 100 °C overnight under nitrogen, cooled, poured into water, and extracted with ether. The ether was washed with brine, dried, and evaporated. Distillation of the residue gave 3.18 g (80%) of **13** as a colorless oil, which crystallized when scratched after standing in the refrigerator overnight, bp 140 °C sharp (1.3 mm) [lit.[17] bp 147 °C (2 mm)]; mp 32–34 °C; IR 3.40, 6.00, 6.13, 6.24, 6.76 μm; NMR ($CDCl_3$) δ 2.00 (s, 8 H, cyclopentyl), 6.19 (d, 1 H, J = 10 Hz, vinyl), 6.90 (d, 1 H, J = 10 Hz, vinyl), 7.41 (m, 3 H, aryl), 8.10 (broadened d, 1 H, J = 7 Hz, *peri*-).

3-Methylcyclohex-2-enone (15). Using technical formaldehyde, a yield of 43% of **15** was obtained by the published procedure[20] as a colorless liquid, bp 82–84 °C (12.3 mm) [lit.[20] bp 195–202 °C].

6-Methyl-2-oxo-7-oxabicyclo[4.1.0]heptane (16). The epoxidation method described by Wasson and House[25] (alkaline hydrogen peroxide in methanol) was applied to **15.** The reaction time was shortened from 3 to 1.5 h, to give 58% of **16** as a colorless liquid, bp 80–82 °C (12.4 mm) [lit.[21] bp 201–202 °C].

3-Methyl-2,3-dicyanocyclohexanone (21). To 5.0 g (0.1 mol) of sodium cyanide in 100 mL of methanol at room temperature was added 6.3 g (50 mmol) of **16.** The mixture was refluxed for 2 h, after which most of the solvent was evaporated (the salt **20** precipitated), and the residue was diluted with water. The aqueous solution was washed with ether to remove any neutral impurities and then acidified. The ether extract of the acidified solution was washed with water and brine, dried, and evaporated. Recrystallization of the residue from benzene gave 4.6 g (57%) of **21** as an almost white powder, mp 106–107 °C; IR (KBr) 2.92, 3.40, 4.47, 5.82, 6.1 sh μm; NMR ($CDCl_3$ with some acetone-d_6) δ 1.5–2.9 (m, 9 H, alkyl with methyl signal protruding at δ 1.66), 4.00 (brd s, 0.2–0.3 H, α-H), 4.21 (brd s, 0.1 H, α-H), 7.4–8.0 (low, rounded, 0.7 H, OH of enol).

Anal. Calcd for $C_9H_{10}N_2O$: C, 66.64; H, 6.21; N, 17.28; MW 162. Found: C, 66.49; H, 6.12; N, 17.38; *m/e* 162.

2′-Methylspiro[cyclopentane-1,1′(2′*H*,3′*H*,4′*H*)-naphthalen]-4′-one (22). To a suspension of 3.81 g (20 mmol) of cuprous iodide in 100 mL of dry ether at 0 °C under nitrogen was added methyllithium (1.7 M solution in ether) until a clear solution was obtained. A few crystals of cuprous iodide were then added to ensure[26] the absence of excess methyllithium (a yellow precipitate of methylcopper was observable), and the mixture was then stirred an additional 15 min at 0 °C. The enone **13** (0.01 m, 198 g) was then added in a little ether (a transient reddish color was observed on contact), and the resulting yellow mixture was stirred at 0 °C for 1 h. The mixture was quenched by pouring it into 10% aqueous ammonia, and the separated ether layer was washed with 10% aqueous ammonia and brine, dried, and evaporated. Distillation of the residue gave 2.0 g (93%) of **22** as a colorless oil, bp 137–139 °C (1.5 mm); IR 3.40, 5.90, 6.27, 6.80 μm; NMR (CCl_4) δ 0.7–3.2 (m, 12 H, alkyl with methyl doublet, J = 7 Hz, protruding at δ 0.90 and doublets, J = 5 Hz, protruding at δ 2.47 and 2.70 from the CH_2 adjacent to the carbonyl), 7.1–7.6 (m, 3 H, aryl), 7.85–8.15 (m, 1 H, *peri*-).

Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47; MW 214. Found: C, 83.81; H, 8.31; *m/e* 214.

2,4-dinitrophenylhydrazone derivative: orange crystals from ethanol and ethyl acetate, mp 166.0–166.5 °C.

2′-Methyl-3′-bromospiro[cyclopentane-1,1′(2′*H*,3′*H*,4′*H*)-naphthalen]-4′-one (23). The same method used to obtain **12** was applied to **22.** From 1.07 g (5 mmol) of **22** was obtained 1.54 g of crude product as an oil. Recrystallization of a sample from methanol gave nearly white crystals of **23,** mp 53–54 °C; IR (KBr) 3.40, 5.87, 6.24, 6.80 μm; NMR ($CDCl_3$) δ 1.08 (d, 3 h, J = 7 Hz, Me), 1.6–2.8 (m, 9 H, alkyl), 5.40 (d, 1 H, J = 4 Hz, α-H), 7.1–7.7 (m, 3 H, aryl), 7.9–8.2 (m, 1 H, *peri*-).

Anal. Calcd for $C_{15}H_{17}BrO$: C, 61.44; H, 5.85; Br, 27.26; MW 293. Found: C, 61.43; H, 5.90; Br, 26.98; *m/e* 293.

2′-Methylspiro[cyclopentane-1,1′(4′*H*)-naphthalen]-4′-one (24). The same method used to obtain the enone **13** was applied to **23.** From 1.1 g of crude **23** was obtained 0.63 g (80%) of **24.** A portion was recyrstallized from hexane with difficulty to give light yellow crystals, mp 65.6–66.5 °C; IR (KBr) 3.40, 6.07, 6.26, 6.87 μm; NMR ($CDCl_3$) δ 2.12 (s, 11 H, alkyl), 6.32 (s, 1 H, vinyl), 7.3–7.7 (m, 3 H, aryl), 8.1–8.3 (m, 1 H, *peri*-).

Anal. Calcd for $C_{15}H_{16}O$: C, 84.86; H, 7.60; MW 212. Found: C, 84.52; H, 7.45; *m/e*212.

2′-Methyl-2′,3′-dicyanospiro[cyclopentane-1,1′(2′*H*,3′*H*,4′*H*)-naphthalen]-4′-one (25). The enone **24** was treated with alkaline hydrogen peroxide,[25] and the crude epoxide was then treated with sodium cyanide by the same procedure used to obtain the dinitrile **21.** From 0.38 g of crude **24** was obtained, after recrystalization from cyclohexane with a little chloroform, 0.16 g (34%) of **25** as white crystals, mp 169–170 °C; IR (KBr) 3.1–3.2, 3.40, 4.54, 5.89, 6.19, 6.40, 6.80 μm; NMR (acetone-d_6) δ 0.6–2.2 (m, 11 H, alkyl with methyl signals protruding at δ 1.52, 1.55, and 1.59), 4.70 (brd s, 0.2 H, α-H), 6.8–7.7 (m, 4 H, aryl).

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60; MW 264. Found: C, 77.25; H, 6.15; N, 10.44; *m/e* 264.

1-Benzylcyclopentanecarbonitrile (26a). A solution of 1.9 g (20 mmol) of cyclopentanecarbonitrile and 2.53 g (20 mmol) of benzyl chloride in THF (50 mL) was cooled to −78 °C under nitrogen. A solution of lithium diisopropylamide, prepared by adding 2.02 g (20 mmol) of diisopropylamine to 0.02 mol of butyllithium (12.5 mL of 1.6 M solution in hexane) in 20 mL of THF, was cooled to −78 °C in a separate vessel. The solutions were quickly mixed, and the resulting mixture was kept at −78 °C for 3 h and then allowed to stand at room temperature overnight. The mixture was quenched with water, washed with brine, dried, and evaporated. Distillation of the residue gave 2.24 g (61%) of **26a** as a colorless liquid, bp 127–129 °C (2.8 mm) [lit.[31] bp 155–157 °C (12 mm)]; IR 3.30, 3.39, 4.47, 6.24, 6.70, 13.10, 14.26 μm; NMR (CCl_4) δ 1.80 (brd s, 8 H, cyclopentyl), 2.81 (s, 2 H, benzylic), 7.25 (s, 5 H, aryl).

1-Methoxymethylcyclopentanecarbonitrile (26b). By the above method using 1.61 g (20 mmol) of methyl chloromethyl ether as the halide was obtained 0.87 g (31%) of **26b** as a colorless liquid, bp 106–108 °C (20 mm); IR 3.40, 4.49, 9.0 μm; NMR (CCl_4) δ 1.82 (brd s, 8 H, cyclopentyl), 3.35 and 3.40 (overlapping s, 5 H, Me and CH_2).

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06; MW 139. Found: C, 68.83; H, 8.92; N, 9.80; *m/e* 139.

1-Methoxyethylcyclopentanecarbonitrile (26c). By the above method using 1.90 g (20 mmol) methyl 2-chloroethyl ether (prepared from the corresponding alcohol with phosphorus trichloride[34]) was obtained 1.00 g (33%) of **26c** as a colorless liquid of 98% purity by GC, bp 118–120 °C (20 mm); IR 3.40, 4.50, 8.9 μm; NMR δ 1.3–2.4 (m, 10 H, cyclopentyl and branch CH_2), 3.33 (s, 3 H, Me), 3.59 (t, 2 H, J = 7 Hz, CH_2O).

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14; MW 153. Found: C, 70.39; H, 9.85; N, 9.20; *m/e* 153.

α-Cyano-β-(1-benzylcyclopentyl)cinnamonitrile (27a). Phenyllithium was generated by stirring 0.02 mol (12.50 mL of a 1.6 M solution) of butyllithium in hexane with 3.14 g (20 mmol) of bromobenzene in 20 mL of THF at −78 °C for 15 min. Then 3.70 g (20 mmol) of **26a** was added, and the mixture was stirred for 20 min without any outside cooling, cooled again to −78 °C, and quenched with 2.7 g (40 mmol) of malononitrile.[8b] The solution was allowed to warm to room temperature and then quenched with water, washed with brine, dried, and evaporated. Recrystallization of the residue from methanol gave 3.81 g (61%) of **27a** as white needles, mp 115–116 °C; IR (KBr) 3.41, 4.50, 6.45, 6.75, 13.19, 13.90, 14.35 μm; NMR ($CDCl_3$) δ 1.5–2.3 (m, 8 H, cyclopentyl), 3.27 (s, 2 H, benzyl), 6.44 (m, 2 H, aryl ortho on one of the rings), 7.34 (m, 8 H, aryl).

Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97; MW 312. Found: C, 84.38; H, 6.27; N, 8.97; *m/e* 312.

α-Cyano-β-(1-methoxymethylcyclopentyl)cinnamonitrile (27b). By the above method using 2.78 g (20 mmol) of **26b, 27b** was obtained (3.85 g, 72%) as white crystals from methanol, mp 99–100 °C; IR (KBr) 3.50, 4.54, 6.45, 6.80, 13.15, 13.99, 14.35 μm; NMR ($CDCl_3$) δ 1.5–2.2 (m. 8 H, cyclopentyl), 3.45 (s, 3 H, MeO), 3.67 (s, 2 H, CH_2O), 7.2–7.7 (m, 5 H, aryl).

Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.51; MW 266. Found: C, 76.32; H, 6.54; N, 10.28; *m/e* 266.

α-Cyano-β-(1-benzylcyclopentyl)-*p*-methoxycinnamonitrile (27d). By the method used for the preparation of **27a** using 3.74 g (20 mmol) of *p*-bromoanisole instead of bromobenzene was obtined 5.06 g (74%) of **27d** as white crystals from ethanol, mp 125.0–125.5 °C; IR (KBr) 3.40, 4.50, 6.25, 6.70 μm; NMR ($CDCl_3$) δ 1.7–2.5 (m, 8 H, cyclopentyl), 3.35 (s, 2 H, benzyl), 3.85 (s, 3 H, MeO), 6.43 (d, 2 H, J = 8 Hz, aryl ortho to MeO), 6.88 (d, 2 H, J = 8 Hz, aryl ortho to C═C), 7.5–8.0 (m, 5 H, aryl).

Anal. Calcd for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.47; N, 8.18; MW 342. Found: C, 80.83; H, 6.72; N, 8.00; *m/e* 342.

α-Cyano-β-(1-phenylcyclopentyl)cinnamonitrile (27e). By the method used for the preparation of **27a** using 1-phenylcyclopentanecarbonitrile (**26d**) instead of **26a** was obtained 2.30 g (39%) of **27e** as white crystals from methanol (after previously heating the crude product under vacuum), mp 87.5–88.5 °C; IR 3.40, 4.50, 6.40, 6.75 μm; NMR ($CDCl_3$) δ 1.4–2.7 (m, 8 H, cyclopentyl), 6.8–7.6 (m, 10 H, aryl).

Anal. Calcd for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39; MW 298. Found: C, 84.76; H, 5.73; N, 9.56; *m/e* 298.

β-(1-Hydroxymethylcyclopentyl)-α-cyano-*trans*-cinnamic Acid Lactone (29). A solution of 1.00 g (3.8 mmol) of **27b** in 7 mL of concentrated sulfuric acid was maintained at 50 °C for 15 min and then poured over ice. The combined organic layers from benzene and THF extractions were washed with 5% $NaHCO_3$, dried, and evaporated. Recrystallization of the residue from methanol gave 0.11 g (12%) of **29** as white crystals, mp 166.0–167.5 °C; IR (KBr) 3.41, 4.51, 5.81, 6.30, 6.85, 13.29, 14.15 μm; NMR ($CDCl_3$) δ 1.78 (s, 8 H, cyclopentyl), 4.31 (s, 2 H, CH_2), 7.2–7.7 (m, 5 H, aryl).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53; MW 253. Found: C, 75.73; H, 5.79; N, 5.80; *m/e* 253.

Registry No.—**3,** 64871-55-2; **4,** 64871-56-3; **7,** 64871-57-4; **8,** 64871-58-5; **9,** 64871-59-6; **11,** 4889-95-6; **12,** 64871-60-9; **13,** 64871-61-0; **15,** 1193-18-6; **16,** 21889-89-4; **21,** 64871-62-1; **22,** 64871-63-2; **22**-DNP, 64871-64-3; **23,** 64871-65-4; **24,** 64871-72-3; **25,** 64871-73-4; **26a,** 64871-66-5; **26b,** 64871-74-5; **26c,** 64871-75-6; **26d,** 77-57-6; **27a,** 64871-76-7; **27b,** 64871-77-8; **27d,** 64871-78-9; **27e,** 64871-67-6; **29,** 64871-68-7; phenylacetonitrile, 140-29-4; 1,4-dichlorobutane, 110-56-5; cyclopentanecarbonitrile, 4254-02-8; ethyl 1-cyanocyclopentanecarboxylate, 28247-14-5; 1,4-dibromobutane, 110-52-1; 2-methyl-2-phenylcyclohexylidenemalononitrile, 64871-69-8; 1-methylcyclopentanecarbonitrile, 64871-70-1; propionitrile, 107-12-0; α-cyano-β-(1-methylcyclopentyl)cinnamonitrile, 64871-71-2; phenyllithium, 591-51-5; malononitrile, 109-77-3; sodium cyanide, 143-33-9; methyl iodide, 74-88-4; benzyl chloride, 100-44-7; methyl chloromethyl ether, 107-30-2; methyl 2-chloroethyl ether, 627-42-9; bromobenzene, 108-86-1; *p*-bromoanisole, 104-92-7.

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Ring Expansions of Medium-Sized Ring Potassium Alkoxides. Unusually Fast [1,3]Sigmatropic Shifts

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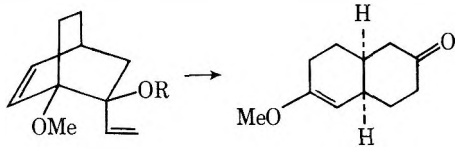
A series of cyclic 1-vinyl alcohols having either a double bond or a benzo group at the 3 position were rearranged under the influence of potassium hydride to the ring-expanded ketones, e.g., 1-vinylcyclonon-3-en-1-ol to 5-cycloundecenone. In hexamethylphosphoric triamide (HMPT) or dimethoxyethane (DME)/18-crown-6 media, the [1,3]sigmatropic shifts take place at room temperature. 1-Cyclopropyl analogues undergo ring cleavage rather than rearrangement.

Evans and Golob recently reported[1] that the bicyclic oxy-Cope system (1) underwent a [3,3]sigmatropic rearrangement



1a, R = H
b, R = K

at an enormously enhanced rate when treated with potassium hydride in tetrahydrofuran (THF) or HMPT. The epimer of **1**, where the geometry precludes a concerted 3,3-shift process, was reported to not rearrange when treated with potassium hydride in refluxing THF. Although [1,3]sigmatropic shifts are possible for **1** and its epimer, none were reported. It was not clear whether 1,3 shifts should be enhanced since they generally show activation parameters that are more suggestive of a nonconcerted process than is the case for 3,3-shift processes.[2,3] We have subsequently found that 1,3 shifts in oxy-Cope[4] systems are enhanced under appropriate conditions.[4,5]

Our previous studies[2,6,7] have shown that 1-trimethylsiloxy-1-vinyl-3-cycloalkenes, **2** (R = $SiMe_3$), undergo thermal rearrangements at 240–300 °C which lead mainly to two-carbon ring expansion products, **3** and **4**, except for **2d**, where the 3,3-shift product **5** predominates.

We now report the reactions of the potassium alkoxides of these and the related systems **6** and **8** in highly dissociating media.

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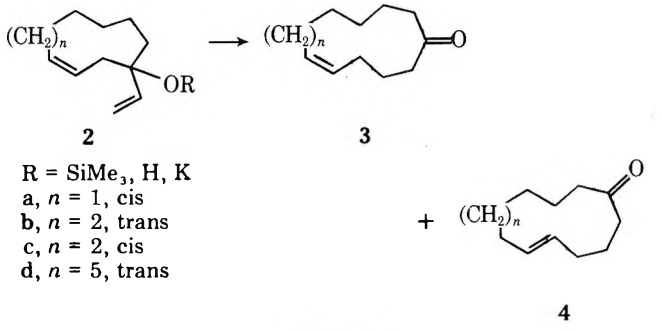
Table I. Products Resulting from Treatment of 1-Vinylcycloalk-3-en-1-ols with Potassium Hydride[a]

Compd	Registry no.	Time, h	Temp, °C	Solvent	Product, % 2	3	4	5	Acidic product, %	$\sim t_{1/2}$,[d] h
2a	31925-18-5	1.5	25	HMPT	5	30	19	6	5	0.67
		2.75	25	HMPT	1	34	20	7	7	
		2.75	25	HMPT[b]	2	36	23	7	3	
		5.5	25	HMPT	0	28	14	7	9	
		17	25	DME[c]	0	30	1	2	16	5
		2	66	THF	67	–	–	–	?	
2b	51284-48-1	3	25	HMPT	2	0	57	8	8	0.77
		14	25	DME[c]	3	0	39	7	?	
		183	66	THF	0	0	29	2	?	139
2c	51284-49-2	27.5	25	HMPT	11	31	0	0	10	15.7
2d	57969-16-1	4.5	60	HMPT	0	0	9	61	8	

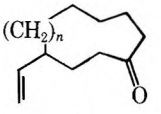
[a] The percentages of **2, 3, 4,** and **5** represent yields determined in triplicate by GLC by adding a known weight of internal standard. The percent of acidic product was determined by actual weight recovered by basic extraction, correcting for solvent by NMR. [b] HMPT was degassed by the freeze–thaw method. [c] A 1.1-equiv amount of 18-crown-6 was also present. Similar results were obtained with THF and added crown ether. [d] The approximate half-life was obtained by measuring the time when the volatile products peak areas equaled the peak area for the starting alcohol. This does not take into account the loss of starting material or products by other pathways. Reasonably good first-order plots were obtained in HMPT.



2 **3**

R = $SiMe_3$, H, K
a, n = 1, cis
b, n = 2, trans
c, n = 2, cis
d, n = 5, trans

4



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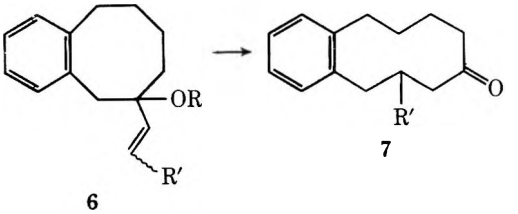
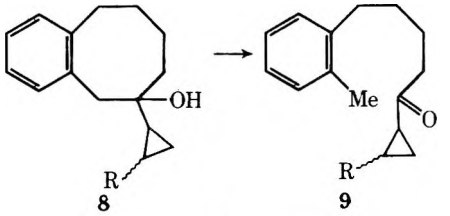


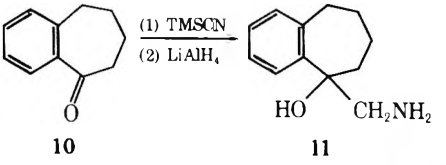
6 **7**

a, R = $SiMe_3$; R′ = H
b, R = H; R′ = H
c, R = H; R′ = CH=CH_2
d, R = H; R′ = CH=$CHCH_3$

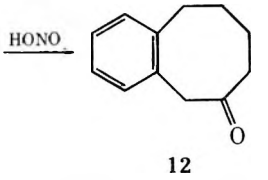


8 **9**

a, R = H
b, R = CH=CH_2



10 **11**



12

Results

The syntheses of **2a–d** have been reported previously.[2,6,7] The syntheses of **6** and **8** are somewhat more challenging because relatively few effective routes to benzo-substituted medium-sized rings are available.[8] In this work, benzosuberone (**10**) was converted to the amino alcohol **11** using trimethylsilyl cyanide (TMSCN) followed by lithium aluminum hydride reduction.[9] Although yields of ca. 80% were realized with either potassium cyanide/18-crown-6 complex or zinc iodide catalysts, the yields with zinc iodide were less reproducible. Treatment of **11** with nitrous acid gave highly preferential aryl migration, leading to ketone **12** with less than 7% of the α-keto isomer[10] that would result from alkyl migration. The expansion of **10** to **12** was also carried out by adding dibromomethyllithium to the carbonyl of **10** followed by treatment with butyllithium.[11] Formation of **12** was highly selective, but the overall yields were erratic and at best 50% for that method. Conversion of **12** to **6** or **8** followed normal Grignard procedures, except as indicated below. For the diene cases (**6**, where R′ = CH=CH_2 and CH=$CHCH_3$) the acetylenic lithium reagent, generated from butenyne or pent-3-en-1-yne, was added, and the triple bond was reduced to a mixture of cis–trans double-bond isomers using lithium aluminum hydride. Formation of cis and trans isomers parallels one earlier result;[12] however, several earlier systems have been reported to give only the trans isomer.[13] Attempts to generate pure cis isomer by reduction with Lindlar catalyst failed even though the catalyst was demonstrated to give clean monoreduction with phenylacetylene. For the case of **8** where R = CH=CH_2, vinylcyclopropyllithium[14] was used rather than the Grignard reagent.

Alcohols **2a–d** (R = H) were rearranged by treatment with potassium hydride in highly dissociating media, viz., HMPT or 18-crown-6 with either dimethoxyethane (DME) or tetrahydrofuran (THF), with the results shown in Table I. The structures of **3a–d, 4a–d,** and **5a–d** were assigned by GLC and spectral comparisons with samples assigned in earlier work.[2,6,7] For the medium-sized rings **2a–c,** the predominant process is a 1,3-shift ring expansion leading to **3** and/or **4.** In contrast, the large ring system **2d** rearranges principally by the 3,3 process, leading to **5.** A substantial loss of double-bond stereochemistry is observed for the nine-membered ring case

Table II. Rearrangements of 6-Vinyl-7,8,9,10-tetrahydro-6(5*H*)-benzocyclooctenol (6) and Related Compounds[a]

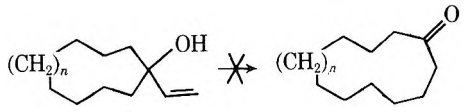
Compd	Conditions	Product, % 6	7	14	15	Acidic product, %
6a	350 °C, 9.75 h	13	31	–	–	–
	350 °C, 11 h	16	47	–	–	–
	350 °C, 24 h	4	9	14	–	–
6b	KH, HMPT, 25 °C, 5.5 h	3	56	–	–	5
	KH, DME,[b] 25 °C, 174 h	15	27	–	–	43
	KH, THF, 66 °C, 26.3 h	1	–	–	55[c]	*d*
6c	KH, HMPT, 25 °C, 3.92 h		20	–	–	*d*
6d	KH, HMPT, 25 °C, 4.5 h		33	–	–	3

[a] The percentages of **6, 7, 14,** and **15** are determined as in footnote *a*, Table I. *b* See footnote *c*, Table I. [c] Only one yield determination was made. A variety of other minor products were also formed (each <10%). [d] No analysis was made for acidic products.

2a, but no such loss is seen for the ten-membered ring cases **2b** and **2c** (see later discussion).

The yield of products **3–5** generally did not exceed 60%, partly because some sodium bicarbonate soluble material is usually formed. In one experiment where the solvent was degassed, the yield of this material decreased, suggesting a known process[15] in which adventitious oxygen in the presence of strong base in highly dissociating media oxidatively cleaves ketones to diacids. The spectral properties are consistent with such diacids, but the mixtures were too complex to assign further. The benzo analogue **6b** gave a clear example of this process (see below). Most of the remaining byproducts were nonvolatile, although a dimeric molecular weight (*m/e* 332) was observed in the mass spectrum for a long retention-time GLC peak from **2a,** suggesting "aldol" side reactions of the ketone products.

Unsaturation homoallylic to the hydroxyl appears to be critical to the rearrangement process. The saturated analogues of the above systems, i.e., **13a** and **13b,** were treated with po-



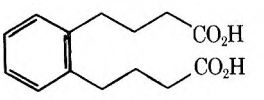
13a, $n = 1$
b, $n = 2$

tassium hydride in HMPT at room temperature for 4 h and 24 h, respectively, but gave no cyclododecanone or cycloundecanone.

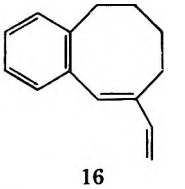
The rearrangements of the previously unstudied benzo eight-membered ring cases **6a–d** are shown in Table II. The thermal rearrangement of **6a** to ketone **7** is clean since no 3,3 shift or geometric isomerism is possible, but the yield for the thermal isomerization was low, presumably because of the stringent conditions necessary to induce reaction. If the reaction was pushed to completion, unidentified shorter retention-time material (**14**) was also formed. The structural assignment for **7** is based largely on the NMR spectrum; viz., the relatively narrow four-proton aromatic band indicates that the substituents remain ortho and that the carbonyl is not α to the aromatic ring, the overlapping multiplets at ca. δ 2.7 indicate two benzylic methylenes and rule out a β-carbonyl, and the lack of terminal methyl peaks supports the ten-membered ring structure. The 1700-cm^{-1} IR band also supports the lack of a conjugated system. Shift reagent studies were undertaken to rule out the possibility that the carbonyl could be γ to the aromatic ring, which would leave the δ position as the only possible structure. Unfortunately, the shift reagents caused excessive peak broadening with either **7** or the corresponding alcohol such that no useful data could be obtained. Structure **7** has thus been assigned as the δ-carbonyl structure shown rather than the γ-carbonyl isomer from two chemical reactions: (1) the thermal 1,3-shift reaction has precedent in very similar systems, whereas a mechanism leading to a γ-carbonyl isomer is not obvious, and (2) oxidative cleavage (see below) leads mainly to *o*-benzenedibutanoic acid, which is only possible from the δ-carbonyl structure **7.**

Treatment of **6b** with potassium hydride in HMPT gave **7** in somewhat better yield than the thermal process. As in the earlier cases some acidic material was formed along with some nonvolatile product. When DME was used along with 18-crown-6 and potassium hydride the reaction was much slower and the cleavage to acidic products was much more pronounced. Fortunately, crystallization of the acidic material led to isolation of a pure diacid **15,** which could be assigned the *o*-benzenedibutanoic acid structure from the high degree of symmetry evident in the clean four-proton methylene patterns in the NMR spectrum. This presumably results from the known[15] oxidative cleavage α to ketone groups by adventitious oxygen under these conditions. In principle, cleavage could take place on either side of the carbonyl group, which would lead to **15** and an unsymmetrical diacid; however, since the crude diacid NMR spectrum looks nearly the same as recrystallized **15,** the cleavage must be highly selective.

The anionic rearrangements of all the above systems normally require either HMPT or 18-crown-6; however, Table I shows one case, system **2b** (R = K), that rearranges in THF alone at reflux temperature. Under the same conditions, **6b** gave an unusual result; viz., it eliminated water, forming **16.**



15



16

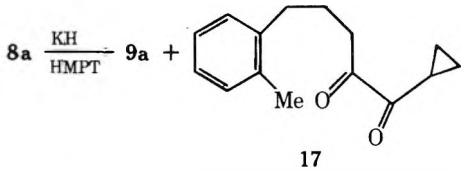
The structure of **16** follows from the UV and NMR spectra, in particular the coupling patterns of the vinyl protons.

The successful two-carbon ring expansion of **6b** prompted investigation of possible four-carbon ring expansions of **6c** and **6d.** A mixture of cis and trans isomers was used, recognizing that a concerted 1,5 shift is only possible for the cis isomer. In the event, only 1,3-shift products (**7c** and **7d**) were observed from **6c** and **6d** upon treatment with potassium hydride in HMPT. The NMR spectrum of **7c** clearly shows the characteristic terminal vinyl group coupling. For **7d** the NMR spectrum plus decoupling experiments clearly showed the two vinyl protons with couplings to a methyl and a single proton. Shift reagent studies were attempted to further substantiate the structural assignments, but no decisive evidence could be obtained. The structures shown are fully consistent with the spectral data and are mechanistically reasonable; however, the data do not completely rule out the vinyl or propenyl groups being attached at another carbon on the ring.

Since **7c** and **7d** showed no propensity toward further rearrangement under anionic conditions, the gas phase thermal rearrangements of **7d** were examined. Stringent conditions (350 °C, 5 h) were required to effect rearrangement, and the

yields were extremely low (<1%). Two rearranged ketones were formed in a 2:1 ratio; the major ketone showed spectral data that is consistent with a 1,3-shift product, but no definite assignment could be made. Thermal rearrangements of the trimethylsilyl derivatives of **6c** and **6d** were also examined in the 260–350 °C range, but only low yields of complex mixtures were obtained.

Possible three- or five-carbon ring expansions were also examined for **8a** and **8b**, respectively. Unfortunately, treatment of either **8a** or **8b** with HMPT/KH gave no ring expanded ketone products, but rather gave only cleavage (ca. 30% yield) to the open-chain ketones **9a** and **9b**. In the case of **8a**, formation of dione **17** was also observed in variable



17

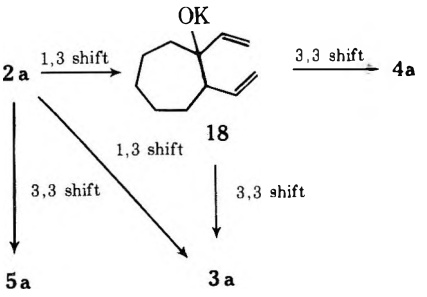
amounts, presumably depending on the amount of adventitious oxygen present.

Discussion

It is most striking that these [1,3]sigmatropic rearrangements normally requiring temperatures near 300 °C, with activation parameters consistent with a diradical process,[2,3] proceed at room temperature for the potassium alkoxides in highly dissociating media. Comparing the half-life estimates for the alkoxides **2a–c** (R = K) in HMPT (Table I) with the earlier thermal rates for the trimethylsiloxy derivatives[2,6,7] gives approximate rate enhancements for the alkoxide process of 10^{15}–10^{17}, which are comparable to those observed by Evans and Golob[1] for the 3,3 shift of **1b** in HMPT relative to the thermal rearrangement of **1a**. As was the case for **1b**, 18-crown-6 promotes the rearrangements of the **2** and **6** systems; however, it is markedly less effective for these rearrangements than HMPT. For example, rearrangement of **2a** is 5–7 times faster and is higher in yield in HMPT than with DME/18-crown-6. In contrast, the 3,3 rearrangement of **1b** is about twofold faster in THF/18-crown-6 than in HMPT. The rearrangement of **1b** in THF is 180 times slower if no 18-crown-6 is added, whereas the rearrangements of the **2** and **6** systems generally will not take place at all in THF without added crown ether. The one exception is the trans-ten-membered ring case **2b** (R = K) that rearranges in poor yield in refluxing THF with an approximate half-life which indicates that at the same temperature the rate would be >2000 times slower without crown ether. Of the systems studied, **2a** and **2b** have the greatest ring strain, but **2b** releases more ring strain upon two-carbon ring expansion,[2] which may explain why **2b** is the only one to rearrange in THF with no crown ether. It is the most reactive system thermally and is about the same reactivity as **2a** in HMPT.

It is clear that dissociation of the potassium alkoxide is critical for both the 1,3 and 3,3 shifts. Evans[1] has ruled out a homolytic cleavage mechanism for the 3,3-shift cases on the basis that the decrease in the bond dissociation energy on going from hydroxyl to alkoxide for such a process is too small to account for the observed rate enhancement. Complete retention of stereochemistry supports a concerted process for the 3,3-shift cases.[1] In like manner, the rate enhancement for the 1,3 shifts is too large to indicate a homolytic process. We postulate that if these rearrangements are concerted, the enormous rate enhancements seen for the anionic shifts are partly due to the naked anion becoming delocalized in the transition state leading to the resonance-stabilized enolate and partly due to the better donor properties of the anion moiety relative to the neutral compounds. The latter postulate

Scheme I



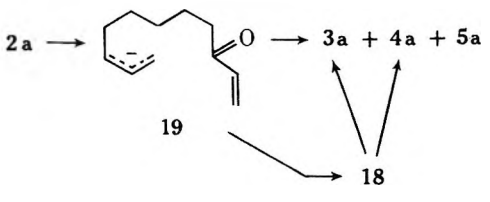
derives from the suggestion by Epiotis[16] that concerted processes become more favorable as the donor–acceptor qualities of the system increase. This implies that electron-accepting groups on the π bond (or benzo group) in the ring should accelerate the rate, providing that they don't simply give fragmentation of the type illustrated by system **8**.

The rearrangements of **2** and **6** may be easily visualized in terms of concerted rearrangements; however, the geometrically isomerized ring-expansion product from **2a** (i.e., **4a**) would require more than one step. As in the thermal cases,[6,2] a 1,3-shift ring contraction to **18** would allow formation of both **3a** and **4a** via 3,3 shifts (Scheme I). Ring strain changes for **2a** going to **18** are somewhat more favorable[2] than for the ten-membered ring systems **2b** and **2c** going to the eight-membered ring analogue of **18**; however, it is surprising that **2a** shows more geometric isomerization than the thermal reaction, whereas **2b** and **2c** show no such isomerization.

Usually, concerted [3,3]sigmatropic shifts are much more favorable than 1,3 shifts; however, for the medium-sized ring systems **2a–c** the transition states for such 3,3 shifts are highly unfavorable because of the crowded center of the ring.[7] Thus, it is consistent with the concerted scheme that both thermal and KH treatments of **2a–c** produce only a small amount of 3,3-shift product **5**, whereas **5d** becomes the major product for the large ring system **2d**, where the concerted 3,3-shift transition state is much less hindered.[7]

To our knowledge, systems **2a–d** are the only reported cases of anionic 1,3 rearrangements of 1,5-hexadien-3-ol systems, but a few other anionic 1,3 shifts are known; e.g., treatment of certain β,γ-unsaturated carboxylic acids with methyllithium leads to products in which the carbonyl group has undergone a 1,3 shift,[17] certain bicyclic semidiones (radical anions) interconvert by 1,3 shifts,[18] and 7-norbornadienol rearranges in the presence of sodium hydroxide to tropyl oxide, apparently by way of a 1,3 anionic shift.[19] The alkoxide of 3-methyl-3-vinyldec-1-en-4-ol has recently been shown to undergo 1,3 shifts with dramatic cation and solvent effects.[20] Perhaps the most interesting example is that of rearrangements of the alcohols that result from addition of allyl Grignard reagents to hindered ketones.[21] For these cases, anionic 1,3 shifts are observed; crossover experiments indicate a fragmentation–recombination mechanism. Such a mechanism provides an alternative rationale for the present results.[5] For example, **2a** could cleave to an allylic anion and an α,β-unsaturated ketone connected by the methylene chain (**19**, Scheme II). Michael addition from the two ends of the allylic anion would give **3a** and **5a**. The geometrically isomerized

Scheme II



product **4a** could arise by geometric isomerization of the allylic anion prior to the Michael addition or by formation of **18** followed by 3,3 shifts. It is not clear at the present time whether **19** is an intermediate along the pathway to **3–5**, but if not it clearly can become a competing process. The cyclopropyl systems **8a,b** cleave and presumably transfer an α hydrogen rather than undergo a homo Michael addition. No such cleavage was seen for the **6** systems, where the "toluene" methyl should be readily seen in the NMR, but such cleavage has been seen in the reaction of 3-methyl-4-phenylbut-1-en-3-ol, an open-chain analogue.[22] The lack of reactivity of the saturated ring compounds **13a,b** would be consistent with the Scheme II mechanism since a nonallyl anion would be much higher in energy than the allylic anions from **2a–d**. It should be noted, however, that the unsaturation in the ring appears to be highly important to the concerted process as well,[2,3] so that Scheme I is also viable.

From the synthetic standpoint, the anionic 1,3-shift ring expansion offers a useful alternative to the thermal counterpart. Although the media is highly basic, it avoids the high temperatures and gas phase conditions, it can give appreciably better yields (e.g., **6b** vs. **6a**), and it can give a cleaner product (e.g., **2b** and **2c**). The major side reactions give acidic or nonvolatile byproducts which are readily removed.

Experimental Section

General. Spectral measurements utilized Beckman IR-8, Perkin-Elmer 727B, Perkin-Elmer 621, Varian Associates HA-100, Cary 15, Atlas CH-7, and CEC 110B instruments. Gas–liquid chromatography (GLC) analyses were carried out on Varian 920 (thermal conductivity detector, 0.25 in columns) and Varian 1200 instruments (flame ionization detector, 0.125 in or less columns) using the columns designated below: (A) 9 ft × 0.25 in, 3% AN600 on Chromosorb B, (B) 50 ft × 0.03 in, OV-101 P.L.O.T.,[23] (C) 16 ft × 0.25 in, 2.5% OV-101 on Chromosorb G, (D) 20 ft × 0.125 in, 4.9% OV-101 on Chromosorb G, (E) 5 ft × 0.25 in, 1.6% stabilized DEGS on Chromosorb G, (F) 75 ft × 0.01 in, DEGS capillary, (G) 4.8 ft × 0.25 in, 6.5% OV-101 on Chromosorb G, (H) 5 ft × 0.25 in, 1.5% OV-101 on Chromosorb G, (I) 5 ft × 0.25 in, 5% OV-101 on Chromosorb G, (J) 8.5 ft × 0.25 in, 3% AN600 on Chromosorb G. (K) 6 ft × 0.125 in, 7.5% OV-101 on Chromosorb W, (L) 50 ft × 0.03 in, DEGS P.L.O.T.,[23] (M) 5.25 ft × 0.25 in, 7.4% stabilized DEGS on Chromosorb G. and (N) 6 ft × 0.375 in, 4.9% OV-101 on Chromosorb B.

Tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), and bis(2-methoxyethyl) ether (diglyme) were distilled from the sodium benzophenone dianion under nitrogen. Hexamethylphosphoric triamide (HMPT) was dried by heating the solvent under nitrogen at 200 °C over 13X molecular sieves (predried under nitrogen at 350 °C for 4 h) overnight.[24] Other solvents were dried by standard published procedures.[25,26] All reactions involving air- or moisture-sensitive materials were conducted under a nitrogen atmosphere.

Benzosuberone (10). Cyclization of 25.0 g of δ-phenylvaleric acid by the method of Gilmore and Horton[27] followed by distillation (97 °C at 3 mm) gave 8.9 g (40%) of a clear liquid. The IR spectrum of the liquid (neat) matched that of an authentic sample (Aldrich).

5-Aminomethyl-6,7,8,9-tetrahydro-5-benzocycloheptenol (11) was prepared by a procedure similar to that of Evans, Carroll, and Truesdale.[9] A 100-mL, one-neck flask (equipped with a magnetic stirrer and nitrogen atmosphere) was charged with 2.0 g (0.05 mol) of lithium aluminum hydride and 50 mL of dry ether. This mixture was stirred for 30 min and then allowed to settle. Another 100-mL flask (similarly equipped) was charged with 5.02 g (0.031 mol) of benzosuberone (Aldrich, freshly vacuum transferred), and the flask was cooled in an ice bath. Meanwhile, a 4-in test tube was loaded with ca. 1 g (3 mmol) of zinc iodide (City Chemical Co.) and quickly evacuated to 0.2 mm. The zinc iodide was then sublimed twice with gentle flame heating, cooled, and placed under a nitrogen atmosphere. The test tube was then equipped with a stirring bar, 5 mL (ca. 0.043 mol) of trimethylsilyl cyanide was added via syringe, and the mixture was stirred for 5 min. The trimethylsilyl cyanide/zinc iodide slurry was added to the ice-cold benzosuberone over ca. 1 min, and this mixture was stirred for 15 min. The reaction vessel was then equipped with a dropping funnel which was loaded with the clear part of the lithium aluminum hydride/ether mixture (prepared in the first part of the procedure). This solution was added (over 15 min) to the ice-cold trimethylsilyl cyanohydrin just formed. The rest of the gray lithium aluminum hydride/ether suspension was added dropwise with a large bore pipette. The mixture was then stirred vigorously for 15 min at ice temperature and 30 min at room temperature and recooled in the ice bath. The reaction mixture was then quenched by cautious addition of 2 mL of water, 2 mL of 15% sodium hydroxide, and 6 mL of water. The mixture was stirred until the solids became white and granular (ca. 1 h) and then filtered. The solids were washed thoroughly with twelve 25-mL portions of ether, and the combined ether layer was extracted with six 50-mL portions of 8.6% sulfuric acid. The acidic extract was made basic (pH ca. 10) with ca. 125 mL of 15% sodium hydroxide with frequent cooling in a cold water bath. The basic layer was then extracted with six 50-mL portions of chloroform, and the chloroform extract was dried over magnesium sulfate, filtered, and most of the solvent removed by rotary evaporation. The material was placed under a 0.2-mm vacuum overnight, and 5.07 g (84%) of a white solid (mp 74.0–76.3 °C) was obtained. This material was recrystallized from redistilled petroleum ether to yield crystals of mp 73.0–73.8 °C. The material was recrystallized again from petroleum ether to give a white solid, mp 94.3–94.5 °C. Samples of the material from different preparations gave the higher melting range when recrystallized from petroleum ether. The spectral data and analysis are for the material with the higher melting range: NMR ($CDCl_3$) δ 7.6–7.8 (m, 1 H), 7.0–7.35 (m, 3 H), 2.7–3.36 (m, 4 H), 1.5–2.5 (broad m, 9 H; reduces to 6 H when treated with D_2O); IR (KBr) 3350, 3300, 3100, 2910, 2850, 1600, 1480, 1450, 1360, 1330, 1280, 1230, 1200, 1170, 1120, 1090, 1040, 1000, 990, 950, 860, 760, 740 cm^{-1}; mass spectrum, *m/e* 191 (1.7), 161 (100). Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.49; H, 8.95; N, 7.41.

Essentially the same procedure was used with a 1:1 complex of NaCN and 18-crown-6 as the catalyst instead of ZnI_2, which gave similar yields and was more reproducible.

7,8,9,10-Tetrahydro-6(5*H*)-benzocyclooctenone (12). A 4.77-g (0.025 mol) portion of unrecrystallized **11** was taken up in 50 mL of 10% acetic acid, and the mixture was cooled in an ice bath. Then 32 mL (0.04 mol) of 1.25 M sodium nitrite was added, and the mixture was stirred for 30 min at ice temperature and overnight at room temperature. The reaction mixture was then rechilled in an ice bath and made basic (pH ca. 10) with 15% NaOH. The basic mixture was extracted with five 20-mL portions of ether. The ether extract was washed with two 10-mL portions of saturated ammonium chloride, dried over magnesium sulfate, concentrated, and vacuum transferred (120 °C at 1 mm), producing 3.49 g (80%) of a clear liquid that was 82% pure by GLC (column L, 155 °C). The semicarbazone was prepared and precipitated twice from benzene to give a white solid, mp 163–166.5 °C (lit.[28] 177.5–178 °C). The material was purified by GLC (column I, 215 °C) to provide the analytical samples: NMR (CCl_4) δ 7.05–7.2 (m, 4 H), 3.68 (s, 2 H), 2.73–2.9 (m, 2 H), 2.17–2.33 (m, 2 H), 1.55–2.0 (broad m, 4 H); IR (neat) 3060, 2030, 2940, 2860, 1700, 1600, 1580, 1500, 1450, 1350, 1330, 1280, 1260, 1240, 1190, 1170, 1120, 1040, 1000, 960, 880, 760, 720, 710 cm^{-1}; mass spectrum, *m/e* 174 (68.3), 118 (100). Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.45; H, 8.13.

7,8,9,10-Tetrahydro-6-vinyl-6(5*H*)-benzocyclooctenol (6b). A vinylmagnesium bromide in THF solution was prepared as described earlier[6] from 7 mL (ca. 0.1 mol) of vinyl bromide, 1.4 g (0.06 g-atom) of magnesium, and 20 mL of THF. To this was added dropwise a solution of 3.00 g (0.014 mol) of 82% ketone **12** and 10 mL of THF. The mixture was heated at ca. 40 °C for 1.5 h and then quenched by the cautious addition of 15 mL of water. The organic layer was washed with 10% H_2SO_4 and saturated $NaHCO_3$ and then dried ($MgSO_4$), concentrated, and vacuum transferred (130–140 °C at ca. 0.1 mm), which produced 3.22 g (91% yield) of a clear, viscous oil (81% pure by GLC, column I, 225 °C). Analytical samples were purified by GLC (column I, 235 °C): NMR (CCl_4) δ 7.06 (s, 4 H), 6.03 (dd, J = 11, 18 Hz, 1 H), 5.26 (dd, J = 2, 18 Hz, 1 H), 5.05 (dd, J = 2, 11 Hz, 1 H), 2.6–3.0 (broad m, 4 H), 1.2–1.9 (broad m, 7 H); IR (neat) 3400 broad, 3070, 3030, 2940, 2860, 1645, 1500, 1475, 1455, 1420, 1170, 1140, 1120, 1050, 1000, 930, 760, 715 cm^{-1}; mass spectrum, *m/e* 202 (8.3), 184 (100), 55 (100). Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.93; H, 8.75.

7,8,9,10-Tetrahydro-6-trimethylsiloxy-6-vinyl-5*H*-benzocyclooctene (6a) was prepared by the published method[29] and vacuum transferred (120 °C at 0.2 mm; 70% yield). The 91% pure clear oil was purified by GLC (column I, 210 °C): NMR (CCl_4, *p*-dioxane reference) δ 7.05 (s, 4 H), 6.04 (dd, J = 11, 17 Hz, 1 H), 5.12 (dd, J = 2, 17 Hz, 1 H), 5.10 (dd, J = 2, 11 Hz, 1 H), 2.56–2.88 (broad m, 4 H), 1.26–1.86 (broad m, 6 H), 0.04 (s, 9 H); IR (neat) 3070, 3030, 2950, 2870, 1640, 1500, 1480, 1460, 1420, 1360, 1310, 1260, 1230, 1190, 1170, 1140, 1120, 1090, 1070, 1050, 1000, 960, 920, 910, 840, 760, 730 cm^{-1}; mass spectrum, *m/e* 274 (2.7), 140 (100); exact mass, *m/e* 274.174 (calcd for

$C_{17}H_{26}OSi$, 274.175).

6-(3-Buten-1-ynyl)-7,8,9,10-tetrahydro-6(5*H*)-benzocyclooctenol (21). The procedure for making the lithium salt of 1-buten-3-yne was similar to that used earlier[30] for the production of propynyllithium. A mixture of 25 mL of ether and 8 mL (21 mmol) of 2.6 M methyllithium in ether was cooled under N_2 in an ice bath as 3.5 mL (ca. 24 mmol) of 1-buten-3-yne (Chemical Samples Co., 50% in xylene) was added with a cold syringe. The ice bath was removed after a few minutes, and the reaction mixture was stirred overnight at room temperature. The ether was evaporated under a nitrogen stream, and then 25 mL of THF was added. The mixture was warmed in a 50-°C bath, and a solution of 2.03 g (9.6 mmol) of **12** (82% pure) in 8 mL of THF was added over 5 min. The mixture was stirred for 8 h and then cooled in an ice bath and quenched by the cautious addition of 10 mL of water. The organic layer was washed with saturated NaCl, dried ($MgSO_4$), concentrated, and vacuum transferred (130–150 °C at 0.2 mm) to give 2.31 g of a viscous oil that contained 77% of **21** by GLC analysis (column C, 254 °C). Purification by GLC (column G, 235 °C) gave the analytical samples: NMR (CCl_4) δ 7.0–7.3 (m, 4 H), 5.81 (dd, J = 10, 17 Hz, 1 H), 5.53 (dd, J = 4, 17 Hz, 1 H), 5.41 (dd, J = 4, 10 Hz, 1 H), 3.03 (s, 2 H), 2.65–2.9 (broad m, 2 H), 1.2–2.0 (broad m, 7 H); IR (neat) 3600–3150, 3100, 3060, 3010, 2930, 2850, 1610, 1490, 1470, 1450, 1410, 1360, 1340, 1300, 1260, 1230, 1160, 1150, 1110, 1070, 1020, 975, 950, 920, 750, 725 cm^{-1}; UV (95% EtOH) λ_{max} 214 nm (ε 15 000), 223 (13 000), 234 (10 000); mass spectrum, m/e 226 (17.7), 79 (100); exact mass, m/e 226.135 (calcd for $C_{16}H_{18}O$, 226.136).

***cis*- and *trans*-6-(1,3-Butadienyl)-7,8,9,10-tetrahydro-6(5*H*)-benzocyclooctenol (6c)** were formed by the method of Chanley and Sobotka.[31] A solution of 0.404 g (1.4 mmol) of 77% pure 21 and 3.2 mL of ether was added at 25 °C to a suspension of 0.12 g (3 mmol) of $LiAlH_4$ and 4 mL of ether, and the mixture was refluxed for 4 h. The excess $LiAlH_4$ was quenched by the cautious addition of 0.12 mL of water, 0.12 mL of 15% sodium hydroxide, and 0.36 mL of water, and the white precipitate which formed was filtered off and washed thoroughly with ether. The filtrate and washings were dried over $MgSO_4$ and concentrated, giving 0.382 g of **6c**, which showed a strong band at 3600–3100 cm^{-1} (OH) in the IR spectrum. The NMR spectrum indicated that no starting butenynol **21** remained.

The above **6c** alcohols were silylated,[6] affording 0.63 g of crude silyl derivative. A 187-mg portion was vacuum transferred (115 °C at 0.45 mm) to give 0.170 g of a clear oil, which was purified and analyzed by GLC (column P, 255 °C). The analysis indicated that the material contained 70% of the trimethylsiloxy derivative of the **6c** alcohols in a 1:3 ratio of the shorter and longer retention-time isomers. The shorter retention-time isomer: NMR (CCl_4) δ 7.06 (s, 4 H), 4.95–6.4 (m), 2.65–2.85 (m, 4 H), 1.15–1.85 (broad m); UV (95% EtOH) λ_{max} 218 nm (ε 27 000), 227 (25 000); mass spectrum, m/e 300 (5), 285 (1), 210 (25), 105 (100); exact mass, m/e 300.191 (calcd for $C_{19}H_{28}OSi$, 300.191).

The longer retention-time isomer: NMR (CCl_4) δ 7.01 (s, 4 H), 5.31–6.51 (m, 3 H), 5.15 (dd, J = 2, 15 Hz, 1 H), 5.01 (dd, J = 2, 8 Hz, 1 H), 2.55–3.05 (broad m, 4 H), 1.3–1.87 (broad m, 6 H); IR (CCl_4) 3055, 3015, 2920, 2845, 1255, 1245, 1175, 1000, 970, 900, 840, 735 cm^{-1}; UV (95% EtOH) λ_{max} 218 nm (ε 25 000), 227 (25 000); mass spectrum, m/e 300 (20.8), 285 (5.8), 247 (18.6), 73 (100); exact mass, m/e 300.190 (calcd for $C_{19}H_{28}OSi$, 300.191).

(*cis*-3-Penten-1-ynyl)-7,8,9,10-tetrahydro-6(5*H*)-benzocyclooctenol (20). The lithium salt of *cis*-3-penten-1-yne was formed as above (see **21**) from 4.6 g (0.070 mol) of *cis*-3-penten-1-yne[32] in ether, which was replaced by 50 mL of THF. A 20-mL solution in THF of 10.0 g (0.047 mol) of 82% pure **12** was added over 2 h to the refluxing solution, which was then cooled and quenched with 10 mL of saturated NH_4Cl. The organic layer was washed successively with H_2O, saturated NH_4Cl, 10% H_2SO_4, and saturated $NaHCO_3$ and then dried ($MgSO_4$) and concentrated. Vacuum transfer (100 °C at 0.1 mm) gave 10.6 g of clear oil. Remaining starting ketone was removed using 7.0 g of Girard's Reagent T as described earlier.[33] This gave 7.43 g (43% yield) of pentenynol **20**, which was 79% pure by GLC (column H, 205 °C).

The pentenynol was silylated[29] and purified by GLC (column O, 260 °C): NMR (CCl_4, Me_4Si reference) δ 6.95–7.3 (m, 4 H), 5.9 (dq, J = 7, 10 Hz, 1 H), 5.47 (dq, J = 2, 10 Hz, 1 H), 3.05 (s, 2 H), 2.65–2.9 (broad m, 2 H), 1.3–2.0 (broad m, 9 H, 1.82 (dd, J = 2, 7 Hz); NMR (CCl_4, CH_2Cl_2 reference) δ 0.19 (s, 9 H); IR (neat) 3060, 3030, 2940, 2850, 1495, 1470, 1450, 1400, 1360, 1320, 1300, 1250, 1230, 1190, 1160, 1150, 1110, 1070, 1030, 990, 950, 920, 900, 890, 840, 755, 720, 680 cm^{-1}; mass spectrum, m/e 312 (15.7), 297 (34.7), 73 (100); exact mass, m/e 312.190 (calcd for $C_{20}H_{28}OSi$, 312.191).

***cis* and *trans*-6-(1,3-(*Z*)-Pentadienyl)-7,8,9,10-tetrahrydro-6(5*H*)-benzocyclooctenol (6d)** were prepared by $LiAlH_4$ reduction of **20** in the same way as above (see **6c**). A 0.286-g portion was silylated[29] and vacuum transferred (115 °C at 0.35 mm), yielding 0.320 g (64% yield) of clear oil, which GLC (column, C, 235 °C) indicated was 76% trimethylsiloxy dienes. The two isomers (2:1 ratio) were separated by GLC (column O, 260 °C) to give long and short retention-time components. The shorter retention-time component: NMR (CCl_4) δ 7.0–7.1 (s, 4 H), 5.3–6.6 (m, 4 H), 2.65–3.0 (broad m, 4 H), 1.3–1.9 (broad m, 9 H), 1.75 (dd, J = 2, 7 Hz); IR (CCl_4) 3060, 3020, 2940, 2860, 1495, 1470, 1455, 1410, 1375, 1360, 1255, 1080, 980, 975, 845, 750 cm^{-1}; UV (95% EtOH) λ_{max} 235 nm (ε 19 000); mass spectrum, m/e 314 (47), 299 (30), 73 (100); exact mass, m/e 314.207 (calcd for $C_{20}H_{30}OSi$, 314.207).

The longer retention-time component: NMR (CCl_4) δ 6.91–7.15 (s, 4 H), 5.3–6.91 (m, 4 H), 2.99 (s, 2 H), 2.6–2.9 (broad m, 2 H), 1.1–1.9 (broad m, 9 H), 1.78 (dd, J = 2, 7 Hz); IR (CCl_4) 3060, 3020, 2930, 2850, 1265, 1255, 1070, 1000, 915, 846, 740 cm^{-1}; UV (95% EtOH) λ_{max} 239 nm (ε 22 000); mass spectrum, m/e 314 (100), 299 (48), 196 (100).

6-Cyclopropyl-7,8,9,10-tetrahydro-6(5*H*)-benzocyclooctenol (8a). A mixture of 0.60 g (5 mmol) of cyclopropyl bromide (Aldrich), 5 mL of THF, and 0.11 g (4.5 g-atom) of magnesium was treated with a few crystals of iodine.[34] A vigorous reaction ensued, and the mixture was stirred for 30 min. A solution of 0.533 g (2.5 mmol) of 82% pure **12** in 3.5 mL of THF was then added over 10 min, and the mixture was stirred for another 1.33 h, at which time 5 mL of saturated NH_4Cl and 30 mL of ether were added. The organic layer was washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated to afford 0.613 g of a light amber oil. A 241-mg portion was vacuum transferred (90–100 °C at 0.4 mm) to give 0.180 g (50% yield) of a clear oil, which was analyzed by GLC (column G, 215 °C) and found to contain 33% of starting ketone **12** and 58% of **8a**. Pure **8a** was obtained by preparative GLC (column G, 225 °C): NMR (CCl_4, CH_2Cl_2 reference) δ 7.15 (s, 4 H), 2.7–3.0 (m, 4 H), 1.3–1.95 (m, 6 H), 0.85–1.2 (m and broad s, 2 H; s shifts on warming to 60 °C), 0.25–0.7 (m, 4 H); IR (neat) 3700–3200, 3080, 3070, 3000, 2910, 2850, 1600, 1490, 1470, 1450, 1390, 1360, 1330, 1310, 1300, 1250, 1220, 1200, 1170, 1140, 1100, 1040, 1020, 1000, 990, 940, 920, 890, 880, 860, 820, 750, 730, 700 cm^{-1}; mass spectrum, m/e 216 (50.9), 198 (11.3), 84 (100); exact mass, m/e 216.151 (calcd for $C_{15}H_{20}O$, 216.151).

1-Bromo-2-vinylcyclopropanes. The method of Seyferth, Yamazaki, and Alleston[35] produced 3.88 g (82%) of 1-bromo-2-vinylcyclopropanes from 7.29 g (32 mmol) of 1,1-dibromo-2-vinylcyclopropane[36,37] and 9.42 g (32 mmol) of tri-*n*-butyltin hydride. The material was isolated by distillation of the crude product at room temperature (0.2 mm) into a 78-°C trap. An earlier attempt to distill the material at 62–74 °C (90 mm)[35] resulted in extensive decomposition of the product. The NMR and IR spectra agreed with the spectra described by Landgrebe and Becker,[38] and the NMR spectrum indicated that the trans/cis ratio is ca. 40:60.

7,8,9,10-Tetrahydro-6-(2-vinylcyclopropanyl)-6(5*H*)-benzocyclooctenols (8b). Use of the general procedure of Wender and Filosa[39] produced 0.60 g of the vinylcyclopropanols **8b** from 2.5 mL (5.8 mmol) of 2.3 M *tert*-butyllithium in pentane (Ventron), 0.80 g (5.4 mmol) of a mixture of 1-bromo-2-vinylcyclopropanes, and 0.48 g (2.3 mmol) of 82% pure **12**. The oil was vacuum transferred (135 °C at 0.4 mm) to give 0.55 g (63% yield) of product. GLC analysis (column J, 225 °C) showed that the product contained 14% of **13** and 77% of **8b** (28:72 ratio). Purification by GLC (column O, 250 °C) gave the analytical samples of **8b**. The shorter retention-time sample: NMR (CCl_4) δ 7.05 (s, 4 H), 4.66–5.56 (m, 3 H), 2.66–2.94 (m, 4 H), 1.2–1.85 (broad m, 7 H), 0.7–1.1 (m, 4 H); IR (CCl_4) 3620, 3400, 3070, 3050, 3010, 2990, 2920, 2840, 1630, 1490, 1465, 1450, 980, 890 cm^{-1}; mass spectrum, m/e 242 (2), 188 (100); exact mass, m/e 242.165 (calcd for $C_{17}H_{22}O$, 242.167).

The longer retention-time sample: NMR (CCl_4) δ 7.06 (s, 4 H), 5.76–6.32 (m, resembles septet, 1 H), 5.0–5.3 (m, 1 H), 4.76–4.98 (m, 1 H), 2.84–2.96 (m, 2 H), 2.64–2.84 (m, 2 H), 1.24–1.86 (broad m, 7 H), 0.7–1.24 (m, 4 H); IR (CCl_4) 3620–3400, 3070, 3050, 3010, 2990, 2920, 2840, 1625, 1490, 1465, 1450, 995, 890 cm^{-1}; mass spectrum, m/e 242 (5), 188 (100); exact mass, m/e 242.166 (calcd for $C_{17}H_{22}O$, 242.167).

1-Vinylcyclononanol (13a). Cyclooctanone was ring expanded using the same sequence[9] as for ketone 12 and gave cyclononanone (matches published spectra[40]) in 68% yield. Treatment with vinylmagnesium bromide as before[6] gave a 45% yield of **13a**: NMR (CCl_4) δ 5.92 (dd, J = 11, 18 Hz, 1 H), 5.14 (dd, J = 2, 18 Hz, 1 H), 4.92 (dd, J = 2, 11 Hz, 1 H), 1.2–1.9 (m, 17 H); IR (neat) 3600–3200, 3090, 2920, 1640, 995, 910 cm^{-1}; exact mass, m/e 168.151 (calcd for $C_{11}H_{20}O$, 168.151).

General Procedure for Rearrangements in Hexamethylphosphoric Triamide (HMPT). A 50-mL conical flask was charged

with 0.75 g (4.7 mol) of 25% potassium hydride in oil (Ventron) and placed in a nitrogen atmosphere. The oil was rinsed from the potassium hydride with five 7.5-mL portions of hexane by adding hexane, stirring briefly (magnetic stirrer), and allowing the hydride to settle. The hexane–oil layer was carefully removed with a pipette. A 23-mL amount of HMPT was added, followed by a solution of 1.5 mmol of alcohol in 2 mL of HMPT. The mixture was stirred for 10 min and then allowed to stand for the required amount of time at room temperature, unless otherwise noted in the tables. The reaction was then quenched by addition of a few milliliters of water, acidified with 10% sulfuric acid, and diluted with 125 mL of water. The aqueous layer was either continuously extracted with 200 mL of ether or manually extracted with five 25-mL portions of ether. The ether layer was extracted with five 30-mL portions of 5% sodium hydroxide and washed with two 30-mL portions of saturated ammonium chloride and 30 mL of brine. Finally, the ether layer was dried over magnesium sulfate and filtered, and the ether was removed by rotary evaporation. The basic extract from above was acidified with 6 N hydrochloric acid, cooled, and extracted with five 30-mL portions of ether. The ether extract was then washed with three 30-mL portions of water and 30 mL of brine, dried over magnesium sulfate, and filtered, and the ether was removed at reduced pressure.

General Procedure for Rearrangements in 1,2-Dimethoxyethane (DME) with 18-Crown-6. A factory bottle containing 18-crown-6 (Aldrich) was warmed to just above the melting point (ca. 40–50 °C), and about 1 g of the crown ether was transferred to a dry, tared 5-mL volumetric flask. The flask was evacuated to 1 mm and warmed at 80 °C for 2 h. The flask was then weighed, and enough DME was added to make 5 mL of solution. A 25-mL conical flask was charged with 0.5 g (3.1 mmol) of 22.1% potassium hydride in oil (Ventron) and placed under a nitrogen atmosphere. The oil was rinsed from the potassium hydride with five 5-mL portions of hexane in the same manner as in the experiments with HMPT. A 13-mL amount of DME was then added, followed by a solution of 0.75 mmol of alcohol in 2 mL of DME and enough crown ether solution to contain 0.80 mmol of 18-crown-6. The mixture was stirred for 10 min and allowed to stand for the required amount of time. The reaction was then quenched by addition of 1 mL of water and transferred to a separatory funnel with 25 mL of ether. The organic layer was extracted with five 5-ml portions of saturated sodium bicarbonate, dried over magnesium sulfate, and filtered, and the ether was removed by rotary evaporation. The basic extract was cautiously acidified with 6 N hydrochloric acid and extracted with five 5-mL portions of ether. The ether layer was then dried and concentrated as above.

Rearrangements of the 1-vinyl-3-cycloalkenols 2a–d were carried out by the standard procedures and analyzed by GLC on columns A–E at temperatures ranging from 120 to 180 °C. Yields were determined by adding starting alcohol (**2a–d**) as an internal standard. The yields and product ratios are presented in Table I. All products were identified by GLC and spectral comparison with known compounds.[2,6,7]

Attempted Rearrangements of the Potassium Salt of 1-Vinylcyclodecanol (13b) and 1-Vinylcyclononanol (13a). 1-Vinylcyclodecanol[2] was subjected to the usual conditions for rearrangements in HMPT for 4.17 h at 25 °C. The progress of the reaction was followed by GLC (column F, 105 °C), and the formation of a new product at ca. 60% of the retention time of the starting material was observed. The standard workup (manual extraction) produced an oil containing 31% of the starting alcohol **13b** and 23% of the new product. The yields were determined by GLC (column B, 140 °C) using cycloundecanone (Aldrich) as an internal standard and assuming the response factors to be equal. The retention time of the new product was shorter than that of cycloundecanone. If cyclododecanone had been formed, it would be expected to have a longer retention time than cycloundecanone.

A similar experiment with **13a** reacting for 24 h gave back only starting material (54% recovery; identical GLC, IR, and NMR).

Rearrangements of the potassium salt of 6-vinyl-7,8,9,10-tetrahydro-6(5*H*)-benzocyclooctenol (6b) in HMPT were conducted by the standard procedure, and the yields of the reaction are presented in Table II. The yield studies were done by GLC (column G, 210 °C, and column H, 175 °C) using benzosuberone as an internal standard correcting for response factor. The product, ketone **7b**, was purified by GLC (column A, 225 °C, or column I, 210 °C) to provide the analytical samples: NMR (CCl_4) δ 7.0–7.25 (m, 4 H), 2.5–2.8 (m, 4 H), 1.5–2.4 (broad m, 10 H); IR (neat) 3055, 3010, 2995, 2930, 2860, 1700, 1600, 1490, 1470, 1445, 1420, 1410, 1370, 1330, 1260, 1240, 1215, 1200, 1160, 1150, 1120, 1105, 1045, 1000, 960, 950, 840, 800, 785, 760, 730, 700 cm^{-1}; mass spectrum, *m/e* 202 (89.8), 129 (100); exact mass, *m/e* 202.138 (calcd for $C_{14}H_{18}O$, 202.136).

Rearrangements of the potassium salt of 6b in DME with 18-crown-6 were carried out in the standard way with the results shown in Table II. The yield studies were carried out by the same procedure used for the analogous HMPT rearrangement. This particular set of conditions gave a considerable amount of acidic product which was isolated by $NaHCO_3$ extraction, followed by acidification, and purified by recrystallization twice from benzene, giving a white solid (**15**), mp 118.0–118.5°C; NMR ($CDCl_3$) δ 10.7–10.9 (broad s, 2 H; shifts on warming to 60 °C), 7.15 (s, 4 H), 2.72 (m, 4 H), 2.45 (t, J = 7 Hz, 4 H), 1.90 (p, J = 7 Hz, 4 H); IR ($CHCl_3$) 3500–2400, 3010, 1710 cm^{-1}; mass spectrum, *m/e* 250 (4.5), 131 (100); exact mass, *m/e* 250.121 (calcd for $C_{14}H_{18}O_4$, 250.121).

Attempted Rearrangement of the Potassium Salt of 6b in THF. A solution of the potassium salt of 0.10 g (ca. 0.4 mmol) of 81% pure **12** in 15 mL of THF was refluxed for 26.33 h. The reaction mixture was then taken up in 25 mL of ether, which was washed with 10 mL of water, dried ($MgSO_4$), and concentrated. A 148-mg sample of this material was then vacuum transferred to give 0.077 g of a clear oil. The oil was analyzed and purified by GLC (column M, 210 °C), which indicated that the oil consisted of ca. 50% of **16**, 1% of starting alcohol **6b**, and a variety of other compounds none of which made up greater than 10% of the total area. This analysis indicates a crude yield of ca. 55% for the conversion of alcohol **6b** to compound **16**: NMR (CCl_4) δ 7.0–7.2 (m, 4 H), 6.54 (s, 1 H), 6.45 (dd, J = 11, 18 Hz, 1 H), 5.23 (d, J = 18 Hz, 1 H), 5.04 (d, J = 11 Hz, 1 H), 2.55–2.72 (m, 2 H), 2.05–2.22 (m, 2 H), 1.35–1.90 (m, 4 H); IR (neat) 2950, 2920, 2850, 1470, 1380 cm^{-1}; UV (95% EtOH) λ_{max} 216 nm (ϵ 17 000), 261 (19 000); mass spectrum, *m/e* 184 (39.1), 128 (100); exact mass, *m/e* 184.126 (calcd for $C_{14}H_{16}$, 184.125).

In another experiment the potassium salt of **6b** was refluxed in THF, and the reaction was followed by GLC (column I, 225 °C). Samples were taken at 45 min, 1.75 h, 2.72 h, and 18.25 h, and no appearance of ketone **7b** was observed.

Pyrolyses of 7,8,9,10-tetrahydro-6-trimethylsiloxy-6-vinyl-5*H*-benzocyclooctenes (6a) and subsequent hydrolyses of the trimethylsilyl products were carried out in the same manner as described previously.[6] The product and yield studies used the same conditions as reported above for the HMPT work and are shown in Table II.

Rearrangement of the Potassium Salts of *cis*- and *trans*-6-(1,3-Butadienyl)-7,8,9,10-tetrahydro-6(5*H*)-benzocyclooctenol (6c). A solution of 0.326 g of the crude butadienols (**6c**) in 5 mL of HMPT was added to 20 mL of HMPT containing excess potassium hydride and allowed to stand for 3.9 h. The usual workup (continuous extraction) afforded 0.265 g of neutral material. The material was analyzed by GLC (column K, 175 °C) using butenynol 21 as an internal standard with the results presented in Table II. The product was purified on a 2 ft × 0.375 in stainless steel column containing 33 g of Woelm neutral alumina (activity II), eluting with hexane and then a linear gradient[41] of ether/hexane. Fractions containing material with R_f 0.38 (TLC on silica gel; solvent, chloroform) were collected and repurified by GLC (column G, 240 °C) to provide the analytical samples of 5,6,9,10,11,12-hexahydro-6-vinyl-8(7*H*)-benzocyclodecenone (**7c**): NMR (CCl_4) δ 6.95–7.25 (m, 4 H), 5.9–6.4 (broad m, 1 H), 5.01 (dd, J = 2, 11 Hz, 1 H), 4.99 (dd, J = 2, 16 Hz, 1 H), 2.85–3.2 (broad m, 2 H), 2.45–2.85 (broad m, 3 H), 1.9–2.45 (broad m, 6 H), 1.55–1.9 (m, 2 H); IR (neat) 3060, 3010, 3000, 2930, 2680, 1700, 1640, 1490, 1470, 1450, 1425, 1410, 1370, 1120, 1000, 990, 920, 800, 780, 760, 740, 710 cm^{-1}; mass spectrum, *m/e* 228 (47.9), 174 (33.4), 118 (100); exact mass, *m/e* 228.151 (calcd for $C_{16}H_{20}O$, 228.151).

Rearrangement of the Potassium Salts of *cis*- and *trans*-6-(1,3-*cis*-Pentadienyl)-7,8,9,10-tetrahydro-6(5*H*)-benzocyclooctenol (6d) in HMPT. A solution of 0.77 g of 81% pure dienols **6d** in 5 mL of HMPT was added to 45 mL of HMPT containing excess potassium hydride, and the whole solution was allowed to stand for 4.5 h at room temperature. The usual workup (continuous extraction) afforded 0.66 g of neutral material and 0.022 g (adjusted for HMPT content by NMR) of acidic material. A 278-mg portion of the neutral material was purified on a 2 ft × 0.375 in stainless steel column containing 33 g of Woelm neutral alumina (activity II). The column was eluted with hexane and then a linear gradient[41] of hexane and 50:50 ether/hexane. Fractions containing material with R_f 0.5 (TLC on silica gel; solvent, chloroform) were collected to give 0.086 g of material. A 50-mg amount of this material was vacuum transferred (130 °C at 0.35 mm) to give 0.047 g of 6-(*cis*-1-propenyl)-5,6,9,10,11,12-hexahydro-8(7*H*)-benzocyclodecenone (**7d**): NMR ($CDCl_3$) δ 7.03–7.3 (m, 4 H), 5.3–5.8 (m, 2 H), 3.12–3.5 (broad s, 1 H), 2.8–3.12 (m, 1 H), 2.45–2.8 (m, 3 H), 2.2–2.45 (m, 3 H), 1.87–2.2 (m, 3 H), 1.5–1.87 (m, 5 H), 1.72 (d, J = 5 Hz); IR (neat) 3050, 3010, 2930, 2860, 1700, 1490, 1470, 1450, 1420, 1400, 1360, 1330, 1270, 1230, 1190, 1110, 990, 920, 790, 770, 750, 730, 710 cm^{-1}; mass spectrum, *m/e* 242 (23.2), 174 (32.3), 118 (100);

exact mass, *m/e* 242.167 (calcd for $C_{17}H_{22}O$, 242.167).

Pyrolysis of 6-(1-*cis*-Propenyl)-5,6,9,10,11,12-hexahydro-8(7*H*)-benzocyclodecenone (7d) was carried out as described previously.[2] A 3 cm × 28 cm glass ampoule containing 0.36 g of crude **7d** was heated for 6.25 h at 350 °C. Separation of the products by GLC (column I, 265 °C) gave a very low yield (<1%) of two ketones in a 2:1 ratio, for which spectra are listed although the samples were too weak for reliable integration. Major ketone: NMR (CCl_4) δ 6.9–7.3 (m), 5.2–5.65 (m), 3.7–4.1 (m), 2.5–3.1 (broad m), 1.9–2.4 (m), 2.15 and 2.08 (s), 1.5–1.9 (broad m), 0.85–1.15 (m, possible overlapping triplets, *J* = 7 Hz); IR (neat) 3070, 3020, 2960, 2940, 2860, 1710, 1500, 1460, 1360, 1170, 980, 760 cm^{-1}; mass spectrum, *m/e* 242 (25.4) 224 (10.7), 213 (11.7), 199 (100); exact mass, *m/e* 242.165 (calcd for $C_{17}H_{22}$, 242.167).

Minor ketone: NMR (CCl_4) δ 6.9–7.3 (m), 5.2–5.7 (m), 0.8–3.1 (broad m); IR (neat) 3070, 3020, 2960, 2940, 2880, 1710, 1500, 1460, 980, 750 cm^{-1}; mass spectrum, *m/e* 244 (21.8), 243 (14.9), 242 (86.0), 299 (12), 129 (100); exact mass, *m/e* 242.166 (calcd for $C_{17}H_{22}O$,[42] 242.167).

Rearrangement of the Potassium Salt of 6-Cyclopropyl-7,8,9,10-tetrahydro-6(5*H*)-benzocyclooctenol (8a) in HMPT. A solution of the potassium salt of 0.029 g (0.1 mmol) of **8a** in 1.2 mL of HMPT was allowed to stand at room temperature for 45.6 h. Quenching the reaction mixture with water followed by the normal workup (manual extraction) afforded 0.010 g of neutral material. The material was analyzed by GLC (column J, 205 °C) and found to contain 18% starting material, 5% unknown substances, and 77% (<34% overall yield) of 1-cyclopropyl-5-(*o*-tolyl)-2,3-pentanedione (**17**). The mixture was purified by GLC (column J): NMR (CCl_4) δ 7.01 (s, 4 H), 2.5–2.9 (m, 4 H), 2.28 (s, 3 H), 1.6–2.2 (m, 2 H), 1.2–1.4 (m, 1 H), 0.8–1.2 (m, 4 H); IR (CCl_4) 3080, 3020, 2940, 2860, 1700, 1500, 1460, 1390, 1040, 950 cm^{-1}; mass spectrum, *m/e* 230 (23.5), 161 (100), 105 (69.9), 69 (64.1); exact mass, *m/e* 230.130 (calcd for $C_{15}H_{18}O_2$, 230.131).

In another experiment a solution of the potassium salt of 0.114 g of a mixture containing 58% of **8a** and 33% of **12** in 5 mL of freshly dried HMPT was allowed to stand at 25 °C for 46 h. The reaction mixture was quenched with water and worked up by the normal procedure (manual extraction), giving 0.089 g of neutral material and 0.019 g of acidic material. A 70-mg amount of the neutral material was then vacuum transferred (120 °C at 0.35 mm), producing 0.064 g of a light yellow oil, which was separated by GLC (column J, 210 °C) and shown to contain 32% of **12**, 6% of **8a**, and 59% of 1-cyclopropyl-5-(*o*-tolyl)-1-pentanone (**9a**): NMR (CCl_4, CH_2Cl_2 reference) δ 7.15 (s, 4 H), 2.55–3.01 (m, 4 H), 2.38 (s, 3 H), 1.45–2.09 (m, 5 H), 0.75–1.21 (m, 4 H); IR (neat) 3050, 3000, 2920, 2850, 1695, 1600, 1490, 1460, 1450, 1390, 1190, 1080, 1050, 1020, 900, 820, 740 cm^{-1}; mass spectrum, *m/e* 230 (3.4), 216 (33.3), 105 (63.5), 84 (63.5), 69 (100); exact mass, *m/e* 216.151 (calcd for $C_{15}H_{20}$, 216.151).

Rearrangements of the potassium salts of 7,8,9,10-tetrahydro-6(2-vinylcyclopropanyl)-6(5*H*)-benzocyclooctenols 8b in HMPT were carried out by the standard procedure and analyzed by GLC (column K, 165 °C) using **20** as an internal standard. Separation by GLC (column A, 190 °C) gave 5-(*o*-tolyl)-1-(2-vinylcyclopropyl)-1-pentanone (**9b**): NMR (CCl_4) δ 7.01 (s, 4 H), 5.11–5.56 (m, 2 H), 4.85–5.01 (m, 1 H), 2.43–2.67 (m, 4 H), 2.25 (s, 3 H), 1.25–1.91 (m, 7 H), 0.75–0.91 (m, 1 H); IR (CCl_4) 3080, 3020, 2940, 2870, 1700, 1640, 1500, 1460, 1390, 1100, 990, 910 cm^{-1}; mass spectrum, *m/e* 242 (1.6), 105 (100); exact mass, *m/e* 242.166 (calcd for $C_{17}H_{22}O$, 242.167).

Acknowledgment. This investigation was supported by NIH Research Grant RO1 HDO8550 from the National Institute of Child Health and Human Development. We wish to thank Professors D. A. Evans and S. R. Wilson for informative discussions regarding this work. We thank Susan Randall for capable NMR assistance and Richard Weilesec for mass spectra on the CEC 110B instrument at the University of Oregon.

Registry No.—**6a**, 62297-12-5; **6b**, 64871-09-6; **6b** (K salt), 62297-13-6; *cis*-**6c**, 64871-11-0; *trans*-**6c**, 64871-12-1; *cis*-**6c** (Me_4Si deriv), 64871-13-2; *trans*-**6c** (Me_4Si deriv), 64871-14-3; *cis*-**6c** (K salt), 64871-15-4; *trans*-**6c** (K salt), 64871-16-5; *cis,cis*-**6d**, 64871-17-6; *trans,cis*-**6d**, 64871-03-0; *cis,cis*-**6d** (Me_4Si deriv), 64871-04-1; *trans,cis*-**6d** (Me_4Si deriv), 64871-05-2; *cis,cis*-**6d** (K salt), 64871-06-3; *trans,cis*-**6d** (K salt), 64871-07-4; **7b**, 62297-14-7; **7c**, 64870-85-5; **7d**, 64870-86-6; **8a**, 64870-87-7; **8a** (K salt), 64870-89-9; **8b**, 64870-88-8; **8b** (K salt), 64870-90-2; **9a**, 64870-91-3; **9b**, 64870-92-4; **10**, 826-73-3; **11**, 64870-93-5; **12**, 62297-15-8; **13a**, 64870-94-6; **13b** (K salt), 64870-95-7; **15**, 64870-96-8; **16**, 64870-97-9; **17**, 64870-98-0; **20**, 64871-00-7; **20** (Me_4Si deriv), 64871-01-8; **21**, 64870-99-1; δ-phenylvaleric acid, 2270-20-4; trimethylsilyl cyanide, 7677-24-9; vinyl bromide, 593-60-2; 1-buten-3-yne (Li salt), 51042-24-1; methyllithium, 917-54-4; 1-buten-3-yne, 689-97-4; *cis*-3-penten-1-yne (Li salt), 64871-02-9; *cis*-3-penten-1-yne, 1574-40-9; cyclopropyl bromide, 4333-56-6; *trans*-1-bromo-2-vinylcyclopropane, 15136-02-4; *cis*-1-bromo-2-vinylcyclopropane, 15136-01-3.

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Hydroboration. 49. Effect of Structure on the Selective Monohydroboration of Representative Conjugated Dienes by 9-Borabicyclo[3.3.1]nonane

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The exceptionally high sensitivity toward structure exhibited by 9-borabicyclo[3.3.1]nonane (9-BBN) in the hydroboration of simple olefins and nonconjugated dienes carries over to conjugated dienes with one major difference. Conjugation markedly decreases the reactivity of the system toward hydroboration. For example, a nonconjugated diene, such as 1,4-hexadiene, is selectively hydroborated by 9-BBN in the presence of a related conjugated diene, such as 1,3-pentadiene. Moreover, this deactivation of the system by conjugation often causes the second stage of the hydroboration to be considerably faster than the first, making it difficult to control the reaction to achieve monohydroboration. Thus, treatment of 1,3-butadiene with 9-BBN in a 1:1 molar ratio gives approximately 50% residual 1,3-butadiene and 50% of the 1,4-diborabutane derivative. On the other hand, in cases where the two olefinic centers of the diene possess structures which differ considerably in reactivity toward 9-BBN, clean monohydroboration can be achieved. Thus, *trans*-1,3-pentadiene is readily converted into the monohydroboration product, *B*-(*trans*-3-penten-1-yl)-9-BBN. In certain dienes, the initial reaction product is the allylic, rather than the more usual homoallylic, derivative. In such cases, 1,3-cyclohexadiene and 2,5-dimethyl-2,4-hexadiene, the reaction is more easily controlled to achieve monohydroboration. A knowledge of the relative reactivities of simple olefin structures is helpful in predicting and rationalizing the behavior of these conjugated dienes toward hydroboration with 9-BBN.

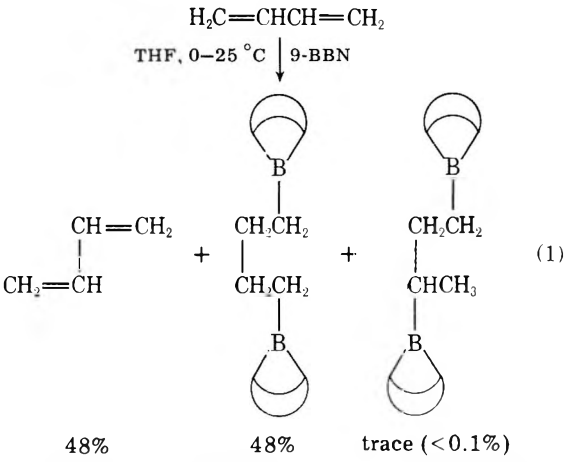
In previous studies, it has been pointed out that 9-borabicyclo[3.3.1]nonane (9-BBN) is an interesting hydroboration agent which exhibits unusual regio-[3] and stereospecificity[4] and remarkable sensitivity to the structures of olefins.[5] With such valuable characteristics, it appeared appropriate to examine the utility of this reagent for the hydroboration of representative nonconjugated dienes,[6] conjugated dienes (present study), allenes,[7] and acetylenes.[8]

The study of the hydroboration of representative nonconjugated dienes[6] established that the relative reactivities of simple olefinic structures toward hydroboration with 9-BBN[5] could be carried over to predict reliably the course of the reaction. Such regularity greatly facilitates applying hydroboration of nonconjugated dienes with 9-BBN as a synthetic route in organic synthesis. Consequently, we undertook a study of the hydroboration of conjugated dienes by 9-BBN in order to ascertain whether these structures would reveal a similar regular pattern of reactivity.

Results and Discussion

The reaction procedure was identical to that used for the nonconjugated dienes.[6] It involved the addition of a standard solution of 9-BBN in tetrahydrofuran (THF) to an equivalent amount of the diene. The reaction mixture was 0.5 M in each component. An internal standard suitable for GC analysis was introduced. The reaction was allowed to proceed to completion, usually at 25 °C. The reaction product was then oxidized with alkaline hydrogen peroxide in the usual manner.[9] GC examination for residual diene was used to establish the extent of monohydroboration (0% diene = 100% monohydroboration; 50% diene = 0% monohydroboration). The mono-ol and diol products revealed the point or points of attack. In some cases, prior to the oxidation the boron intermediate was treated with acetone to convert reactive allylic 9-BBN derivatives to alcohol derivatives suitable for GC analysis.[13]

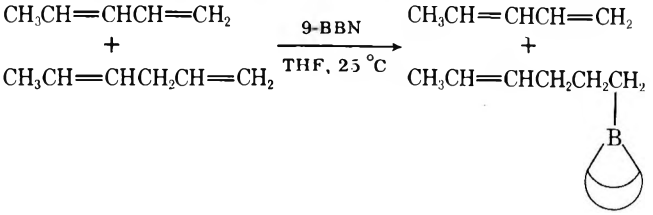
Symmetrical Acyclic Conjugated Dienes. The reaction of 9-BBN with a symmetrical nonconjugated diene, such as 1,5-hexadiene, in a 1:1 molar ratio proceeds in an essentially statistical manner, giving approximately 25% residual diene, 50% monohydroboration product, and 25% dihydroboration product.[6] However, a conjugated diene, 1,3-butadiene, behaves quite differently. Here the reaction product consists of equal amounts of residual diene and 1,4-dihydroboration product (eq 1).



(1)

It was observed previously that conjugation in dienes greatly decreases their reactivity towards hydroboration, either by diborane[10] or by disiamylborane.[11] The results with 1,3-butadiene are consistent with such a deactivating conjugation. Thus, the first hydroboration should produce *B*-(3-buten-1-yl)-9-BBN. Here the homoallylic double bond should possess a reactivity comparable to that of 1-butene, far more reactive than the conjugated double bonds of the parent diene. Accordingly, the second stage should be much faster than the first stage, and the dihydroboration product will dominate (eq 1).

In order to test this interpretation, we undertook a competitive hydroboration of an equimolar mixture of a nonconjugated diene, 1,4-hexadiene (cis and trans), and a related conjugated diene, *cis*-1,3-pentadiene, with 1 equiv of 9-BBN (eq 2). Nearly all of the *cis*-1,3-pentadiene remained unconsumed in the reaction mixture following utilization of the 9-BBN. Following oxidation of the product, GC examination



(2)

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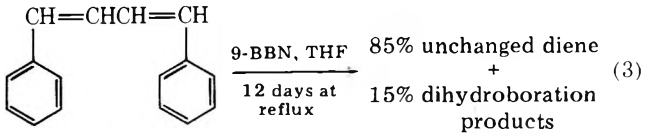
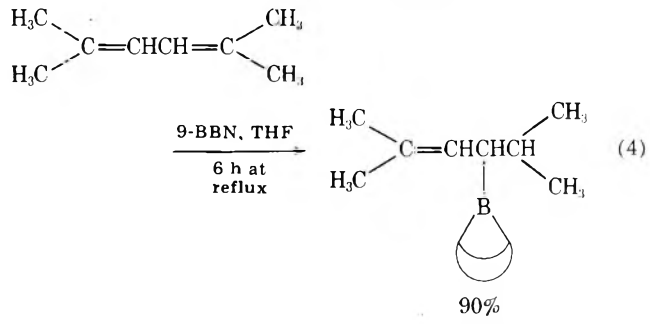
revealed only a trace amount of *cis*-3-penten-1-ol attributable to the hydroboration of *cis*-1,3-pentadiene (see below).

1,4-Diphenyl-1,3-butadiene, representative of dienes with even more extensive conjugation, proved to be remarkably resistant toward hydroboration with 9-BBN. An equimolar solution of 9-BBN and this diene failed to react to any significant extent, even after 12 days in refluxing THF. Analysis of the reaction mixture revealed the presence of 85% residual diene with only 15% of dihydroborated derivatives (not identified) (eq 3).



(3)

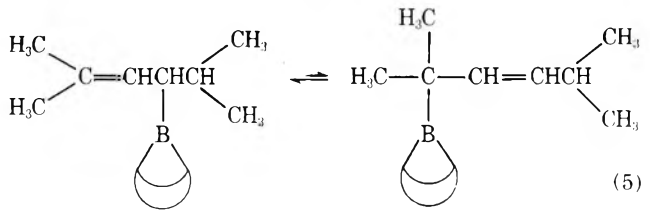
On the other hand, the hydroboration of 2,5-dimethyl-2,4-hexadiene with 9-BBN proceeds relatively rapidly to the monohydroboration product (eq 4). It should be noted that



(4)

in this case the influence of the geminal methyl groups directs the boron atom to the allylic position, in contrast to the homoallylic position taken by 9-BBN in the initial hydroboration of 1,3-butadiene. Possibly the large steric requirements of the 9-BBN moiety in the allylic position resists a second hydroboration which would place a second 9-BBN moiety in the adjacent, relatively crowded position.

It is probable that the allylic boron intermediate is in equilibrium with its isomer (eq 5). However, it would be anticipated that the boron atom would prefer to be attached to the secondary rather than the tertiary center, so that the product would consist predominantly of the secondary isomer.[12] Indeed, oxidation with alkaline hydrogen peroxide gives the corresponding secondary alcohol, 2,5-dimethyl-4-hexen-3-ol. On the other hand, acetone reacts with allylic rearrangement to produce 2,3,3,6-tetramethyl-4-hepten-2-ol in 80% yield (eq 6).[13]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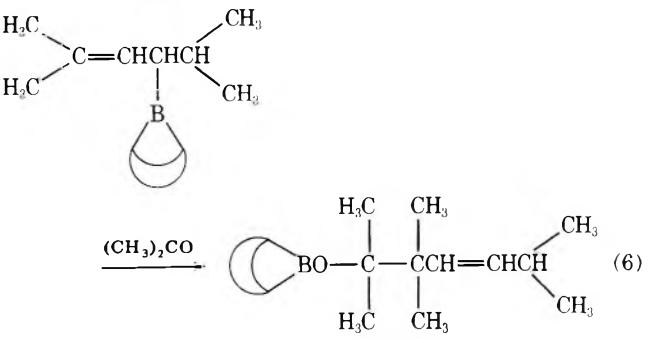
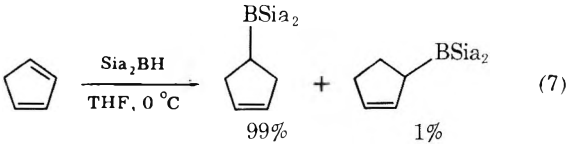


(6)

The hydroboration of the related isomeric 2,4-hexadienes is more complex and discussion of these results will be deferred until later in the paper.

Symmetrical Cyclic Conjugated Dienes. 1,3-Cyclopentadiene is readily monohydroborated by disiamylborane[11] or by diisopinocampheylborane[14] to give the homoallylic derivatives (eq 7). Unfortunately, hydroboration with 9-BBN

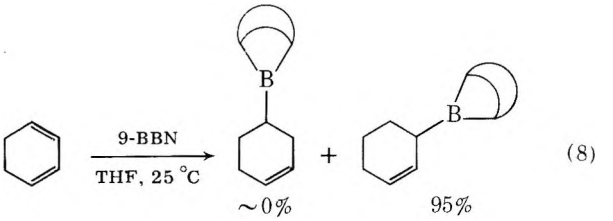


(7)

is slower, and dimerization of the 1,3-cyclopentadiene competes with the hydroboration, yielding complex products.

On the other hand, hydroboration of 1,3-cyclohexadiene proceeds smoothly to the monohydroboration stage. In agreement with this result, tests revealed that in the reaction with 9-BBN under identical conditions, 1,3-cyclohexadiene is indeed more reactive than cyclohexene. For example, 1,3-cyclohexadiene reacts completely with 1 equiv of 9-BBN in 6 h at 5 °C, whereas the corresponding reaction with cyclohexene is only 88% complete in 24 h.[3]

Either conjugation between the two double bonds is much less effective in 1,3-cyclohexadiene than in 1,3-butadiene in deactivating the system toward hydroboration, or the unusual inertness of cyclohexene toward hydroboration[3,5] is responsible for this capability exhibited by the reaction to stop at the monohydroboration stage. The product of the reaction is exclusively the allylic derivative, with none of the homoallylic derivative detected (eq 8).



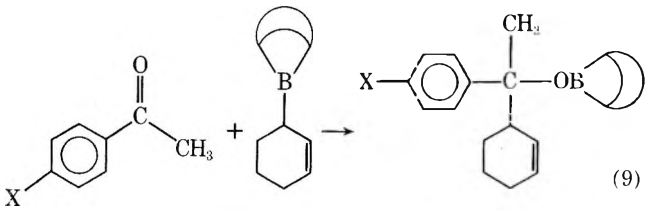
(8)

It was previously suggested that this difference in the position taken by boron in the hydroboration of 1,3-cyclopentadiene and 1,3-cyclohexadiene with disiamylborane might be the result of differences in the steric requirements of the planar C-5 ring and the puckered C-6 ring.[11] The same explanation may be utilized for 9-BBN.

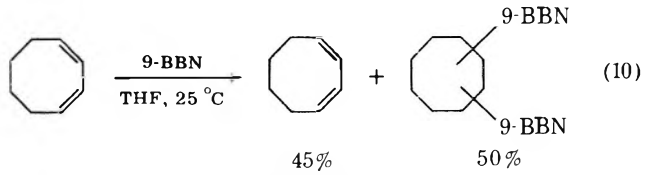
In the case of 2,5-dimethyl-2,4-hexadiene, discussed earlier, the directive influence of the terminal methyl substituents directs the 9-BBN moiety to the allylic position (eq 4). Here the reaction can also be controlled to yield the monohydroboration product predominantly. It was suggested that further hydroboration would be resisted since it would place the second 9-BBN moiety in the crowded adjacent position. Possibly the same explanation may hold for the cyclohexenyl intermediate (eq 8). Irrespective of the precise explanation of the phenomenon, the fact is that the reaction readily proceeds cleanly to give the allylic derivative. Such allylic derivatives are quite reactive, readily adding to the carbonyl group of aldehydes and ketones.[13]

Recently, we had occasion to synthesize a series of tertiary alcohols with the structure 1-aryl-1-(Δ^2-cyclohexenyl)ethanol. Apparently, it is not feasible to convert 1-chloro- or 1-bromo-2-cyclohexene into the corresponding Grignard reagents. The synthesis was successfully accomplished by treating the corresponding acetophenone derivatives with the 9-BBN adduct (eq 9).[15]

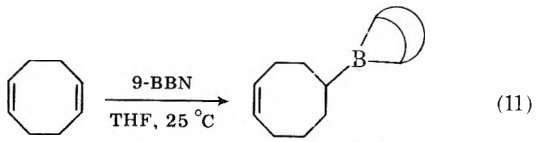
In contrast to the behavior of 1,3-cyclohexadiene, 9-BBN reacts with 1,3-cyclooctadiene to give predominantly dihy-


(9)

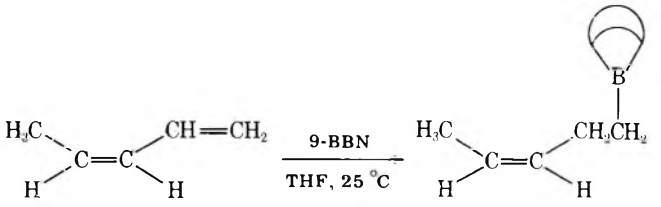
droboration products (not characterized). Thus, the second stage must be considerably faster than the first (eq 10).


(10)

This behavior contrasts with that of the nonconjugated 1,5 derivative. Here the monohydroboration product is readily synthesized[6] (eq 11).


(11)

Unsymmetrical Acyclic Conjugated Dienes. Unlike 1,3-butadiene, the next higher homologues, *cis*- and *trans*-1,3-pentadiene, are readily converted into the corresponding monohydroboration derivatives (eq 12, 13).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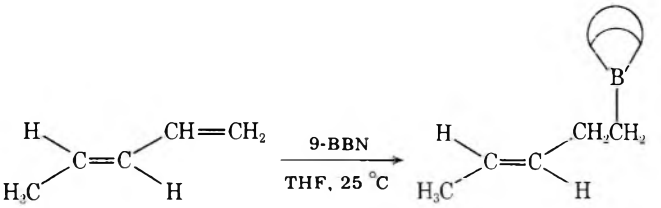
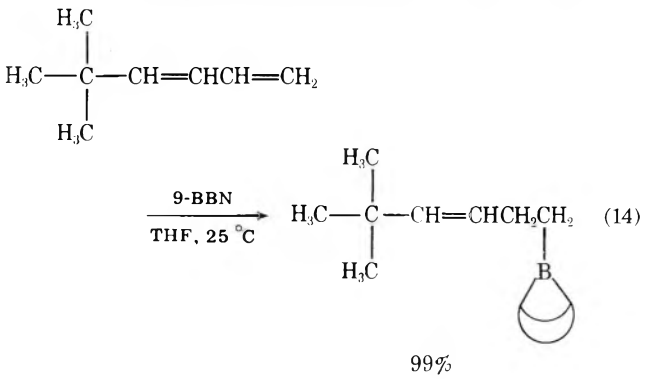
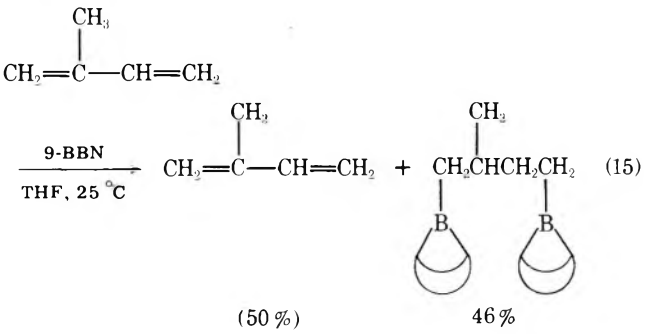

(13)

A simple terminal olefin is considerably more reactive toward 9-BBN than a related internal olefin. Thus, 1-hexene is about 100 times as reactive as *cis*-2-pentene.[6] This decreased reactivity of internal olefins is evidently sufficient to allow satisfactory yields of the monohydroboration products (eq 12, 13).

Similarly, 5,5-dimethyl-1,3-hexadiene undergoes clean conversion to the monohydroboration product (eq 14).

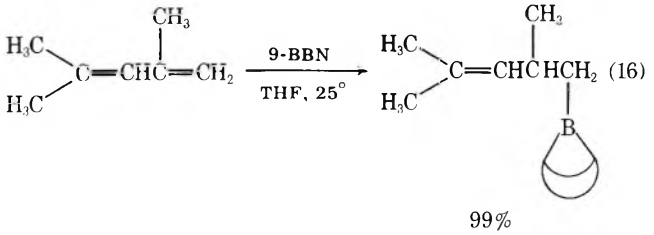

(14)

Isoprene, which undergoes significant monohydroboration with disiamylborane,[11] does not do so with 9-BBN (eq 15).


(15)

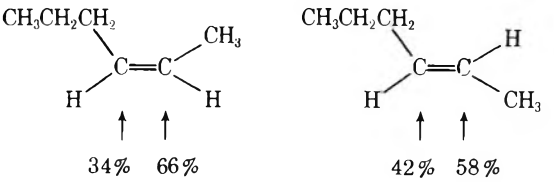
Evidently, this is a consequence of the difference in the behavior of the two reagents toward the structures $RCH{=}CH_2$ and $RC(CH_3){=}CH_2$. Disiamylborane is far more reactive towards the former than the latter, whereas 9-BBN is actually somewhat more reactive towards the 2-methyl-1-alkene structure.[6]

With *gem*-dimethyl substituents introduced into the 4 position of the isoprene molecule, monohydroboration again becomes feasible (eq 16).


(16)

The 2,4-Hexadienes. The hydroboration of the isomeric 2,4-hexadienes exhibits both interesting features and complexities which make it desirable to consider them as a separate group.

In the case of 1,3-butadiene, the monohydroboration product is evidently the homoallylic product, which is rapidly consumed by a second hydroboration to give the 1,4-diborabutane derivative (eq 1). On the other hand, the monohydroboration of 2,5-dimethyl-2,4-hexadiene proceeds to place



the boron in the allylic position (eq 4) with little dihydroboration. The structure of 2,4-hexadiene is halfway between these two extremes, and the hydroboration exhibits features common to both.

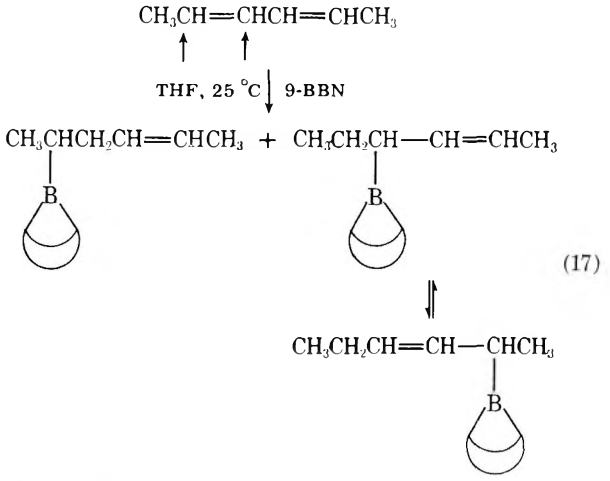
The reaction of 9-BBN with *cis*- and *trans*-2-hexene proceeds to place boron at both C-2 and C-3. Accordingly, it was anticipated that the monohydroboration of *cis,cis*-, *cis,trans*-, and *trans,trans*-2,4-hexadiene with 9-BBN would produce both the allylic and homoallylic 9-BBN derivatives (eq 17). The *B*-allyl-9-BBN component would undergo the usual fast allylic rearrangement,[12,13] providing an equilibrium mixture of the two allylic boranes (eq 17).

Unlike the previously discussed case of 2,5-dimethyl-2,4-hexadiene, the monohydroborated products from 2,4-hexadiene should readily react further with 9-BBN since the remaining double bonds are not highly sterically encumbered.

Table I. Monohydroboration of 2,4-Hexadienes with 9-BBN[a]

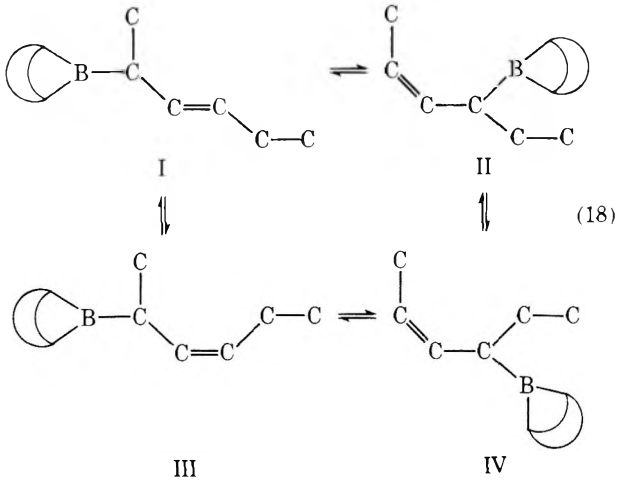
Isomer	Registry no.	Solvent	Residual diene,[b] %	Allylboranes, %			Diols,[c] %
				Total	I + III[h,i]	II + IV[h,j]	
Cis,cis	6108-61-8	Pentane[d]	30[f]	36	60	40	36
Cis,cis		THF[e]	19[g]	41	60	40	33
Trans,trans	5194-51-4	Pentane[d]	33[f]	16	60	40	50
Trans,trans		THF[e]	23[g]	19	60	40	45
Cis,trans	5194-50-3	THF[e]	18[g]	29	60	40	43

[a] Registry no.: 9-BBN, 280-64-8. [b] Residual diene isomer was identical to starting diene isomer. [c] 2,4-Hexanediol was the major component (>90%) in each case; diols were analyzed as bis(TMS) derivatives. [d] Reaction time, 10 days. [e] Reaction time, 55.5 h. [f] Analysis before oxidation. [g] Analysis after oxidation; some diene probably lost during oxidation. [h] See eq 18; allylboranes analyzed as their acetone derivatives. [i] Equal amounts of product from I and III were found. [j] Equal amounts of product from II and IV were found.



(17)

Assuming that a significant amount of allylborane is formed, the permanent allylic rearrangement should result in a mixture of four isomers (two cis/trans pairs) (eq 18). In



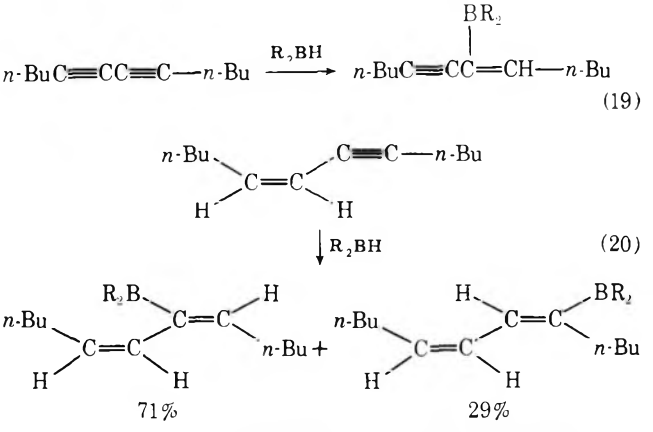
(18)

such equilibrium mixtures, boron generally prefers the least hindered position.[12] Consequently, we would expect that I and III will predominate in the mixture since in these isomers boron is flanked by a methyl group instead of an ethyl group. However, the difference in steric requirements of methyl, in I or III, vs. ethyl, in II or IV, is not large; the preference for I and III should not be great. If the permanent allylic rearrangement is important, the same isomer distribution of allylboranes, or their derivatives, should be found irrespective of which isomer of 2,4-hexadiene is hydroborated.

On the other hand, the amount of homoallylic derivative formed should depend somewhat on the particular isomer of 2,4-hexadiene hydroborated. Accordingly, we examined the hydroboration of all three isomeric 2,4-hexadienes. The cis,cis- and trans,trans isomers were hydroborated in pentane with 9-BBN, and all three isomers were hydroborated in THF with the reagent. Following completion of the hydroborations, the reaction products were first treated with excess acetone to convert the allylic boranes into the corresponding tertiary alcohol derivatives[13] and then oxidized with alkaline hydrogen peroxide to convert any homoallylic product into the corresponding homoallylic alcohol.[9] The experimental results are summarized in Table I.

With one exception, the results are in good agreement with expectations based upon the considerations presented. Dihydroboration is competitive with monohydroboration. The product distribution depends upon the particular diene used. However, the same mixture of allylboranes is formed from the three isomers. The products derived from I and III are found in larger amounts (~60%, 50% from I and 50% from III) than those from II and IV (~40%, 50% from II and 50% from IV).

Unexpectedly, no homoallylic alcohol was found in the oxidized products. This means that the initial hydroboration product does not contain a significant amount of the homoallylic 9-BBN derivative (eq 17). Possibly the −I inductive effect of the double bond is sufficient to direct the boron atom preferentially into the allylic, rather than the homoallylic, position. Such a directive effect has been observed previously. Thus, Zweifel and Polston reported that conjugated diynes exhibit a similar directive influence in hydroboration with either disiamylborane or dicyclohexylborane[16] (eq 19). The corresponding enyne exhibits a similar directive effect[16] (eq 20).



Superimposed on this directive influence favoring the formation of the allylic isomer in the monohydroboration product may be a reactivity factor, favoring the further hydroboration of the homoallylic derivative over the allylic isomer.

The diol formed is predominantly (>90%) the 2,4-hexanediol, accompanied by only a small amount of the 2,5 isomer. This would appear to require that the allylic isomers (eq 18) must resist hydroboration to place the two 9-BBN moieties in adjacent positions.

Another puzzling feature is the relative reactivities. In the reaction with 9-BBN, trans olefins are more reactive than cis.[5]

Table II. Hydroboration–Oxidation Product Distribution in the Reaction of Conjugated Dienes with One Equivalent of 9-BBN (0.5 M) in THF at 25 °C

Diene	Registry no.	Residual diene,[a] %	Unsaturated alcohols (%)	Diols,[b] %
1,3-Butadiene	106-99-0	48	Trace	48
1,4-Diphenyl-1,3-butadiene	886-65-7	85		~15[c]
2,4-Hexadiene[d]		18–33	Isomeric allylic derivatives (16–41)	33–50
2,5-Dimethyl-2,4-hexadiene	764-13-6	4	2,5-Dimethyl-4-hexen-3-ol (90)	
1,3-Cyclohexadiene	592-57-4	Trace	2-Cyclohexen-1-ol (85)	5[e]
1,3-Cyclooctadiene	1700-10-3	45		50[e]
cis-1,3-Pentadiene	1574-41-0	Trace	*cis*-3-Penten-1-ol (95)	3
trans-1,3-Pentadiene	2004-70-8	5	*trans*-3-Penten-1-ol (85)	8
2-Methyl-1,3-butadiene	78-79-5	50[f]	2-Methyl-3-buten-1-ol (7.4) 3-Methyl-3-buten-1-ol (3.7)	46
5,5-Dimethyl-1,3-hexadiene	1515-79-3	0	5,5-Dimethyl-3-hexen-1-ol (99)	0
2,4-Dimethyl-1,3-pentadiene	1000-86-8	Trace	2,4-Dimethyl-3-penten-1-ol (99)	0

[a] Analysis after oxidation with alkaline hydrogen peroxide. [b] Based on diene. [c] Not isolated or identified (see Experimental Section). [d] Data for isomeric 2,4-hexadienes. [e] Unresolved mixture of isomers. [f] Estimated by difference.

Yet the evidence is that the *cis,cis*-2,4-hexadiene is considerably more reactive than the *trans,trans*-2,4-hexadiene. The former reached a constant concentration (completion of reaction) within 48 h, whereas the latter required several days. Perhaps the higher reactivity arose from the lesser conjugation in the cis,cis structure, where steric interactions of the terminal methyl groups could affect the planarity of the π system. Such interactions would be absent in the trans,trans isomer.

These results for the hydroboration of 2,4-hexadienes with 9-BBN establish that it is not useful for synthetic applications. However, the system is of considerable interest theoretically, and further study is desirable to establish the precise course of the reaction and to provide a better understanding of the experimental observations.

Conclusion

For convenience, the results are summarized in Table II.

The hydroboration with 9-BBN of conjugated dienes exhibits certain characteristics which offer promise for applying this reaction to achieve the synthesis of desired boron intermediates and to apply those intermediates for synthetic purposes. Thus, conjugation frequently reduces the reactivity of dienes to the point where it is often feasible to hydroborate a nonconjugated double bond in the presence of a conjugated diene moiety.

Certain symmetrical conjugated dienes, such as 2,5-dimethyl-2,4-hexadiene and 1,3-cyclohexadiene, can be monohydroborated to give the corresponding allylic derivatives. However, others, such as 1,3-butadiene and 1,3-cyclooctadiene, afford dihydroborated products.

In the case of unsymmetrical dienes, it is possible to take advantage of substantial differences in the reactivities of the two olefin moieties constituting the diene to achieve monohydroboration at the more reactive site. Thus, unsymmetrical dienes, such as 1,3-pentadiene, 5,5-dimethyl-1,3-hexadiene, and 2,4-dimethyl-1,3-pentadiene, are readily monohydroborated with 9-BBN to yield the homoallylic 9-BBN derivatives.

Such homoallylic and hindered allylic 9-BBN derivatives can be oxidized to the corresponding alcohols[9] or utilized for the many reactions which organoboranes undergo.[9] In addition, the allylic 9-BBN derivatives can be utilized for additions to the carbonyl groups of aldehydes, ketones, and other carbonyl derivatives.[13]

It follows that the selective hydroboration with 9-BBN of dienes, both conjugated and nonconjugated,[6] provides a valuable entry to the conversion of such dienes into synthetically valuable intermediates.

Experimental Section

General Comments. In general, the techniques described in Chapter 9 of ref 9 were employed. All glassware, syringes, and needles were oven-dried at 150 °C for 4 h before use, assembled hot, and cooled under a stream of prepurified nitrogen. Syringes were assembled and fitted with needles while hot and then cooled as assembled units. They were flushed with nitrogen immediately before use. All reactions were stirred magnetically and were carried out under a static pressure of nitrogen.

Materials. The *n*-alkanes (Phillips) employed as internal GC standards were used as received. Technical grade pentane was stirred over concentrated sulfuric acid to remove any olefinic impurities, washed with aqueous base, dried over anhydrous magnesium sulfate, and distilled under nitrogen from lithium aluminum hydride. THF was distilled from lithium aluminum hydride prior to use. All conjugated dienes used in this study, except 1,3-cyclooctadiene (Cities Service), were purchased from Chemical Samples Co. and were used after checking their ^{1}H NMR spectra, indices of refraction, and GC analyses. 2,3-Hexanediol and 3,4-hexanediol were synthesized according to known procedures.[17,18] Other diols and alcohols used for identification purposes were either commercial materials, were available from previous studies,[10–13] or were isolated by preparative GC from the oxidized reaction mixtures. 9-BBN (mp 151–153 °C) was prepared and purified, and its solutions were standardized as reported previously.[4,5,9,12]

Hydroboration of 1,3-Butadiene. The determination of the stoichiometry of the reaction of 1,3-butadiene with 9-BBN offered difficulties because of the volatility of the diene. A detailed description of the procedure is provided to facilitate the work of others who may wish to do quantitative work in this area. To an oven-dried, nitrogen-flushed, flamed-out, 50-mL flask fitted with a reflux condenser, septum inlet, and magnetic stirring bar was added 9.26 mL of 0.540 M 9-BBN in THF (5.00 mmol) and 0.50 mL of *n*-tridecane (2.05 mmol; standard for GC analysis). The mixture was cooled to 0 °C (with crystallization of 9-BBN). The 1,3-butadiene, Phillips special purity (122.6 mL of gas at 23 °C, 753 mmHg, 5.00 mmol), was bubbled in slowly utilizing a gas-tight syringe.[3] The reaction mixture was allowed to come to room temperature with stirring. After 1 h, GC analysis indicated that the amount of residual diene was constant (48%). After a further 24 h, 0.37 mL of acetone (5.0 mmol) was added to react with any allylic intermediates, and the mixture was stirred for an additional hour. The reaction mixture was then treated with 1.73 mL of 2.89 M aqueous sodium hydroxide (5.0 mmol) and the organoborane intermediates oxidized with 1.8 mL of 34% hydrogen peroxide at 50 °C, maintaining the temperature there for 2 h. Excess potassium carbonate (9.0 g) was added to facilitate recovery of the diols.[10] The THF layer was separated, and the aqueous layer was extracted with THF (3 × 10 mL). The combined extracts were dried over anhydrous magnesium sulfate, followed by crushed 3Å molecular sieves. Samples were analyzed on a HP 5752B gas chromatograph, using a 6 ft × 0.25 in 10% XE-60 column, for ene-ols, including the acetone adduct 2,3-dimethyl-4-penten-2-ol. None were found. An aliquot of the dried extracts, 0.2 mL, was treated with 0.3 mL of BSTFA + 1% trimethylchlorosilane. This was heated for 3 h at 50 °C. The resulting bis(TMS) derivatives of the diols were analyzed on a Perkin-Elmer 226 gas chromatograph on a 150 ft × 0.01 in Golay column coated with OS-138. Only 1,4-butanediol (48%) and *cis*-

1,5-cyclooctanediol (96%), along with a trace (<0.1%) of 1,3-butanediol (as their TMS ethers), were detected.

Hydroboration of Conjugated Dienes. The following dienes were hydroborated, oxidized, and analyzed in the same manner: 2,4-dimethyl-1,3-pentadiene, 5,5-dimethyl-1,3-hexadiene, 2,5-dimethyl-2,4-hexadiene, *cis*-1,3-pentadiene, and *trans*-1,3-pentadiene.

General Reaction Procedure. An oven-dried, 100-mL flask equipped with a septum inlet, magnetic stirring bar, and reflux condenser was connected to a mercury bubbler. The system was purged with nitrogen and the inert atmosphere maintained until the oxidation stage. Normally, 10.0 mmol of olefin was added via syringe along with 3 mmol of a suitable internal standard. 9-BBN (0.5 M in THF), 10.0 mmol, was added to the reaction flask slowly via syringe. After sufficient time for complete reaction, the mixture was oxidized. Aqueous sodium hydroxide (3 M, 3.3 mL) was injected into the flask followed by the dropwise addition of hydrogen peroxide (30% solution, 3.3 mL) over 10–15 min. The reaction mixture was maintained at 50 °C for 1 h and then cooled to room temperature. The aqueous layer was saturated with anhydrous potassium carbonate, and the organic layer was separated and dried over anhydrous magnesium sulfate. The aqueous layer was extracted with 15 mL of pentane, dried over magnesium sulfate, and combined with the first extract. A small aliquot (~3 mL) was further dried over 3Å molecular sieves and used for GC analyses. Pentane (25–50 mL) was added to the remaining organic fraction to precipitate *cis*-1,5-cyclooctanediol. The pentane was decanted from the diol, which appeared as a viscous oil or a crystalline solid on the bottom of the flask. Preparative gas chromatography (10% XE-60, 5 ft × 0.5 in column) of the organic mixture afforded essentially pure >98% unsaturated alcohol. ^{1}H NMR (Varian T-60) and IR (PE-137 and PE-700) spectra were taken to confirm the structure of the product.

2-Methyl-1,3-butadiene and 1,3-cyclohexadiene were hydroborated and oxidized according to the above general procedure. However, the products were not isolated since authentic samples were available for GC analysis.

1,3-Cyclooctadiene was hydroborated and oxidized following the general procedure described above. Analysis of the oxidation products proved difficult. No conditions were found to effect complete separation of the diols. However, bis(TMS) derivatives were partially resolved into two peaks (10:1 ratio) on a 10% neopentyl glycol adipate (6 ft × 0.25 in) column. The structures of the products were assumed to be cyclooctanediols by comparison of their retention times (usually identical) with that of *cis*-1,5-cyclooctanediol on several columns of differing polarity (10% XE-60, 10% SE-30, 10% DC-710; all 12 ft × 1/8 in). The bis(TMS) derivatives of the cyclooctanediols were prepared as described above for the butanediol mixture.

Hydroboration–Derivatization of the Isomeric 2,4-Hexadienes. The isomeric dienes (*cis,cis*-, *cis,trans*-, and *trans,trans*-2,4-hexadienes) were subjected to identical reaction conditions following the general procedure described above up to the oxidation stage. After 55 h in THF, GC analysis showed no further decrease in diene concentration, and then acetone (0.74 mL, 10.0 mmol) was added. The reaction flask became warm with the addition of the acetone. After 1 h, aqueous sodium hydroxide (3 M, 3.3 mL) and hydrogen peroxide (30% solution, 3.3 mL) were added in the usual fashion followed by the normal workup procedure. The TMS derivatives were prepared in the same manner as described previously. GC analyses were performed on a Perkin-Elmer 226 capillary chromatograph using two OS-138 Golay columns in series (two 150 ft × 0.01 in). The TMS derivatives of 2,4-, 2,4-, 2,3-, and 3,4-hexanediol were easily separated under these conditions. Attempts to separate the isomeric homoallylic alcohols (from the reaction of allylboranes I–IV with acetone) by GC, either directly or as their TMS derivatives, were unsuccessful. However, the use of NMR shift reagents [Eu(fod)$_3$ and Pr(fod)$_3$] allowed the interpretation of the ^{1}H NMR spectrum of the mixture. Product identification was based on splitting patterns and coupling constant data, while quantitation was based on the relative areas of the *gem*-dimethyl signals from the methyl groups nearest the hydroxyl moiety.[19] The product distribution of the reaction is presented in Table I.

Competitive Hydroboration. An oven-dried, 100-mL flask equipped with a septum inlet, magnetic stirring bar, and reflux condenser was connected to a mercury bubbler. The system was purged with nitrogen, and the inert atmosphere was maintained until the oxidation stage. *cis*-1,3-Pentadiene (0.645 g, 9.5 mmol) and a cis/trans mixture of 1,4-hexadiene (0.872 g, 10.6 mmol) were added to the flask via syringe. *n*-Nonane (0.499 g, 3.78 mmol) was added as a GC internal standard. 9-BBN, 0.5 M in THF (20.0 mL, 10.0 mmol), was added also via syringe. After 3 h at room temperature, aqueous sodium hydroxide (3 M, 3.3 mL) and hydrogen peroxide (30% solution, 3.3 mL) were added followed by the standard oxidation workup. GC analysis on a 10% SE-30 (12 ft × 1/8 in) column revealed 9.7 mmol of *cis*- and *trans*-4-hexen-1-ol, a trace amount of *cis*-3-penten-1-ol, and 8.9 mmol of *cis*-1,3-pentadiene.

Hydroboration–Oxidation of 1,4-Diphenyl-1,3-butadiene. The general reaction procedure was followed. The reaction was allowed to proceed at reflux in THF for 12 days. The reaction mixture was oxidized and worked up in the usual manner. 1,4-Diphenyl-1,3-butadiene, 85% by weight, was isolated unchanged after the reaction. GC analysis on a 10% SE-30 (12 ft × 1/8 in) column revealed a small amount (~15%, based on diene) of material with a high retention time characteristic of a diol. No attempt was made to isolate or further identify this material.

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Hydrolithiation of α-Olefins by a Regiospecific Two-Step Process. Transformation of Alkyl Phenyl Sulfides to Alkyllithium Reagents

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The cleavage of primary alkyl phenyl sulfides by lithium naphthalene or lithium dispersion in tetrahydrofuran has been studied. Cleavage takes place in the direction of alkyllithium and lithium thiophenoxide. Preparation of alkyl phenyl sulfides by the anti-Markownikoff addition of thiophenol to α-olefins and subsequent cleavage by lithium led to the regiospecific addition of the elements of lithium hydride to the olefinic double bond. The overall yields of the alkyllithium products ranged from 40 to 90%. The preparation of a number of new mono- and dilithium organometallics is reported, some of which bear functional groups, e.g., $O(CH_2CH_2CH_2Li)_2$, $PhCH_2O(CH_2)_nLi$ (n = 3, 4), and $PhS(CH_2)_nLi$ (n = 3, 4, 5, 6).

The cleavage of a carbon–halogen bond by lithium metal is certainly the method of choice in preparative organolithium chemistry.[1] However, other heteroatoms bonded to carbon exhibit to a varying extent the same tendency to undergo cleavage[2] by lithium or other alkali metals and give products containing metal bonded to carbon. Ethers,[3,4] sulfides,[5] phosphines,[6] and several other classes of organic compounds are known to undergo cleavage by alkali metal, dissolving metals, or aromatic radical anions.[7] In very few cases, however, such reactions have found some utility in organometallic synthesis. For example, the preparation of benzyllithium,[3b] allyllithium,[4] and 2-phenylisopropylpotassium[8] utilizes the facile cleavage of benzyl, allyl, and 2-phenylisopropyl methyl ethers, respectively.

It has been proposed[9] that the cleavage of alkyl aryl ethers follows a three-step sequence involving two single electron transfer steps

$$ArOR \xrightarrow{+e^-} (ArOR)^-\cdot \longrightarrow ArO^- + R\cdot \xrightarrow{+e^-} ArO^- + R^- \quad (1)$$

When the reaction takes place at sufficiently low temperature, the fission of the radical anion $(ArOR)^-\cdot$ is mainly controlled by thermodynamic rather than kinetic factors, and in such a case the product-determining step is the one in which the most stable anion and the most stable radical are to be produced. Thus, alkyl aryl ethers tend to cleave to the phenoxide anion and alkyl carbanion.[9] It appears that the reaction is dominated by the stability of the phenoxide, since it is derived from a relatively strong acid; pK_a for phenol = 10. The alternative mode of cleavage which would lead to the formation of the alkoxide, pK_a of an alcohol usually around 18, and phenyl radical appears to have unfavorable energetics.

Along this line of reasoning the group PhS– would be expected to be a better leaving group than phenoxide in the cleavage of alkyl phenyl sulfides; pK_a of thiophenol = 6.5. Indeed, the group PhS– behaves sometimes as a pseudohalogen.[10] Besides its ready cleavage by alkali metals, which is reminiscent of halogen-like behavior, thiophenol is closely analogous to HBr as far as its mode of addition to an olefinic double bond in the presence of peroxide[11] is concerned.

The purpose of this paper is to demonstrate that the constituents of lithium hydride can be added regiospecifically to α-olefins by a two-step reaction sequence. The direct addition of lithium hydride to an olefin would certainly be a decisive step toward the solution of the problem of total synthesis of organolithium reagents. This goal, however, might prove to be a difficult task, due to lack of solubility of LiH in the usual aprotic solvents. The results given in the following section demonstrate that an alternative indirect "hydrolithiation" can be achieved in two steps, giving regiospecifically the primary organolithium compound. This method exploits two reactions, each of which is usually of high yield, namely, (1) the free-radical addition of thiphenol to α-olefins and (2) the cleavage of the C–S bond by lithium metal or lithium arenides, in a reaction which leads to the formation of organometallic products.

$$RCH{=}CH_2 + PhSH \xrightarrow{\text{peroxide}} RCH_2CH_2SPh$$

$$RCH_2CH_2SPh + 2Li \rightarrow RCH_2CH_2Li + PhSLi \quad (2)$$

Until the direct addition of lithium hydride to olefins becomes feasible the above alternative could be useful in certain cases in preparative organolithium chemistry.

Results and Discussion

In Table I are summarized the yields of the sulfides obtained by the AIBN or photochemically induced addition of thiophenol to various olefins, including a few with functional groups. The yields of the corresponding alkyllithiums by the method of lithium naphthalene and of lithium dispersion are also included in the table.

Particularly facile is the addition of thiophenol to activated olefins such as styrene, 1,1-diphenylethylene, and diallyl ether. Generally, the yields of the distilled sulfides range from good to excellent.

Alkyl phenyl sulfides undergo a rather facile cleavage by lithium naphthalene in tetrahydrofuran (THF) solvent. Of course, the cleavage reaction must be carried out at low enough temperature in order to prevent organolithium loss by THF cleavage.[12] Even at temperatures as low as −70 °C RSPh and $Li^+C_{10}H_8^-\cdot$ react at an appreciable rate. Generally, accumulation of phenyl groups in the sulfide molecule increases the ease of cleavage of the sulfide.[13] This might well mean that the higher the electron affinity of the sulfide the more facile the cleavage.[14] Thus a sulfide such as n-octyl phenyl cleaves considerably less readily than Ph_2CHCH_2SPh for example. It appears that sulfides behave like their oxygen counterparts[9] as far as the reaction with aromatic radical ions is concerned. The rate-determining step in most cases[14] is the transfer of the odd electron from the aromatic radical ion to the sulfide, a process which, of course, is governed by the relative electron affinities of the aromatic hydrocarbon and the sulfide.[15a] Reaction times usually range between 0.1 and 0.5 h at temperatures from −55 to −20 °C.

Our expectations about the leaving aptitude of the thiophenoxy group have not been disappointed. Cleavage occurred according to the expected mode (eq 3) and the yields of the

$$RSPh + 2Li^+C_{10}H_8^-\cdot \begin{cases} \xrightarrow{\times} PhLi + RSLi \\ \longrightarrow RLi + PhSLi \end{cases} \quad (3)$$

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Table I. Two-Step Hydrolithiation of Some Olefins

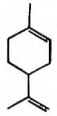
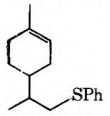
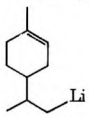
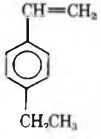
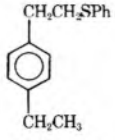
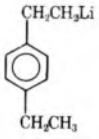
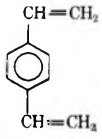
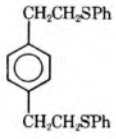
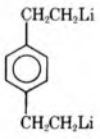
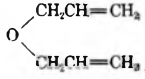
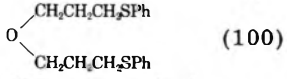
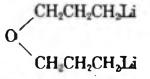
Olefin	Registry no.	Sulfide (% yield)	Registry no.	Alkyllithium	Registry no.	% yield of RLi by $Li^+C_{10}H_8^{-\cdot}$	% yield of RLi by Li dispersion
$CH_3(CH_2)_4CH{=}CH_2$	592-76-7	$CH_3(CH_2)_6SPh$ (72)	13910-15-1	$CH_3(CH_2)_6Li$	25047-67-0	87	62
$CH_3(CH_2)_5CH{=}CH_2$	111-66-0	$CH_3(CH_2)_7SPh$ (78)	13910-16-2	$CH_3(CH_2)_7Li$	3314-49-6	93	61
$CH_3(CH_2)_3C(Et){=}CH_2$	1632-16-2	$CH_3(CH_2)_3CH(Et)CH_2SPh$ (67)	13910-17-3	$CH_3(CH_2)_3CH(Et)CH_2Li$	13067-81-7	61	70
$(CH_3)_3CCH{=}CH_2$	558-37-2	$(CH_3)_3CCH_2CH_2SPh$ (60)	15672-95-4	$(CH_3)_3CCH_2CH_2Li$	6909-52-0	100	80
$PhCH_2CH{=}CH_2$	300-57-2	$Ph(CH_2)_3SPh$ (80)	30134-12-4	$Ph(CH_2)_3Li$	64740-46-1	70	79
$PhCH_2CH_2CH{=}CH_2$	768-56-9	$Ph(CH_2)_4SPh$ (83)	64740-40-5	$Ph(CH_2)_4Li$	64740-47-2		74
	138-86-3	 (70)	64740-41-6		64740-48-3	74	55
$PhCH{=}CH_2$	100-42-5	$PhCH_2CH_2SPh$ (95)	13865-49-1	$PhCH_2CH_2Li$	42808-98-0	83	65
$PhC(CH_3){=}CH_2$	98-83-9	$PhCH(CH_3)CH_2SPh$ (94)	4148-81-6	$PhCH(CH_3)CH_2Li$	64740-49-4	82	89
	3454-07-7	 (>90)	64740-42-7		64740-50-7	71	80
	105-06-6	 (>90)	64740-43-8		64740-51-8	100	94
$Ph_2C{=}CH_2$	530-48-3	Ph_2CHCH_2SPh (100)	13112-47-5	Ph_2CHCH_2Li	64740-52-9	96	87
$PhCH_2OCH_2CH{=}CH_2$	14593-43-2	$PhCH_2O(CH_2)_3SPh$ (70)	64740-44-9	$PhCH_2O(CH_2)_3Li$	64740-53-0	70	
	557-40-4	 (100)	64740-45-0		64740-54-1	88	90
$ClCH_2CH{=}CH_2$	107-05-1	$Cl(CH_2)_3SPh$ (70)	4911-65-3	$PhS(CH_2)_3Li$	64740-55-2	59	

Table II. Transformation of Certain Sulfides, Bearing a Second Functional Group, to Substituted Alkyllithiums

Starting material	Registry no.	Sulfide (% yield)	Registry no.	Alkyllithium	Registry no.	% yield
$ClCH_2CH_2Cl$; PhSH	107-06-2; 108-98-5	$PhSCH_2CH_2SPh$ (90)	622-20-8	$PhSCH_2CH_2Li$	64740-26-7	0
$Cl(CH_2)_4Cl$; PhSH	110-56-5; –	$Cl(CH_2)_4SPh$ (65)		$PhS(CH_2)_4Li$	64740-27-8	75
$Cl(CH_2)_5Cl$; PhSH	628-76-2; –	$Cl(CH_2)_5SPh$ (70)	14633-28-4	$PhS(CH_2)_5Li$	64740-28-9	66
$Cl(CH_2)_6Cl$; PhSH	2163-00-0; –	$Cl(CH_2)_6SPh$ (75)	64740-56-3	$PhS(CH_2)_6Li$	64740-29-0	62
$Cl(CH_2)_4SPh$; PhOH	14633-31-9; 108-95-2	$PhO(CH_2)_4SPh$ (93)	59950-11-7	$PhO(CH_2)_4Li$	64740-30-3	83
$Cl(CH_2)_4SPh$; $PhCH_2OH$	–; 100-51-6	$PhCH_2O(CH_2)_4SPh$ (53)	64740-57-4	$PhCH_2O(CH_2)_4Li$	64740-31-4	61
$Cl(CH_2)_4Cl$; PhSH		$PhS(CH_2)_4SPh$ (95)	5330-89-2	$PhS(CH_2)_4Li$		80
$Br(CH_2)_5Br$; PhSH	111-24-0; –	$PhS(CH_2)_5SPh$ (90)	40340-02-1	$PhS(CH_2)_5Li$		75
$Cl(CH_2)_6Cl$; PhSH		$PhS(CH_2)_6SPh$ (90)	55129-89-0	$PhS(CH_2)_6Li$		65
Ph_3CH; $BrCH_2CH_2SPh$	519-73-3; 4837-01-8	$Ph_3CCH_2CH_2SPh$ (81)	64740-24-5	Ph_3CLi	733-90-4	54
Ph_2CH_2; $BrCH_2CH_2SPh$	101-81-5; –	$Ph_2CHCH_2CH_2SPh$ (79)	64740-25-6	Ph_2CHLi	881-42-5	88

alkyllithium reagents ranged in most cases from 70 to 100%. Yields and product characterization were based on the carboxylic acids produced by carbonation of the alkyllithium compounds.

Considerably less ready is the cleavage of the sulfides with lithium metal in THF. The use of lithium dispersion and a catalytic amount of naphthalene, especially in conjuction with the employment of a Hershberg stirrer, was found to be a useful method. In this case, however, reaction times of 1–3 h are required at temperatures from −40 to −20 °C. This inconvenience is offset by the absence of naphthalene in the products. Organolithium yields by the method of lithium dispersion ranged from 55 to 94%. It must be noted that the cleavage reaction of a given sulfide by the two methods was not run at the same temperature and therefore any conclusions drawn on the basis of the two sets of yields could be risky.

Thiophenol and naphthalene could be a problem in product isolation when the organolithium prepared by this method is used to make a derivative other than a carboxylic acid. Acidic derivatives can be separated from thiophenol by oxidizing the latter to the corresponding disulfide, PhSSPh, with alkaline hydrogen peroxide. Another way of converting thiophenol to a neutral, less malodorous derivative is by reacting it with dimethyl sulfate, i.e., by converting it to thioanisole. The separation of a neutral product from naphthalene could be a more serious problem. Naphthalene is very volatile in steam, and steam distillation should be the method of choice for separating naphthalene from a neutral product whenever possible. We did not experience any difficulties in separating naphthalene from alkyldiphenylcarbinols by steam distillation.

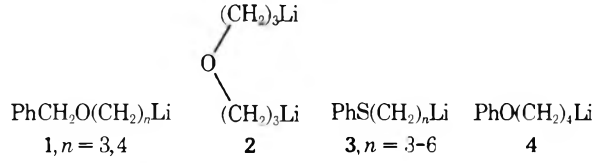
Complications could arise in the sulfide cleavage reaction in cases where other reactive sites are present in the sulfide molecule, for example, the presence of an acidic C–H bond,[15b] in which self-metalation can take place:

$$ArCH_2SPh + 2Li \rightarrow ArCH_2Li + PhSLi$$

$$ArCH_2Li + ArCH_2SPh \rightarrow ArCH(Li)SPh + ArCH_3$$

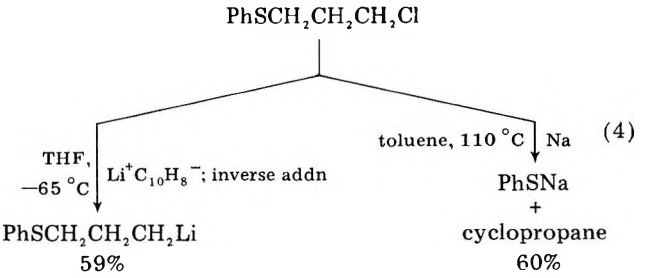
Although this situation does not occur in the case of the sulfides prepared by the anti-Markownikoff addition of thiophenol to olefins, it can happen in cleavage of sulfides prepared by other methods. The presence of other cleavable groups such as halogen–carbon, PhO–C, Ph_2P–C, and others could make the reaction complicated. The order, however, of cleavability according to our results is Cl–C > PhS–C > PhO–C > Ph_2P–C, an order that varies inversely with the acid pK_a values of HCl, PhSH, PhOH, and Ph_2PH, respectively: −6.1; 6.5; 9.99; 21.7.[16]

The marked difference in the cleavability of halogen vs. thiophenoxy and thiophenoxy vs. phenoxy or alkoxy group made possible the preparation of some organolithium reagent containing the functional groups of ether or thioether, such as **1–4**. The results with substituted alkyllithiums are summarized in Table II (see also the last three entries of Table I). Alkoxy sulfides and chlorosulfides or disulfides have been employed in the preparation of the substituted organolithium reagents, some of which are new. Regioselectivity in cleaving one of the two cleavable groups has been achieved by employing inverse addition and just 2 equiv of lithium naphthalene and a low reaction temperature, usually between −70 and −65 °C. Disulfides of the general structure $PhS(CH_2)_nSPh$ can be transformed to $PhS(CH_2)_nLi$ under the above mentioned conditions in a relatively clean reaction. It appears that lithium as a substituent exerts a deactivating effect upon the PhS–C in $PhS(CH_2)_nLi$ toward cleavage. This becomes evident from the longer reaction time which is required for complete reaction of a disulfide with 4 equiv of lithium naphthalene. Under this stoichiometry disulfides react with lithium naphthalene in a complicated manner. Besides the formation of dilithium derivative $Li(CH_2)_nLi$, the main reaction pathway appears to lead to the formation of species derived from the attack of the "radical anion" (**5**) on naphthalene radical anion.



$$LiCH_2(CH_2)_{n-2}CH_2\cdot$$
5

It could be of interest to contrast the different courses that are followed when 3-chloropropyl phenyl sulfide is reacted with sodium metal in refluxing toluene[17] and with lithium naphthalene in THF at −65 °C (eq 4). It is quite possible that



(4)

under the homogeneous conditions fragmentation of the chloro sulfide is avoided due to the lower temperature of reaction.

Despite the employment of low reaction temperatures in this study, fragmentation during sulfide cleavage did occur (see first and the last two entries of Table II). The sulfide $Ph_3CCH_2CH_2SPh$ undergoes fragmentation during reaction with lithium naphthalene according to the equation

$$Ph_3CCH_2CH_2SPh + 2Li^+C_{10}H_8^{-}\cdot \rightarrow Ph_3CLi + CH_2{=}CH_2 + PhSLi + 2C_{10}H_8 \quad (5)$$

This fragmentation is closely analogous to the one observed during reduction of $Ph_3CCH_2CH_2I$ with sodium in liquid ammonia.[18] The sulfides $Ph_2CHCH_2CH_2SPh$ and $PhSCH_2CH_2SPh$ appear to belong to the same category. They too undergo fragmentation and form ethylene during reaction with lithium naphthalene. In the case of the sulfide $Ph_2CHCH_2CH_2SPh$, the extrusion of ethylene was inferred not only on the basis of the observed product Ph_2CHLi but also on the actual trapping of ethylene by cyclohexyllithium[19]

$$Ph_2CHCH_2CH_2SPh \xrightarrow[-PhSLi]{+2Li^+C_{10}H_8^{-}\cdot} Ph_2CHLi + CH_2{=}CH_2$$

$$\xrightarrow{c\text{-}C_6H_{11}Li} Ph_2CHLi + c\text{-}C_6H_{11}CH_2CH_2Li \quad (6)$$

A reasonable mechanism of these fragmentations is depicted in Scheme I. Of course, one can give several other

Scheme I

$$ZCH_2CH_2SPh + Li^+C_{10}H_8^{-}\cdot \rightleftharpoons (ZCH_2CH_2SPh)^-\cdot Li^+ + C_{10}H_8$$

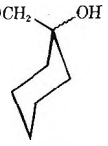
$$(ZCH_2CH_2SPh)^-\cdot Li^+ \rightarrow ZCH_2CH_2\cdot + PhSLi$$

$$ZCH_2CH_2\cdot \rightarrow Z\cdot + CH_2{=}CH_2$$

$$Z\cdot + Li^+C_{10}H_8^{-}\cdot \rightarrow Z^-Li^+ + C_{10}H_8$$

$$Z = Ph_3C, Ph_2CH, PhS$$

Table III. Reaction of Select Organolithium Reagents with Ketones

Organolithium	Ketone	Registry no.	Carbinol	Registry no.	Yield, %	Mp, °C	NMR data
$CH_3CH(Ph)CH_2Li$	$Ph_2C{=}O$	119-61-9	$Ph_2C(OH)CH_2CH(Ph)CH_3$	64740-32-5	68	90–92	1.20 (d, J = 6.0 Hz, 3 H, CH_3); 1.87 (s, 1 H, OH); 2.8 (m, 3 H, $CHCH_2$); 7.25 (m, 15 H, three C_6H_5)
$CH_3(CH_2)_7Li$	$Ph_2C{=}O$		$CH_3(CH_2)_7C(OH)Ph_2$	16727-37-0	76	oil	0.87 (distort t, 3 H, CH_3); 1.25 (s, 12 H, $C(CH_2)_6C$); 2.17 (br s, 3 H, CH_2OH); 7.30 (m, 10 H, two C_6H_5)
$PhS(CH_2)_5Li$	$Ph_2C{=}O$		$PhS(CH_2)_5C(OH)Ph_2$	64740-33-6	33	oil	1.40 (br band, like a diffuse t, 6 H, $C(CH_2)_3C$); 2.15 diffuse t, 2 H, CH_2CO); 2.82 (diffuse t, 2 H, CH_2S); 3.36 (s, 1 H, OH); 7.25 (m, 15 H, three C_6H_5)
$CH_3CH(Ph)CH_2Li$	Cyclohexanone	108-94-1		64740-34-7	22	oil	1.26 (d); 0.89–2.02 (br band); 1.81 (q, 15 H); 3.02 (br m, 2 H, CHPh and OH); 7.25 (s, 5 H, aromatic)
Ph_2CHCH_2Li	$Ph_2C{=}O$		$Ph_2CHCH_2C(OH)Ph_2$	64740-35-8	38	92–94[a]	1.90 (s, 1 H, OH); 3.15 (d, J = 7.0 Hz, 2 H, CH_2CO); 4.04 (t, 1 H, CHPh); 7.15 (m, 20 H, four C_6H_5)

[a] Lit. mp 95–96 °C ("Dictionary of Organic Compounds", Vol. 5, Eyre and Spottiswoode, London, 1965, p 3034).

schemes which can rationalize the observed chemistry in these fragmentations. For example, the radical $ZCH_2CH_2\cdot$ alternatively can be reduced to the corresponding carbanion and then fragment:[18]

$$Z{-}CH_2CH_2^- \rightarrow Z^- + CH_2{=}CH_2$$

There could be not doubt that the driving force for these fragmentations is the thermochemical stability of the fragments.[20,21]

As far as the derivatization of the organolithium reagents prepared by the method described in this paper is concerned, it can be said that carbonation is the reaction which works quite well in all cases. A small number of select organolithium reagents were reacted with benzophenone or cyclohexanone. These results are summarized in Table III. Simple alkyllithium reagents such as *n*-octyl and 2-phenylpropyl gave good yields of carbinols after reaction with benzophenone. All reaction mixtures from the organolithium reagents and benzophenone were blue and paramagnetic. In the particular case of 2-phenylpropyllithium and benzophenone a 15% conversion of benzophenone to the corresponding ketyl could be estimated on the basis of the bulk paramagnetism of the solution. The low yield of the carbinol with the substituted organolithium $PhS(CH_2)_5Li$ could be due to the possible fragmentation of the $PhS(CH_2)_5$ moiety during reaction with benzophenone. Tetrahydrofuran is a notorious solvent for reactions of organolithium reagents with ketones having enolizable hydrogen(s). It appears that enolization was the main reaction between 2-phenylpropyllithium and cyclohexanone, judging from the low yield of the addition product. Lastly, the utility of these organolithium reagents for making derivatives other than carboxyclic acids remains to be determined.

Conclusion

It has been shown that alkyl phenyl sulfides prepared by the anti-Markownikoff addition of thiophenol to compounds bearing an α double bond between carbon atoms or almost any primary alkyl phenyl sulfide can be transformed to the corresponding alkyllithium reagents in yields ranging from fair to excellent. In contrast to the conventional alkyllithium preparation, which depends on the availability of the corresponding alkyl chlorides or bromides, the method described in this paper utilizes cheaper and more readily available starting materials, i.e., olefins. For example, the preparation of 2-phenylpropyllithium according to the conventional method would require 2-phenylpropyl chloride, a compound which is not listed in the catalogues of the major chemical suppliers, whereas the present method utilizes the very cheap α-methylstyrene. Shortcomings of the method could be: (1) the fact that one has to work with a malodorous reagent, thiophenol; (2) problems in product isolation due to the presence of naphthalene and thiophenol in the reaction mixture; and (3) the THF solvent in which extensive enolization occurs during reaction of organolithium reagent with a ketone having enolizable hydrogens. In most cases, however, disadvantages 1 and 2 can be circumvented.

Experimental Section

All boiling points and melting points were uncorrected. Infrared spectra were determined with a Beckman IR-33 spectrophotometer. NMR spectra were obtained on a Varian Associates A-60A spectrometer using Me_4Si as the internal standard and deuteriochloroform as the solvent. Concentrations of paramagnetic compounds were measured with the NMR spectrometer according to the method of Evans[22] as it was adapted[23] to the study of equilibra and kinetics of radical ions. Cyclohexane, 20% v/v in carbon tetrachloride, or *tert*-butyl bromide, 50% v/v in carbon tetrachloride, served as external markers. The high-field band of THF served as the internal marker. In the presence of a paramagnetic solute the NMR signals of THF lose their fine structure and are shifted to higher fields. The shift varies linearly with concentration of the paramagnetic solute. A working curve for shift ($\Delta\nu$) vs. lithium benzophenone ketyl concentration was employed. It has the form:

$$\Delta\nu = -6.5 + 79C$$

where $\Delta\nu$ is the position of the high-field band of THF in the solution

Table IV. Boiling or Melting Points of the Alkyl Phenyl Sulfides

Sulfide	Mp or bp (mm), °C	Lit. mp or bp (mm), °C	Ref[a]
$CH_3(CH_2)_6SPh$	85–90 (0.20)	127–129 (2.0)	*b*
$CH_3(CH_2)_7SPh$	120 (0.8)	175 (18)	*c*
$CH_3(CH_2)_3CH(Et)$-CH_2SPh	97–98 (0.05)	160 (12)	*d*
$PhCH_2CH_2SPh$	110–113 (0.15)	188–189 (15)	*e*
$Ph(CH_2)_4SPh$	135–145 (0.20)	153–154 (1.0)	*f*
$PhCH(CH_3)CH_2SPh$	110–115 (0.15)	177–178 (11)	*g*
$Cl(CH_2)_3SPh$	82–84 (0.10)	116–117 (4)	*h*
$Cl(CH_2)_4SPh$	121 (0.20)	155 (12)	*i*
$Cl(CH_2)_5SPh$	101–102 (0.10)	140 (1)	*i*
$Cl(CH_2)_6SPh$	120–122 (0.10)	8	*j*
$PhS(CH_2)_4SPh$	82–83	84.5	*k*
$PhS(CH_2)_6SPh$	76–78	82	*l*

[a] As a general reference see, for example, "Organic Chemistry of Divalent Sulfure", Vol. II, E. E. Reid, Ed., Chemical Publishing Co., New York, N.Y., 1960. [b] K. Takahashi, K. Ohki, T. Mizura, and S. Toyoshima, *Chem. Pharm. Bull. (Tokyo)*, **8**, 757 (1960). [c] H. Burton and N. A. Davy, *J. Chem. Soc.*, 52 (1947). [d] G. Rabilloud, *Bull. Soc. Chim. Fr.*, **2**, 348 (1907). [e] F. Ashworth and G. N. Burkhardt, *J. Chem. Soc.*, 1791 (1928). [f] V. Traynelis and R. F. Love, *J. Org. Chem.*, **26**, 2728 (1961). [g] J. Kenyon, H. Phillips, V. P. Pittmann, R. B. Shakleton, D. E. Kahn, F. H. Yortson, and N. E. Cochinaras, *J. Chem. Soc.*, 1072 (1935). [h] W. R. Kirner and G. H. Richter, *J. Am. Chem. Soc.*, **51**, 3409 (1929). [i] G. M. Bennett, F. Heathcoat, and A. N. Mosses, *J. Chem. Soc.*, 2567 (1929). [j] C. S. Marvel and R. R. Chambers, *J. Am. Chem. Soc.*, **70**, 993 (1948). [k] G. M. Bennett and A. N. Mosses, *J. Chem. Soc.*, 1697 (1931). [l] F. G. Bordwell, H. M. Anderson, and B. M. Pitt, *J. Am. Chem. Soc.*, **76**, 1082 (1954).

of the paramagnetic compound referred to external 20% cyclohexane in CCl_4, in hertz, and C is the concentration of lithium benzophenone ketyl in moles per liter. By subtracting the underlying diamagnetic shift, −6.5 Hz, the shift vs. concentration relation becomes $\Delta\nu = 79C$. In this case $\Delta\nu$ is the *net* paramagnetic shift of the high-field band of THF from any external marker.

The chemicals used in this work were commercial products of Merck-Schuchardt or Fluka, usually 99% pure, and were used without further purification. 4-Phenyl-1-butene was prepared in 64% yield from benzylsodium and allyl bromide following a procedure for preparing *n*-butylbenzene.[24] Allyl benzyl ether was prepared from sodium benzylate and allyl chloride according to the classic Williamson synthesis.

Purification of Tetrahydrofuran. The solvent was stored at least for 1 week over sodium hydroxide pellets, refluxed under nitrogen for several hours over fresh NaOH pellets, and distilled under nitrogen. The distillate was refluxed with sodium metal under nitrogen, distilled once more, and finally redistilled from lithium aluminum hydride containing triphenylmethane indicator under argon. In absolutely anhydrous THF lithium aluminum hydride metalates Ph_3CH rapidly and therefore the final distillation was done after the appearance of the red coloration due to Ph_3CLi.

Preparation of Alkyl Phenyl Sulfides. (A) Photochemical Initiation. An equimolar mixture of the olefin and thiophenol was irradiated with a General Electric 275 W "sunlamp". The progress of the reaction was followed by NMR analysis on aliquots drawn from time to time. No cooling was applied during irradiation, so the temperature of the reaction mixture was usually between 70 and 90 °C.

(B) Initiation by AIBN. α,α-Azoisobutyronitrile (50–150 mg) was suspended in part of the olefin and the suspension was added slowly to a stirred and heated (80–90 °C) mixture of thiophenol and the rest of the olefin. The total amount of the olefin was equimolar to thiophenol. Reaction times usually ranged from 2 to 5 h. At the end of the reaction (photochemical or free radical) the mixture was diluted with benzene, the unreacted thiophenol was extracted with sodium hydroxide solution, and finally the product was fractionally distilled after removing benzene. Table IV summarizes the boiling or melting points of the known sulfides and Table V summarizes some data of the sulfides which are new.

Lithium Naphthalene. Lithium naphthalene was prepared by stirring equivalent amounts of naphthalene and lithium chips in THF

Table V. Data of New Sulfides

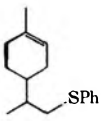
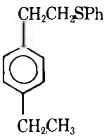
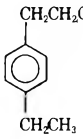
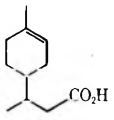
Sulfide	Mp or bp (mm), °C	NMR
$PhO(CH_2)_4SPh$	53	1.76 (m, 4 H, $C(CH_2)C$); 2.86 (t, 2 H, CH_2S); 3.80 (t, 2 H, CH_2O); 7.04 (m, 10 H, two C_6H_5)
$O(CH_2CH_2CH_2SPh)_2$	of high bp	1.84 (m, 4 H, CCH_2C); 2.97 (t, J = 7.5 Hz, 4 H, CH_2S); 3.44 (t, J = 6.1 Hz, 4 H, CH_2O); 7.27 (m, 10 H, two C_6H_5)
	130 (0.15)	1.05 (distorted triplet-like multiplet); 1.73 (br distorted doublet, 14 H); 2.83 (m, 2 H, CH_2S); 5.31 (br s, 1 H, olefinic); 7.20 (m, 5 H, aromatic)
	112–116 (0.05)	1.18 (t, J = 7.8 Hz, 3 H, CH_3); 2.57 (q, 2 H, CH_2CH_3); 2.93 (m, 4 H, CH_2CH_2S); 7.10 (m, 9 H, aromatic)
	of high bp	2.91 (m, 8 H, aliphatic); 7.08 (m, 14 H, aromatic)
$PhS(CH_2)_5SPh$	185–188 (0.03)	1.57 (unsymm t, 6 H, $C(CH_2)_3C$); 2.85 (diffuse t, 4 H, CH_2S); 7.25 (s, 10 H, two C_6H_5)
$PhCH_2O(CH_2)_3SPh$	142–148 (0.10)	1.91 (m, 2 H, CCH_2C); 2.96 (t, J = 7.4 Hz, 2 H, CH_2S); 3.46 (t, J = 6.0 Hz, 2 H, CH_2O); 4.38 (s, 2 H, CH_2Ph); 7.18 (s, 10 H, two Ph)
$(CH_3)_3CCH_2CH_2SPh$	72–74 (0.05)	0.91 (s, 9 H, $(CH_3)_3C$); 1.54 (m, 2 H, CH_2Bu-*t*); 2.85 (m, 2 H, (CH_2S); 7.17 (s, 5 H, aromatic)
$PhCH_2CH_2CH_2SPh$	125–130 (0.20)	1.94 (m, 2 H, CCH_2C); 2.76 (q, 4 H, CH_2Ph, CH_2S); 7.17 (d, 10 H, two C_6H_5)
$PhCH_2O(CH_2)_4SPh$	155 (0.03)	1.70 (m, 4 H, $C(CH_2)_2C$); 2.87 (diffuse t, 2 H, CH_2S); 3.43 (diffuse t, 2 H, CH_2O); 4.42 (s, 2 H, CH_2Ph); 7.25 (s, 10 H, two C_6H_5)
$Ph_2CHCH_2CH_2SPh$	69–71	2.37 (t, $J \simeq$ 7.8 Hz, 2 H, CCH_2C); 2.81 (distorted t, 2 H, CH_2S); 4.09 (t, $J \simeq$ 7.8 Hz, 1 H, CHPh); 7.17 (s, 15 H, three C_6H_5)
$Ph_3CCH_2CH_2SPh$	117–119	2.78 (q, 4 H, aliphatic); 7.17 (s, 20 H, four C_6H_5)
Ph_2CHCH_2SPh	44–46	3.56 (unsym d, J = 7.6 Hz, 2 H, (CH_2S); 4.20 (unsym t, 1 H, (CHPh); 7.20 (s, 15 H, three C_6H_5)

Table VI. Data of New Carboxylic Acids

Carboxylic acid	Registry no.	Mp or bp (mm), °C	NMR
n-BuCH(Et)CH_2CO_2H	14272-47-0	83.5 (0.25)	0.89 (distorted t), 1.29 (m) and 1.92 (br t, 15 H); 2.20 (s, 1 H, $HCHCO_2$); 2.30 (singlet-like d, $J \simeq 1$ Hz, 1 H, $HCHCO_2$); 11.25 (s, 1 H, acidic)
$PhCH(CH_3)CH_2CO_2H$	4593-90-2	94 (0.15)	1.28 (d, $J = 7.0$ Hz, 3 H, CH_3); 2.46 (d, $J \simeq 2$ Hz, 1 H, $HCHCO_2$); 2.59 (s, 1 H, $HCHCO_2$); 3.19 (m, 1 H, CHPh); 7.12 (s, 5 H, arom); 11.35 (s, 1 H, acidic)
	64740-36-9	106–108 (0.15)	1.20 (t, $J = 7.8$ Hz, 3 H, CH_3); 2.65 (m, 6 H, CH_2CH_2 + CH_2CH_3); 7.00 (d, 4 H, arom); 11.45 (s, 1 H, acidic)
$PhS(CH_2)_6CO_2H$	64740-37-0	63–65	1.00–1.90 (br band, 8 H, $C(CH_2)_4C$); 2.23 (unsym t, 2 H, CH_2CO_2); 2.78 (unsym t, 2 H, CH_2S), 7.11 br s, 5 H, arom); 10.6 (s, 1 H, acidic)
	64740-38-1	115–116 (0.20)	1.00 (d); 1.00–2.50 (br unsym d); 2.33 (q, 16 H); 5.31 (br s, 1 H, olefinic); 11.35 (s, 1 H, acidic)
$PhCH_2O(CH_2)_4CO_2H$	64740-39-2	Viscous liquid	1.62 (br s, 4 H, $C(CH_2)_2C$); 2.26 (diffuse t, 2 H, CH_2CO_2); 3.37 diffuse t, 2 H CH_2O), 4.40 (s, 2 H, CH_2Ph); 7.20 (s, 5 H, arom); 11.30 (s, 1 H, acidic)

under argon in a concentration of 1.0 M. Under these conditions the complete dissolution of the metal requires stirring for 6 h or longer, depending on the efficiency of the stirrer. A glass-coated stirring bar should be employed, because lithium naphthalene reacts with Teflon. The total alkalinity in a hydrolyzed aliquot of lithium naphthalene solution can be taken as the concentration of $Li^+C_{10}H_8^-\cdot$, provided the THF used is absolute. This has been checked by double titration using ethylene bromide.

Examplary Runs. (a) With Lithium Naphthalene. (i) Normal Addition. 2-Ethylhexyllithium. The reaction system was a three-neck 100-mL flask equipped with a glass-coated stirring bar and a low-temperature thermometer and connected through the central neck to a vacuum–argon line. The third side neck was stoppered with a rubber septum. The air inside the reaction flask was replaced by pure argon and 20 mL of 1.0 M lithium naphthalene solution was transferred in the flask with a syringe lubricated with silicon oil. The flask was immersed into a dry ice–acetone bath and 2.25 g (10 mmol) of 2-ethylhexyl phenyl sulfide was added with a syringe to the stirred lithium naphthalene at −55 to −45 °C. The resulting mixture was stirred for about 2 min at −50 °C and then the temperature was allowed to rise to −20 °C in order to ensure completion of the reaction. At this stage the color of the mixture was brownish red. The temperature was brought down to −60 °C and the mixture was carbonated with a slurry of crushed solid carbon dioxide in diethyl ether. The carbonation mixture was allowed to attain room temperature, water (50 mL) was added, and the volume of the mixture was reduced in a rotary evaporator. Sodium hydroxide pellets (~2 g) and 1 mL of 30% hydrogen peroxide were added to the carbonation mixture. After stirring for about 0.5 h naphthalene and other neutral products were extracted with 100 mL of benzene, the water layer was extracted once more with 100 mL of hexane, and then it was acidified with 20% sulfuric acid. The liberated carboxylic acid was extracted with 3 × 100 mL of ether, the ether extracts were dried over anhydrous magnesium sulfate for at least 12 h, and after removing the drying agent the ether was distilled to leave 1.33 g (84%) of a liquid acid whose NMR spectrum agreed with the expected structure, *n*-BuCH(Et)CH_2CO_2H.

(ii) Inverse Addition. 3-Thiophenoxypropyllithium. 3-Chloropropyl phenyl sulfide (4.7 g, 25 mmol) was diluted with 20 mL of anhydrous THF and placed in a 250-mL three-necked flask equipped with a glass-coated stirring bar, a pressure-equalizing addition funnel, and low-temperature thermometer and connected to a vacuum–argon line. Under an atmosphere of argon, 50 mL of 1.0 M $Li^+C_{10}H_8^-\cdot$ was transferred in the addition funnel, and the solution was added dropwise at −60 ± 5 °C during a period of about 0.5 h. After the addition the mixture was stirred for 0.25 h between −60 and −70 °C and the reaction became complete by allowing the temperature to rise to −40 °C. The mixture was carbonated as usual and the carbonation mixture was worked up as described in the previous paragraph, avoiding only the treatment with hydrogen peroxide. Acidifcation of the water layer afforded 2.6 g of solid acid and an additional 0.3 g by ether extraction of the filtrate, yielding 2.9 g (59% of theory) of $PhSCH_2CH_2CH_2CO_2H$, which melted at 64–66 °C after one recrystallization from hexane (lit.[25] mp 69–71 °C).

(B) With Lithium Dispersion. 1,7-Dilithio(4-oxaheptane). The reaction system was a 1-L, three-neck flask equipped with a Hershberg stirrer made of Nichrome wire and having a ST 30 ball-joint seal, a thermometer, and a reflux condenser. The stirrer was driven by a ⅛ hp motor operating at 3000 rpm maximum speed (Voss Instruments LTD Maldon, Essex, England). The upper end of the condenser was connected to a system permitting the evacuation of the flask, the filling up of the reaction system with argon, and the maintainance of a small positive pressure of argon during operation. Lithium metal dispersion, prepared in situ from 1.8 g of lithium metal, 100 mL of mineral oil, and 0.3 g of palmitic acid stabilizer, was freed from mineral oil by washing with dry benzene. THF (130 mL) and 1.0 g of naphthalene were added to the reaction and the resulting mixture was stirred while the temperature was brought to −40 °C. 3,3′-Bis(thiophenoxypropyl) ether (15 g, 47 mmol) was added at once. Stirring was continued for 2.5 h, vigorously, while the temperature was kept below −20 °C. The mixture was carbonated by pouring it rapidly into a large beaker containing crushed dry ice and anhydrous ether. When the mixture of carbonation came to room temperature, water (200 mL) was added, followed by 5 g of sodium hydroxide pellets and 13 mL of dimethyl sulfate. After stirring for about 1 h the mixture was evaporated to smaller volume in a rotary evaporator. Thioanisole and other neutral products were removed by washing the water layer with hexane. Acidification with 20% sulfuric acid caused the precipitation of a solid acid which was isolated by ether extraction (3 × 100 mL). The dry product of $O(CH_2CH_2CH_2CO_2H)_2$ weighed 7.61 g, or 90% of theory, and melted at 78–80 °C after one recrystallization from hexane (lit.[26] mp 81 °C).

Table VI summarizes some data of carboxylic acids which have not been reported before.

4-Chlorobutyl Phenyl Sulfide. A mixture of 1,4-dichlorobutane (101.5 g), thiophenol (52 mL, 0.5 mol), water (150 mL), and sodium hydroxide (25 g) was stirred magnetically and refluxed for 2 h. The products and excess dichlorobutane were taken up in benzene (150 mL) and the benzene solution was dried over anhydrous $MgSO_4$ and evaporated to smaller volume in a rotary evaporator. Vacuum distillation gave 64.4 g of 4-chlorobutyl phenyl sulfide (65%), bp 103 °C (0.05 mm), and a residue in the distillation flask (~13 g) which was 1,4-dithiophenoxybutane, mp 82 °C (from methanol) (lit.[27] mp 84 °C).

4-Phenoxybutyl Phenyl Sulfide. Following a procedure for making *sec*-butyl phenyl ether,[28] a solution of 20 g of phenol and 20.05 g (0.1 mol) of 4-chlorobutyl phenyl sulfide in 50 mL of diethylene glycol was heated and stirred in the presence of 15 g of anhydrous potassium carbonate for 1.5 h at 125–135 °C. The mixture was poured into a beaker containing 250 mL of water. A solid product precipitated which was separated and dissolved in 100 mL of benzene, and the

benzene solution was washed with sodium hydroxide solution, then with water and finally dried over anhydrous $MgSO_4$. Evaporation of benzene left 24.0 g (93%) of crystalline product. Recrystallization from ethanol gave shiny flakes, mp 53 °C.

4-Benzyloxybutyl Phenyl Sulfide. Sodium metal (8.0 g) was dissolved in 70 mL of benzyl alcohol, 80 mL of anhydrous THF, and 20 mL of dry benzene by stirring at the reflux temperature for several hours under argon. To this mixture was added 58 g of 4-chlorobutyl phenyl sulfide at once and the resulting mixture was stirred at reflux for 17 h. Water (100 mL) was added followed by benzene (250 mL) and the mixture was stirred for a few minutes, the organic layer was separated, dried over anhydrous $MgSO_4$, and finally concentrated to a smaller volume in a rotary evaporator. Vacuum distillation afforded a fraction boiling (0.05 mm) at 155–160 °C, which weighed 42.5 g (53%), and it was (NMR) 4-benzyloxybutyl phenyl sulfide.

Disulfides $PhS(CH_2)_nSPh$ (n = 2–6). They were prepared from the corresponding dichlorides or dibromides and an excess of thiophenol by refluxing with aqueous sodium hydroxide for 3 h. The yields are given in Table II.

3,3,3-Triphenylpropyl Phenyl Sulfide. This sulfide was prepared by coupling tritylllithium with 2-bromoethyl phenyl sulfide[29] ($BrCH_2CH_2SPh$). To a mixture of triphenylmethane (12.2 g, 50 mmol) and 20 mL of dry benzene under argon was added butyllithium (50 mL, 1,54 M in benzene) followed by 40 mL of absolute THF at 0–10 °C. The resulting mixture was stirred for 24 h at room temperature in order to ensure the complete destruction of the excess butyllithium by THF cleavage. 2-Bromoethyl phenyl sulfide (10.85 g, 50 mmol) was dissolved in 20 mL of dry benzene and added to the tritylllithium solution at 10–35 °C. After stirring for 2 h, the mixture was hydrolyzed and diluted with benzene, and the organic layer was separated, washed with water, and dried over anhydrous $MgSO_4$. Evaporation of benzene in the rotary evaporator left a pale yellow crystalline mass. This material was washed with hot methanol, then recrystallized from hexane to afford 15.4 g (81%) of white crystals, mp 117–119 °C. The NMR spectrum of this compound agreed with the structure of the title compound.

Reaction of 3,3,3-Triphenylpropyl Phenyl Sulfide with Lithium Naphthalene. To 50 mL of 1.0 M lithium naphthalene was added a solution of 9.3 g (25 mmol) of 3,3,3-triphenylpropyl phenyl sulfide in 40 mL of absolute THF at −55 to −50 °C. The red reaction mixture was carbonated as usual. During workup of the carbonation mixture a crystalline precipitate formed from the aqueous layer, which was isolated by filtration. The precipitate was washed with water followed by benzene and air dried. Acidification of the water layer afforded a small amount of acidic product. Both melted at 262–268 °C and the combined yield was 3.92 g (or 54%) of triphenylacetic acid (lit.[30] mp 264–265 °C).

Trapping of Ethylene, Evolved during Reaction of 3,3-Diphenylpropyl Phenyl Sulfide with Lithium Naphthalene, by Cyclohexyllithium.[31] To 50 mL of 1.0 M lithium naphthalene in THF was added chlorocyclohexane (1.7 g, ~14 mmol) dissolved in 10 mL of THF at −40 to −50 °C. Immediately after the addition of the chloride, a solution of 3.75 g (12.5 mmol) of 3,3-diphenylpropyl phenyl sulfide in 15 mL of THF was introduced into the reaction system containing the mixture of cyclohexyllithium and lithium naphthalene at −55 to −50 °C. The resulting mixture was stirred while the temperature was allowed to rise gradually to −10 °C during a period of about 1 h. Carbonation afforded 3.7 g of acidic products, partially crystalline: NMR ($CDCl_3$) 2.32 (distinct triplet, protons α to the carboxyl group[19a] of 3-cyclohexylpropionic acid), ~5.04 ppm (singlet, methinic protons of diphenylacetic acid), along with resonances in the aromatic and aliphatic regions. In a separate experiment 3,3-diphenylpropyl phenyl sulfide was cleaved by lithium naphthalene in the absence of trapping agent. In this case an 88% yield of diphenylacetic acid was isolated after carbonation.

1,1,3-Triphenylbutanol. To a solution of 2-phenylpropyllithium, prepared from 25 mmol of 2-phenylpropyl phenyl sulfide, was added a solution of 4.6 g (25 mmol) of benzophenone in 10 mL of THF at −10 to +20 °C. The resulting blue solution was tested for paramagnetism and it was paramagnetic. A net paramagnetic shift of 4.5 ± 0.5 Hz was measured which corresponds to a benzophenone concentration of 0.057 M. The total volume of the reaction mixture was 65 mL. Thus the total amount of lithium benzophenone ketyl was 65 × 0.057 = 3.7 mmol, or 14.8% based on the benzophenone used. The reaction mixture after stirring for 2 h at room temperature was subjected to steam distillation. The nonvolatile product was extracted with benzene, and the benzene layer was washed with sodium hydroxide solution, then with water, and finally dried over $MgSO_4$. Evaporation of benzene in a rotary evaporator to constant weight left 6.9 g of crude product from which by recrystallization from hexane 5.1 g (68%) of 1,1,3-triphenylbutanol was isolated, mp 90–92 °C, after two recrystallizations from hexane.

1,1-Diphenyl-5-phenylthiohexanol. This carbinol was prepared in a 25 mmol run from benzophenone and 5-thiophenoxypentyllithium. The latter was prepared from 5-chloropentyl phenyl sulfide according to the procedure for preparing 3-thiophenoxypropyllithium. The crude product, which weighed 6.9 g, was applied to a column of 100 g of neutral alumina. Elution with benzene afforded unreacted sulfide. Further elution with ether–benzene (30:70 v/v %) yielded benzophenone. Elution with chloroform gave 2.9 g (33%) of the title carbinol (NMR data in Table III).

1-(2-Phenylpropyl)cyclohexanol. To a solution of 2-phenylpropyllithium, prepared from 25 mmol of 2-phenylpropyl phenyl sulfide, was added 3.5 mL of cyclohexanone at −20 to 0 °C. The mixture was stirred for about 0.25 h and subjected to steam distillation. The nonvolatile product was extracted with benzene and the benzene solution was dried over anhydrous $MgSO_4$ and evaporated to constant weight. The product, a liquid, weighed 3.0 g. A portion of this material (2.35 g) was chromatographed on 100 g of neutral alumina. Elution with benzene yielded unreacted sulfide. Further elution with ethanol–chloroform (30:70 v/v %) afforded 1.20 g (28%) of a liquid whose NMR spectrum (see Table III) agreed with the title compound.

Reaction of $PhS(CH_2)_6SPh$ with 4 Equiv of Lithium Naphthalene. A solution of 3.78 g (12.5 mmol) of 1,6-dithiophenoxyhexane in 25 mL of THF was added to 50 mL of 1.0 M lithium naphthalene at −40 to −30 °C. The resulting mixture was stirred at −60 °C for about 0.25 h and then the temperature was allowed to rise to −30 °C in order to bring the reaction to completion. The mixture was cooled down to −70 °C and carbonated. From the carbonation mixture, after oxidation of thiophenol with alkaline H_2O_2, an acid product was isolated as usual. The acidic product weighed 3.70 g and exhibited an NMR spectrum with resonances in the aromatic region, a broad doublet-like multiplet extending from 6.90–7.65 ppm, a band at 6.1 ppm, dihydronaphthalene derivatives(s) as well as resonances in the aliphatic region. Repeated recrystallizations of the crude product from hexane afforded 0.6 g of 1,8-octanedioic (suberic) acid, mp 135–140 °C (lit.[32] 140–144 °C). Similarly, the disulfides $PhS(CH_2)_nSPh$ (n = 4, 5) upon reaction with 4 equiv of lithium naphthalene and subsequent carbonation afforded acidic products, the weights of which exceeded considerably the corresponding theoretical yields, calculated as $(CH_2)_n(CO_2H)_2$. Their NMR spectra also indicated that they were derivatives of naphthalene.

Registry No.—Lithium naphthalene, 7308-67-0; lithium, 7439-93-2.

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(10) The pseudohalogen behavior of the group PhS^- is also indicated by its ability to undergo a reaction analogous to halogen–metal interconversion: D. Seebach, *Chem. Ber.*, **105**, 487 (1972).

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(12) S. C. Honeycutt, *J. Organomet. Chem.*, **29**, 1 (1971); R. B. Bates, L. M. Kroposki, and D. E. Potter, *J. Org. Chem.*, **37**, 560 (1972); A. Maerker and W. Demouth, *Angew. Chem., Int. Ed. Engl.*, **12**, 75 (1973); G. Köbrich and A. Baumann, *ibid.*, **12**, 856 (1973).

(13) This statement is based on the rapidity with which a sulfide reacts with lithium naphthalene, rather than on the yield of the produced alkyllithium.

(14) This could be true for up to a certain limit of electron affinity of the substrate.

Usually, very high electron affinity is accompanied by great stability of the radical anion produced by electron acceptance. In such a case the fission of the radical anion becomes rate determining.
(15) (a) K. Higashi, H. Baba, and A. Rembaum, "Quantum Organic Chemistry", Interscience, New York, N.Y., 1965, p 312. (b) The pK_a value of benzyl phenyl sulfide, for example, is 30.8: F. G. Bordwell, J. E. Bares, J. E. Bartmess, G. E. Drucker, J. Gerhold, G. J. McCollum, M. Van Der Puy, N. R. Vanier, and W. S. Matthews, *J. Org. Chem.*, **42**, 326 (1977). For its metalation see: J. F. Biellmann and J. B. Ducep, *Tetrahedron Lett.*, 5629 (1968).
(16) (a) The pK_a values of HCl, PhOH, and PhSH were taken from "Lange's Handbook of Chemistry", J. A. Dean, Ed., McGraw-Hill, New York, N.Y., 1973, section 5. (b) The pK_a of Ph_2PH was quoted by A. Tzschach, Abstracts of Papers, 1st European Conference on Organometallic Chemistry (Main Group), Warsaw, Poland, Sept 21-24, 1976, No. II.3.6.
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(21) According to a suggestion made by a referee, these fragmentations are pertinent to the fission of diarylethane radical anions to arylmethyl carbanions, e.g., A. Lagendijk and M. Szwarc, *J. Am. Chem. Soc.*, **93**, 5359 (1971), as both involving C–C bond cleavage. However, in the case of these sulfides the bond which undergoes fission is a C–S bond, followed by fragmentations which leads to a C–C bond cleavage indirectly. The direct C–C fission is a considerably slower process than any of these fragmentations. The Fragmentation reaction was complete on contact of the sulfide with the lithium naphthalene, whereas the direct C–C fission appears to have half-lives of the order of several minutes or longer.
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(24) M. Schlosser, *Newer Methods Prep. Org. Chem.*, **5**, 303 (1968).
(25) G. Kresse, W. Schramm, and G. Cleve, *Chem. Ber.*, **94**, 2060 (1961).
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(27) Footnote *k*, Table IV.
(28) M. Micha-Screttas and C. G. Screttas, *J. Org. Chem.*, **42**, 1462 (1977).
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(30) Reference 16a, section 7-384.
(31) C. G. Screttas, *J. Chem. Soc., Chem. Commun.*, 752 (1972).
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Halogenated Carbonyl Ylides in the Reactions of Mercurial Dihalocarbene Precursors with Substituted Benzaldehydes

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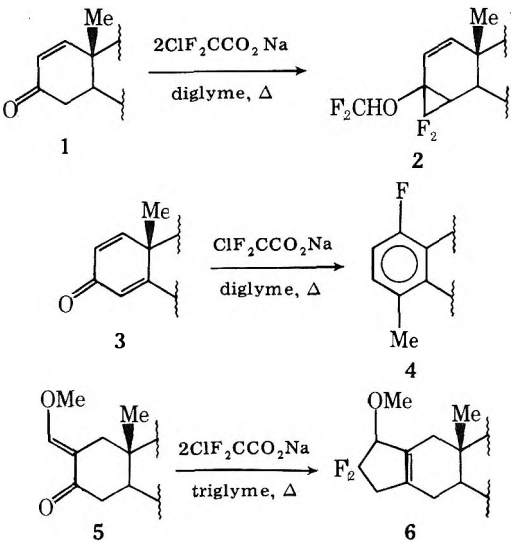
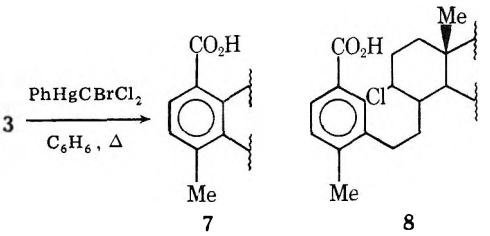
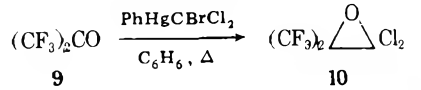
The reactions of phenyl(bromodichloromethyl)mercury (**12**) with several aromatic aldehydes (benzene, 80 °C; followed by treatment with methanol and pyridine at 0 °C) were investigated: [aldehyde (significant products)] **11a** (CO, **13a**, **14a**); **11b** (CO, **13b**, **14b**); **11c** (CO, **14c**, **15c**, **16c**); **11d** (CO, **14d**). Relative reactivities with respect to mercurial **12** (benzene, 80 °C) were 3-CF_3PhCHO (0.08), PhCHO (0.3), *n*-BuCH=CH_2 (0.3), 4-MeOPhCHO (0.9), c-C_6H_{10} (1.0), and Me_2C=CMe_2 (15.0). Complexation between the mercurial and benzaldehyde, which enhanced the rate of decomposition of the mercurial to produce :CCl_2 of the same reactivity as that from the mercurial alone, was observed. Evidence suggests the intermediacy of dichlorocarbonyl ylides.

Despite the availability of dihalocarbene precursors (which upon decomposition do not first produce the trihalomethyl anion), there are few examples of the reactions of such divalent intermediates with simple aldehydes and ketones.[1] Difluorocarbene from the apparently concerted decomposition of sodium chlorodifluoroacetate[3] reacts with steroidal enones such as **1** to produce, among other products, bis(difluorocarbene) adduct **2**,[4] with steroidal dienone **3** to form a small yield of rearranged aromatic fluoride **4**,[4c] and with methoxymethylene keto steroid **5** to form the product of a net 1,4 addition.[5]





The attack of phenyl(bromodichloromethyl)mercury (with presumed intervention of dichlorocarbene)[6] on ketone **3** produced rearranged structures **7** and **8**.[7] Seyferth[8] has found that the attack of the same mercurial on highly halogenated aldehydes and ketones frequently produced isolable dichlorooxiranes. Merz[2d] has shown that dichlorocarbene can be



used to convert aromatic aldehydes to the corresponding mandelic acids.

In preliminary communications[9,10] we have noted a variety of interesting and previously unobserved products from the reaction of phenyl(bromodichloromethyl)mercury (**12**) with benzaldehyde and benzophenone. We now report in more detail on the reactions of the mercurial with a series of substituted benzaldehydes.

Results and Discussion

Mercurial Decomposition. Although the addition of an equimolar amount of phenyl(bromodichloromethyl)mercury

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Table I. Carbonyl Complexes with Phenyl(bromodichloromethyl)mercury[a]

Compd	$\tilde{\nu}_{CO}$ (free)	$\tilde{\nu}_{CO}$ com-plexed	$\Delta\tilde{\nu}_{CO}$	K_{eq}[b]	K_{eq}'[c]
PhCHO	1708.0	1696.0	12	0.57 ± 0.07	4.5 ± 0.5
Ph_2CO	1663.5	1647.5	16	0.56 ± 0.01	2.8 ± 0.1

[a] $\tilde{\nu}$ are given in cm^{-1} and were measured in degassed benzene under argon at ca. 25 °C. [b] For an assumed 1:1 complex. [c] For an assumed 1:2 (mercurial–ligand) complex.

Table II. Relative Reactivities of Selected Aldehydes and Olefins with Phenyl(bromodichloromethyl)mercury[a]

Compd	Registry no.	k_{rel}[b]	k_{rel}'[e]
3-CF_3PhCHO	454-89-7	0.08[c]	
PhCHO	100-52-7	0.3[c]	
4-MeOPhCHO	123-11-5	0.9[c]	
n-BuCH=CH_2	592-41-6	0.3[d]	0.3 (0.2)[f]
c-C_6H_{10}	110-83-8	1.0[d]	1.0 (1.0)[f]
Me_2C=CMe_2	563-79-1	15.0[d]	17.0 (16.0)[f]

[a] Benzene solvent, 48 h, 50 °C. [b] Precision ca. ± 15%. [c] Competition with equimolar amounts of aldehyde, cyclohexene, and mercurial 12. [d] Competition with equimolar amounts of benzaldehyde, cyclohexene, a second olefin, and mercurial 12. [e] Competition between olefins and mercurial 12 in the absence of aldehydes. [f] Data from C. M. Starks, *J. Am. Chem. Soc.*, **93**, 195 (1971), at 30–45 °C.

to a benzene solution of benzaldehyde produces a shift in the NMR position of the aldehyde hydrogen of only +0.01 ppm, a new carbonyl band can be seen in the IR spectrum sufficiently separated from the original bands that overlap at the maximum of the absorption corresponding to uncomplexed aldehyde is negligible. Some infrared data are summarized in Table I. The known formation of a 1:1 complex between mercuric bromide or chloride[11] with benzaldehyde as well as with other aromatic[11] and aliphatic[12] ketones suggests that the stoichiometry for complexation of phenyl(bromodichloromethyl)mercury with benzaldehyde and benzophenone is also 1:1. However, it is known that diphenylmercury and various perfluoroalkylmercurials form both 1:1 and 1:2 (mercurial to carbonyl) complexes with acetone.[13]

Of interest is the observation that the rate of decomposition of mercurial **12** is enhanced somewhat in the presence of an equimolar amount of benzaldehyde.[14] However, as indicated by the kinetic data of Table II, the relative reactivity of mercurial **12** toward several olefins remains essentially unchanged in the presence of a molar equivalent of benzaldehyde, and products derived from these olefins were only the anticipated dichlorocyclopropanes. The kinetic results imply that, once formed, the dichlorocarbene is as free from complexation with a metal-containing species as it is believed to be when no carbonyl compound is present.[17,18]

Aldehyde Reaction Products. The reactions of the aromatic aldehydes with mercurial **12** were carried out with at least a 1.7-fold excess of the aldehyde or ketone and at a temperature of 80 °C (inert atmosphere, usually in benzene; see Table I) for a period of time adequate to ensure complete decomposition of the mercurial.[19] The product mixtures from aldehydes **11** were then filtered and treated at 0 °C with excess methanol and pyridine prior to product analysis by NMR and VPC procedures. Yields are based on mercurial **12**. In every instance the stated products together with unreacted aldehyde or ketone account for essentially all of the starting aldehyde or ketone.

Shown in Table III are the major products observed in the

Table III

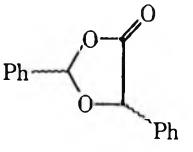
$$\underset{\mathbf{11}}{ArCHO} + \underset{\mathbf{12}}{PhHgCBrCl_2} \xrightarrow[80\ °C]{C_6H_6} PhHgBr + CO + \left[\begin{array}{l}\text{reaction}\\ \text{mixture}\end{array}\right] \xrightarrow[\text{pyridine, 0 °C}]{MeOH}$$

Ar	Additional major products
Ph (**11a**)	PhCH(OMe)OCHPhCO_2Me[a] + $PhCHX_2$[b] **13a** **14a**
3-CF_3Ph (**11b**)	3-CF_3PhCH(OMe)OCH(3-CF_3Ph)CO_2Me[c] **13b** + 3-CF_3PhCHCl_2 **14b**
4-MeOPh (**11c**)	4-MeOPhCHX_2[d] + 4-MeOPhCH$(OMe)_2$ **14c** **15c** + 4-MeOPhCHOHCO_2Me **16c**
2,4,6-Me_3Ph (**11d**)	2,4,6-Me_3PhCHX_2 **14d**

[a] Diasteriomer ratio, 1.8:1. [b] Known to be a substantial mixture of benzal chloride and α-chloro-α-bromotoluene. [c] Diastereomer ratio, 1.2:1. [d] Presence or absence of bromine not determined.

reactions of several benzaldehydes with phenyl(bromodichloromethyl)mercury, while additional data on reaction conditions and product yields are summarized in Table IV.

Acetal esters **13a** and **13b** were found to be a mixture of diasteriomers, but spectral data did not allow threo and erythro stereochemistry to be assigned. Both **13a** and **13b** gave a satisfactory elemental analysis, and **13a**, when treated with aqueous acidic dioxane, was transformed to benzaldehyde and mandelic acid (1:1). In addition, **13a** was prepared by an independent synthesis (the first step of which was patterned after a reported preparation of 1-chlorodioxole)[20] as shown.



17

$\xrightarrow[HgCl_2]{CH_3OCHCl_2}$ [PhCHClOCHPhCOCl] **18** (threo and erythro) $\xrightarrow[\text{pyridine, 0 °C}]{MeOH}$ **13a**

Use of a mercuric chloride catalyst[21] followed by the same workup procedure used in the study of the reaction of benzaldehyde with mercurial **12** resulted in the same 1.8:1 ratio of distereomeric acetal esters **13a**. Acid chlorides **18** are assumed to be the immediate precursors of the observed acetal esters.[22]

Minor products observed in the reaction of aldehyde **11a** with mercurial **12** include the dimethyl acetal of benzaldehyde (5–6%), methyl mandelate (3–4%), and methyl α-chlorophenylacetate (1–2%).

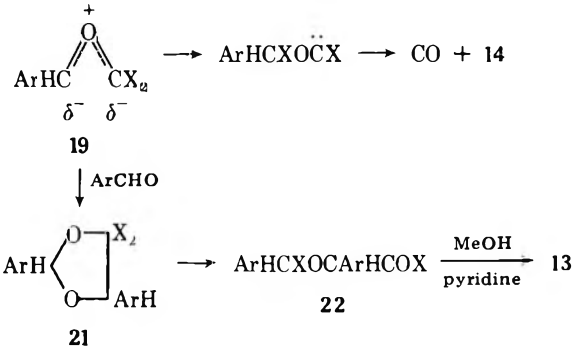
Reaction Pathways. A variety of observations suggest that carbonyl ylides are likely intermediates in the reactions of aromatic aldehydes with phenyl(bromodichloromethyl)mercury (Scheme I). Among the more convincing types of evidence is the fact that the independent synthesis of a sample of acetal esters **13a** from dioxolanone **17** resulted in exactly the same mixture of diastereomeric esters produced in the reaction of mercurial **12** with benzaldehyde (followed by treatment with methanol and pyridine). It is likely that the transformation **17** → **18** involves dioxolane **21** (Ar = Ph),[20] which would be expected as a product of the 1,3-dipolar ad-

Table IV. Summary of Selected Product Data for Reaction of Aromatic Aldehydes with Phenyl(trihalomethyl)mercury[a]

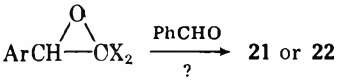
XPhCHO, X	$PhHgCBrY_2$, Y	Registry no.	$\frac{(ArCHO)_0}{(PhHgR)_0}$[b]	Solvent	CO,[c] %	13, %	No. of runs
H	Cl	3294-58-4	1.7	C_6H_6	39 ± 7	32 ± 19	13
			3.4	C_6H_6	36 ± 1	34 ± 7	5
			22.9	ArCHO	78 ± 1	0	2
H	Br	3294-60-8	1.8	C_6H_6	52 ± 18	0	7
			19.5	ArCHO	66	0	2
4-MeO	Cl		1.9	C_6H_6	57 ± 2	*d*	6
3-CF_3[e]	Cl		1.8	C_6H_6	11	60	1[f]
2,4,6-Me_3	Cl		1.7	C_6H_6	63 ± 3	0	6
2,4,6-Me_3	Cl		20.0	ArCHO	70	0	2

[a] Reactions done with 15 mmol of $PhHgCBrY_2$ in 30 mL of solvent for 3–3.5 h at 80 °C; yields based on starting mercurial. [b] ± 0.1. [c] An equimolar amount of $ArCHY_2$ in which Y_2 = Br_2, Cl_2, and BrCl was formed. [d] Unstable to reaction conditions; 25–42% yield of a mixture of **15c** and **16c** was observed. [e] A 23-mmol amount of $PhHgCBrCl_2$ in 35 mL of benzene. [f] Other runs made under somewhat different conditions gave comparable results.

Scheme I



dition of carbonyl ylide **19** (Ar = Ph) to benzaldehyde (Scheme I). Although the direct formation of either dioxolane **21** or acid chloride **22** from oxirane **23** cannot be formally excluded, it seems unlikely in view of the observations that 2,3-dicyano-



2,3-diphenyloxirane[23a] and 2-cyano-2,3-diphenyloxirane[23b] form adducts with dipolarophiles only under conditions where intermediate carbonyl ylides are formed and because the rate law for reaction of tetracyanoethylene oxide with olefins shows prior formation of a reactive intermediate (the carbonyl ylide) rather than direct reaction of the oxirane with olefin.[24] Stable 1,3-dioxolanes isolated in metal-catalyzed[25a–d] or photochemical[25e–g] decompositions of diazo esters,[25a–c] α-diazoacetophenone,[25d] and diazomethane[25e–g] with aromatic and aliphatic aldehydes and ketones (including benzaldehyde)[25b–d] and from the reaction of substituted epoxides with aromatic aldehydes[26] have been attributed to the 1,3 cycloaddition of an intermediate carbonyl ylide to a carbonyl group.

The initial formation of oxirane **23** (rather than carbonyl ylide **19**) requires that the conversion to ylide **19** (or dioxolane **21**) occurs to essentially the complete exclusion of rearrangement (by carbon–oxygen scission) to acid chloride **24**. This seems unreasonable in view of the known facility of the latter reaction[27] (except for dichlorooxiranes substituted with two very powerful electron-withdrawing groups).[8] Furthermore, evidence on carbon–carbon bond scission (analogous to that required to go from oxirane **23** to ylide **19**) in 2-phenyl-3-*p*-tolyloxirane,[28] 2-cyano-2,3-diphenyloxirane,[23b] 2,3-dicyano-2,3-diphenyloxirane,[23a] tetracyanoethylene oxide,[24,29] ethyl 2-methyl-3-phenylglycidate,[26a] and 2,2-dicyano-3-aryloxiranes[26b] indicates that these processes would be quite slow at 80 °C.

The formation of equimolar amounts of CO and *gem*-dihalide **14** coupled with the established ease with which alkoxyhalocarbenes break down with loss of CO[30] indicates the likely intermediacy of carbene **20**, which can arise by 1,3-halogen migration from ylide **19**. A transformation similar to **19** → **20** has been postulated in the sequence of steps used to explain the small yield of aryl fluoride **4**, which is produced from treatment of steroidal dienone **3** with sodium chlorodifluoroacetate.[4c]

Some additional observations are of considerable interest. Reference to the data in Table IV shows that a change in the substituent(s) on the aromatic ring of aldehyde **11** has a distinct effect on the distribution of products. For example, the yield of CO (and benzal halide **14**) increases in the order 3-CF_3PhCHO < PhCHO < 4-MeOPhCHO < 2,4,6-Me_3PhCHO, the order of increasing electron density in the aromatic ring, a trend which would be consistent with the expected facilitation either of rearrangement of the ylide to carbene **20** and/or extrusion of CO from carbene **20**.[30]

The yield of acid chloride **22** (isolated as acetal ester **13**, Table III) decreases in the order 3-CF_3PhCHO > PhCHO > 2,4,6-Me_3PhCHO. Although none of the acetal ester was detected from the reaction of anisaldehyde (**11c**) with mercurial **12**, significant yields of dimethyl acetal **15c** and hydroxy ester **16c** which were observed undoubtedly arose from the acid-catalyzed breakdown in methanol of an initially formed acetal ester. The lack of any acetal ester (or products from its acid-catalyzed methanolysis) from mesitaldehyde (**11d**) may reflect in part the operation of an unfavorable steric interaction in the formation of dioxolane **21**.

Control reactions (see Experimental Section) indicated that the significant amounts of benzal halide product containing both bromine and chlorine observed in the reactions of aldehydes **11a**, **11c**?, and **11d** with mercurial **12** did not arise from a simple exchange reaction of phenylmercuric bromide with the benzal chloride or from the initial production of: CBrCl. Therefore, the presence of an appropriately substituted α-bromo-α-chlorotoluene among the products of reaction of the more electron-rich aldehydes with mercurial **12** must be presumed to involve an exchange between phenylmercuric bromide and one or more of the reaction intermediates.

When benzaldehyde was treated with phenyl(tribromomethyl)mercury (followed by methanol and pyridine at 0 °C), the only observed products were CO and benzal bromide, which can can be rationalized as being due to a facilitation of the process **19** → **CO** + **14** (Scheme I) because of the smaller

C–X bond energy anticipated for bromine relative to chlorine.

$$PhCHO + PhHgCBr_3 \xrightarrow[80\ ^\circ C\ pyridine]{C_6H_6\ \ MeOH} CO + PhCHBr_2$$

Kinetic Considerations. Returning to the data of Table II, one notes that relative reactivities with respect to reaction with dichlorocarbene are 3-CF_3PhCHO ≪ PhCHO ~ *n*-BuCH=CH < 4-MeOPhCHO ~ c-C_6H_{10} ≪ Me_2C=CMe_2. Reactivity increases with increasing nucleophilicity of the carbonyl oxygen, consistent with the known electrophilic behavior of dichlorocarbene in addition reactions to olefins[18] and with the assumption of an early transition state for the attack rather than one which resembles the carbonyl ylide. The latter intermediate, which is isoelectronic with the allylic anion, should be stabilized by electron-withdrawing groups;[31] thus, a transition state resembling the ylide would lead to the opposite reactivity order among the aldehydes than that which was observed.[32]

Conclusions

The reactions of aromatic aldehydes and benzophenone with mercurial **12** in benzene are best described by initial breakdown of both mercurial **12** and a mercurial–carbonyl complex to give dichlorocarbene. The rate of carbene reaction with the carbonyl group was found to increase with increasing electron density in the aromatic ring. Although conclusions about some of the paths leading to observed products must remain tentative, a variety of evidence suggests that attack of dichlorocarbene on the aldehyde or ketone first forms a dichlorocarbonyl ylide. Once formed, the ylide can undergo halogen rearrangement and 1,3 cycloaddition to a second molecule of aldehyde. Similar halocarbonyl ylides have been suggested to explain the products resulting from the reaction of sodium chlorodifluoroacetate with steroidal ketones[4,5] and of mercurial **12** with steroidal ketones[7] and highly halogenated ketones.[8]

Experimental Section

Elemental analyses were performed by the Department of Medicinal Chemistry at the University of Kansas or by Chemalytics, Inc., Tempe, Ariz. Melting points are uncorrected. IR spectra were obtained on Beckman IR-8 and IR-10 instruments with a 1603-cm^{-1} polystyrene peak (vs. air) as reference. Proton NMR spectra were obtained on a Varian A-60 spectrometer. Quantitative analyses of the NMR spectra of mixtures were based on a known amount of added toluene. All chemical shifts are reported as τ values. An F and M Model 700 Chromatograph (thermal conductivity detector) was used for VPC analyses with the following columns: 10% OV-210 on 80–100 mesh Gas Chrom Q (6 ft × ⅛ in. glass), 10% OV-101 on 60–80 mesh Gas Chrom Q (5 ft × ⅛ in. aluminum), and 10% OV-1 on 60–80 mesh Gas Chrom Q (6 ft × ⅛ in., glass). Toluene served as an internal standard; areas (disc integrator) relative to that of toluene were corrected for detector sensitivity.

Reagent grade benzene, toluene, and pyridine were dried and distilled from calcium hydride and stored over Linde 4Å molecular sieves. Anhydrous methanol was dried over Linde 4Å sieves or distilled from magnesium prior to use. Tetrahydrofuran (reagent) was dried over Linde 4Å sieves and rendered peroxide free by passing it through basic alumina prior to use. Aldehydes were dried over Linde 4Å sieves and distilled from calcium hydride under purified dry nitrogen or argon immediately prior to use or stored for ≤24 h under nitrogen or argon. Diglyme was distilled and dried over Linde 4Å sieves. Mercurials were refrigerated and stored under nitrogen or argon.

Samples of 7,7-dichlorononorcarane, 7-chloro-7-bromonorcarane, 1,1-dichloro-2,2,3,3-tetramethylcyclopropane, and 1,1-dichloro-2-butylcyclopropane were prepared from the corresponding olefin by treatment with the appropriate phenyl(trihalomethyl)mercurial.[6]

Phenyl(bromodichloromethyl)mercury was prepared in 74–80% yields (based on PhHgCl) by a modification of the procedure of Seyferth[33] in which the bromodichloromethane (freshly distilled) was added dropwise (30 min) to a cold (−25 °C) solution of phenylmercuric chloride, potassium *tert*-butoxide, and *tert*-butyl alcohol in dry tetrahydrofuran, followed by stirring for 30 min prior to workup. Mp 108–110 °C dec (lit.[33] mp 108–110 °C dec).

Mesital chloride was prepared from mesitaldehyde and thionyl chloride. Mp 34–36 °C (lit.[34] mp 35–36 °C).

α-Bromo-α-chlorotoluene was prepared by the addition of bromine to benzyl chloride at 150 °C under the influence of ultraviolet light.[35] The NMR spectrum (CCl_4) showed a multiplet at τ 2.40–2.82 (5 H) and singlets at τ 3.39 and 3.44 (1 H total), with the latter signal corresponding to benzal bromide impurity.[36]

Dimethyl acetals of benzaldehyde, anisaldehyde, and mesitaldehyde were prepared by treating the aldehyde with an excess of methanol in the presence of *p*-toluenesulfonic acid and removing water with Linde 3Å molecular sieves in a Soxhlet extractor. The distilled product from benzaldehyde had bp 87–88 °C (18 Torr) [lit.[37] bp 88 °C (18 Torr)]; NMR spectrum (CCl_4), multiplet at τ 2.50–2.82 (5 H), singlet at τ 4.63 (1 H), 6.79 (6 H). The product from anisaldehyde had bp 125 °C (13 Torr) [lit.[38] bp 249–250 °C (760 Torr)]; NMR spectrum (CCl_4), A_2B_2 multiplet at τ 2.62, 2.76, 3.13, 3.27 (4 H), singlets at τ 4.68 (1 H), 6.24 (3 H), 6.80 (6 H). The product from mesitaldehyde had bp 116–118 °C (10 Torr) [lit.[39] bp 242–243 °C (741 Torr)]; NMR spectrum (CCl_4), singlets at τ 3.32 (2 H), 4.63 (1 H), 6.75 (6 H), 7.68 (6 H), 7.82 (3 H).

Methyl α-Chlorophenylacetate. α-Chlorophenylacetyl chloride (6.1 g, 0.032 mol) was added slowly (30 min) to a stirred solution of methanol (1.1 g, 0.034 mol) and pyridine (2.6 g, 0.033 mol) in benzene (20 mL). After 4 h the reaction mixture was worked up in the usual manner to give the ester (2.73 g, 0.0148 mol, 46%): bp 121–123 °C (12 Torr) [lit.[40] bp 124 °C (8 Torr)]; NMR spectrum (CCl_4), multiplet at τ 2.50–2.85 (5 H), singlets at τ 4.75 (1 H), 6.40 (3 H); IR spectrum (CCl_4), carbonyl at 1760 cm^{-1}.

Methyl α-bromophenylacetate was prepared from phenylacetic acid,[41] bp 82–83 °C (1 Torr) [lit.[41] bp 122–146 °C (20 Torr)]; NMR spectrum (CCl_4), multiplet at τ 2.60–2.90 (5 H), singlets at τ 4.70 (1 H), 6.50 (3 H).

Methyl *p*-methoxymandelate was prepared from anisaldehyde by the general method of Knorr.[42] Distillation at 5 Torr followed by recrystallization from water produced a white product, mp 39–40 °C; NMR spectrum (CCl_4), A_2B_2 pattern at τ 3.03 (4 H), singlets at τ 5.01 (1 H), 5.93 (1 H), 6.38 (3 H), 6.45 (3 H); IR spectrum (CCl_4), 3450, 2960, 2840, 1735, 1614, 1515, 1442, 1245, 1177, 1080, 1030, 833, 797 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.09; H, 6.28.

Methyl Mesitylglycolate. Mesitylene was first converted to 2,4,6-trimethylacetophenone[43] followed by selenium dioxide oxidation, hydration, and rearrangement to the glycolic acid.[44] Esterification with diazomethane[45] resulted in a white crystalline product, mp 88–90 °C (lit.[44] mp 90–91 °C); NMR spectrum (CCl_4), singlets at τ 3.15 (2 H), 4.43 (1 H), 6.25 (3 H), 6.30 (1 H, broad), 7.68 (6 H), 7.74 (3 H); IR spectrum (CCl_4), 3520, 2960, 2860, 1740, 1610, 1440, 1370, 1230, 1140, 1070, 1030, 970, 850 cm^{-1}.

Methyl α-methoxyphenylacetate was prepared from α-chlorophenylacetyl chloride by treatment with excess sodium methoxide in methanol at reflux for 4 h. The crude product was purified by distillation, bp 123–124 °C (11 Torr) [lit.[46] bp 118–119 °C (8 Torr)]; NMR spectrum (CCl_4), multipet at τ 2.62–2.88 (5 H), singlets at τ 5.37 (1 H), 6.44 (3 H), 6.70 (3 H); IR spectrum (CCl_4), carbonyl at 1745 cm^{-1}.

Treatment of Aldehydes and Ketones with Phenyl(trihalomethyl)mercury. General Procedure. Glassware was cleaned in aqueous ethanolic NaOH solution, thoroughly rinsed, dried for ≥ 6 h at 110 °C, assembled while warm, and purged with argon or nitrogen (dried with Drierite and Linde 4Å molecular sieves). The entire reaction and workup was carried out in a dry, inert atmosphere; liquid transfers were made with oven-dried syringes. The apparatus consisted of a 100-mL four-necked flask (one male joint, capped during the initial reaction) equipped with an inert gas inlet, thermometer, magnetic stirrer, and a condenser attached to a gas burette, manometer, and storage balloon.

After a mixture of phenyl(bromodichloromethyl)mercury (6.61 g, 15 mmol) in benzene (30 mL) was stirred for a few min, benzaldehyde (2.71 g, 25.6 mmol) was added, the manometer was balanced, and initial readings of gas volume, room temperature, and atmospheric pressure were recorded. The reaction mixture was stirred, heated slowly (oil bath) to ca. 80 °C, maintained at that temperature until gas evolution ceased (3–4 h), and cooled to the starting temperature to allow final readings of gas volume to be made; IR of gas, 2120 and 2170 cm^{-1} (carbon monoxide). It was noted that the yield of CO was affected by the heating rate.

After the condenser had been replaced with a stopper, the contents

of the flask were cooled (ice bath) and filtered (inert atmosphere) by connecting the male joint to a sintered glass funnel attached to a small, dry three-necked flask equipped with two stopcocks to control vacuum and inert gas. The precipitate was washed (3 × 20 mL of cold benzene), dried, weighed, and identified as phenylmercuric bromide (90–97% based on a starting mercurial), mp (crude product) 274–276 °C (when mixed with pure authentic phenylmercuric bromide mp 266–280 °C). This material may contain some phenylmercuric chloride.

The filtrate was kept cold (ice bath) while a cold solution of methanol (4 mL, 98.8 mmol) and pyridine (4 mL, 49.7 mmol) in benzene (30 mL) was added. After being stirred for 3–4 h at 0 °C, the reaction mixture was filtered, concentrated at reduced pressure, diluted with ca. 40 mL of benzene–cyclohexane (1:1), filtered, and concentrated at reduced pressure. The products were analyzed by VPC and NMR with a weighed sample of toluene (ca. 15% of the weight of the residue) added as an internal standard. (Nitromethane was added as an internal NMR standard for reactions involving mesitaldehyde.) As a further aid to the identification of products, a portion of the liquid product mixture (after treatment with methanol and pyridine) was sometimes subjected to simple distillation and/or column chromatography on Florisil (dried at 130 °C) with cyclohexane, benzene, and benzene–ether mixtures as eluents.

Variations in the reaction procedures described include changes in the ratio of aldehyde to mercurial, in the reaction time and temperature, in the nature and amount of solvent, and in the details of the workup procedure.

The amount of benzal halides and of acetal ester **13** was determined directly from NMR absorptions for the α-hydrogen of the former and the acetal hydrogen (from each diastereomer) of the latter. Methyl mandelate was determined directly from the tertiary hydrogen. Benzaldehyde dimethyl acetal was determined from the OCH_3 peak by subtracting the contribution to that peak from one OCH_3 group of acetal ester **13**. Corrections for differences in thermal conductivity detector sensitivity for the various compounds were made.

Treatment of Benzaldehyde with α-Chlorophenylacetyl Chloride, Phenylmercuric Bromide, and Benzal Chloride. A mixture of α-chlorophenylacetyl chloride (1.7 g, 9 mmol, freshly distilled), benzal chloride (0.80 g, 5 mmol), phenylmercuric bromide (6.1 g, 17 mmol), benzaldehyde (3.7 g, 35 mmol), and benzene (22 mL) was heated at 77–80 °C for 3.5 h in the same apparatus used for the reactions of benzaldehyde with phenyl(trihalomethyl)mercury. Total gas volume change was 1.0 mL.

The solution was filtered under argon to give phenylmercuric bromide (5.6 g, 97% recovery; mp 278–280 °C). The filtrate was treated with methanol (1.0 g, 31 mmol) and pyridine (1.2 g, 15 mmol) in benzene (15 mL) for 4 h. After workup, NMR analysis showed only methyl α-chlorophenylacetate, benzaldehyde, and benzal chloride. A small singlet at τ 4.43 was not positively identified but may be attributed to the tertiary hydrogen of phenyldimethoxymethane. VPC analysis (10% OV-1, 5 ft, 105 °C) showed only a trace of α-bromo-α-chlorotoluene, which also appeared to be present in the starting benzal chloride.

Treatment of Benzaldehyde with α-Chlorophenylacetyl Chloride and Phenylmercuric Bromide. A mixture of α-chlorophenylacetyl chloride (2.5 g, 13 mmol), benzaldehyde (4.4 g, 42 mmol), and phenylmercuric bromide (10.8 g, 30.2 mmol) in benzene (60 mL) was heated at 75–80 °C for 3.3 h in the same apparatus used for the reactions of benzaldehyde with phenyl(trihalomethyl)mercury. Total gas volume change was 1.6 mL. VPC analysis (6 ft glass, OV-1, 138 °C) showed benzaldehyde, α-chloroacetyl chloride, and a trace of benzal chloride.

Phenylmercuric bromide (10.5 g, 97%; mp 267–273 °C was recovered by filtration, and a portion (17.8%) of the filtrate was added to a solution of methanol (1.2 g, 37 mmol) and pyridine (2.4 g, 30 mmol) and allowed to stand (drying tube with $CaSO_4$) for 3.25 h. After being worked up in the usual manner, the solution was analyzed by NMR, which showed only absorptions for methyl α-chlorophenylacetate and benzaldehyde.

Treatment of Benzaldehyde and Benzal Bromide with Phenylmercuric Bromide, Methanol, and Pyridine. Each of the mentioned compounds (10 mL of each liquid and 10 g of each solid) was dissolved in benzene (30 mL) in the presence of hydrogen bromide gas. The reaction mixture was kept at reflux for 3 h. No benzaldehyde dimethyl acetal was observed by NMR analysis.

2,5-Diphenyl-1,3-dioxolan-4-one was prepared from mandelic acid and benzaldehyde by the general procedure of Salomaa and Sallinen.[47] Recrystallization of the crude product from carbon tetrachloride resulted in white crystalline material, mp 100.5–101.5 °C (lit.[48] mp 104–105 °C); IR spectrum (CCl_4), carbonyl singlet at 1800 cm^{-1}; NMR spectrum (CCl_4), multiplet at τ 2.58 (10 H), doublet at τ 3.53 (1 *H*, *J* = 1 Hz), doublet at τ 4.79 (1 H, *J* = 1 Hz).

Methyl 2,4-Diphenyl-3,5-dioxahexanoate. Dry benzene (13 mL), 2,5-diphenyl-1,3-dioxolan-4-one (6.9 g, 0.029 mol), methyl dichloromethyl ether (5.0 g, 0.044 mol, freshly distilled under argon), and dry mercury(II) chloride (0.03 g) were heated with an oil bath at 105–115 °C (argon atmosphere) for 1–2 days or until an NMR spectrum of a sample of the crude reaction mixture showed none of the starting dioxolanone. The reaction mixture was cooled (ice bath), diluted with benzene (10 mL), and filtered through a fritted glass funnel into a cold, stirred solution of methanol (4.8 g, 0.15 mol) and pyridine (7.9 g, 0.10 mol) in dry benzene (20 mL). After 12 h the reaction mixture was filtered, and the filtrate was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution. Aqueous extracts were washed with benzene, and the combined benzene solutions were dried (K_2CO_3) and concentrated at reduced pressure (2 mm) to give 6.52 g of yellow oil, a portion of which (6 g) was further purified by molecular distillation (10^{-5} Torr; bath, 75 °C) to give an initial fraction (1.7 g) containing impurities and the desired product (3.47 g, 0.0121 mol, 41.8%) as a mixture of diasterioisomers; NMR spectrum (CCl_4), multiplet at τ 2.43–2.85 (10 H, Ph), singlets at τ 4.32 and 4.52 (1 H total, C**H**OMe), 4.87 and 4.89 (1 H total, C**H**CO_2Me), 6.44 and 6.47 (3 H total, **C**H_3OCHPh), 6.83 and 6.85 (3 H total, CO_2CH_3); IR spectrum (CCl_4), 3130, 2850, 1760, 1740, 1540, 1490, 1460, 1440, 1355, 1270, 1250, 1205, 1190, 1170, 1110, 1100, 1075, 1055, 1023 cm^{-1}. The ratio of isomers based on NMR signals at τ 4.32 and 4.52 was 1.8:1, respectively.

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.44; H, 6.22.

A portion of the product (1.23 g, 4 mmol) was hydrolyzed in a 0.6 N hydrochloric acid solution in 50% aqueous dioxane at 90 °C for 1 h under argon. The solution was cooled, made basic with 1 N sodium hydroxide solution (11 mL), and extracted with methylene chloride. The dried ($MgSO_4$) concentrated extract was shown by NMR to contain only benzaldehyde and dioxane. The acidified aqueous phase was extracted with ether, from which mandelic acid (0.62 g, 4 mmol) was isolated, mp 118–120 °C (from benzene). The identity was confirmed by IR and mixture melting point comparisons with an authentic sample.

The title compound was also isolated by molecular distillation (10^{-5} Torr) of the high-boiling product from a reaction of phenyl(bromodichloromethyl)mercury with benzaldehyde, carried out as described previously.

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31: H, 6.34. Found: C, 71.62; H, 6.27.

Methyl 2,4-bis(*m*-trifluoromethylphenyl)-3,5-dioxahexanoate was isolated by preparative VPC of the reaction mixture from the treatment of *m*-trifluoromethylbenzaldehyde with phenyl(bromodichloromethyl)mercury in benzene. The product (a mixture of diastereomers) was purified by molecular distillation (10^{-5} Torr); NMR spectrum (CCl_4), multiplet at τ 2.2–2.7 (8 H), singlets at τ 4.20 and 4.37 (1 H total), 4.78 and 4.82 (1 H total), 6.28 and 6.39 (3 H total), 6.67 and 6.73 (3 H total); IR spectrum (CCl_4), 2980, 2860, 1745 d, 1445 d, 1330, 1175, 1135, 1075, 918, 701 cm^{-1}. The ratio of isomers based on NMR signals at τ 4.20 and 4.37 was 1.2:1, respectively.

Anal. Calcd for $C_{19}H_{16}O_4F_6$: C, 54.03; H, 3.82. Found: C, 53.97; H, 3.88.

Complexation of Phenyl(bromodichloromethyl)mercury with Benzophenone and Benzaldehyde. Measurements were obtained on a Perkin-Elmer Model 421 grating spectrophotometer with CaF_2 matched cells. Benzophenone was recrystallized (cyclohexane) and dried in a desiccator ($CaSO_4$), mp 48–49 °C (lit.[49] mp 48.1 °C). Benzaldehyde was freshly distilled under argon. The mercurial was recrystallized (3:1, hexane–chloroform) at 25 °C, mp 110–111 °C (lit.[50] mp 110–111 °C).

A benzene solution of the mercurial (0.251 M) and benzophenone (0.225 M) balanced against 0.200 M benzophenone (in benzene) in the reference call exhibited a carbonyl absorption at 1647.5 cm^{-1}, distinctly different from the absorption at 1663.5 cm^{-1} for a dilute benzene solution of benzophenone (vs. benzene). Similarly a benzene solution of the mercurial (0.350 M) and benzaldehyde (0.280 M) balanced against 0.240 M benzaldehyde (in benzene) exhibited a carbonyl absorption at 1696 cm^{-1}, compared to the normal carbonyl absorption of benzaldehyde at 1708 cm^{-1}.

A series of benzene solutions of benzophenone and benzaldehyde of known concentrations was used to establish a calibration curve which would allow the determination of the amount of free carbonyl in solutions containing both free and complexed carbonyl at ca. 25 °C. Measurements on benzaldehyde were carried out under argon with deoxygenated benzene and were completed in a few minutes, during

which time no detectable decomposition of the mercurial occurred. Results are summarized in Table I.

Relative Reactivities. Approximate relative rates of reaction of mercurial **12** with aldehydes and olefins were determined at 50 °C (48 h) in benzene with equimolar mixtures of **11a**, **12**, and cyclohexene; **11a**, **12**, cyclohexene, and 2,3-dimethyl-2-butene; **11a**, **12**, cyclohexene, and 1-hexene; **11b**, **12**, and cyclohexene; and **11c**, **12**, and cyclohexene. Product mixtures were then treated with excess methanol and pyridine at 0 °C for 4 h, followed by addition of an internal toluene standard and analysis by NMR and VPC. Relative rates were calculated from a quantitative comparison of the dichlorocyclopropane products from the olefins with the combined yield of CO plus all ester and acetal products from the aldehydes.

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Registry No.—**11d**, 487-68-3; *erythro*-**13a**, 64761-19-9; *threo*-**13a**, 64761-21-3; *erythro*-**13b**, 64761-23-5; *threo*-**13b**, 64761-24-6; **16c**, 13305-14-1; **17**, 56535-98-9; benzophenone, 119-61-9; α-bromo-α-chlorotoluene, 22332-89-4; benzyl chloride, 100-44-7; benzaldehyde dimethyl acetal, 1125-88-8; anisaldehyde dimethyl acetal, 2186-92-7; mesitaldehyde dimethyl acetal, 64761-29-1; methyl α-chlorophenylacetate, 7476-66-6; α-chlorophenylacetyl chloride, 2912-62-1; methyl α-bromophenylacetate, 3042081-7; methyl mesitylglycolate, 63809-19-8; methyl α-methoxyphenylacetate, 3558-61-0; phenylmercuric bromide, 1192-89-8; carbon monoxide, 630-08-0; benzal chloride, 98-87-3; methanol, 67-56-1; sodium methoxide, 124-41-4.

References and Notes

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Geometric Isomerism in the Phenylhydrazones of Some α-Dicarbonyl Compounds

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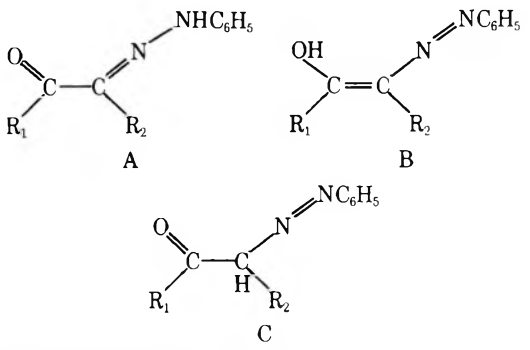
The structures of the phenylhydrazones of four α-dicarbonyl compounds were determined from the IR and NMR spectra of the ^{14}N and ^{15}N isotopomers. The compounds exist only in the phenylhydrazone tautomeric form and, except for the phenylhydrazone of phenylglyoxal in solution, primarily as the geometric isomer with the NHC_6H_5 group oriented away from the carbonyl. The effect of solvent on the composition of the geometric isomerism equilibria is discussed.

The structures of the phenylhydrazones of dicarbonyl compounds have been the subject of a variety of studies since the turn of the century. Many of these compounds have been reported in several, often interconvertible, forms. For monophenylhydrazones of α-dicarbonyl compounds, three tautomeric forms are possible,



A B C

and for each tautomeric form at least two geometric isomers are possible. Previous studies of compounds of this type have indicated, for example, that different geometric isomers of the hydrazone form A ($R_1 = CH_3$, $R_2 = H$) can be obtained by different methods of preparation,[1] that the form of at least one compound ($R_1 = C_6H_5$, $R_2 = H$) can be altered by the action of solvents,[2,3] and, recently, that the phenylhydrazone of phenylglyoxal ($R_1 = C_6H_5$, $R_2 = H$) exists as a mixture of hydrazone (A) and enol (B) forms in pyridine.[4]

The present spectroscopic study of the ^{14}N and ^{15}N isotopomers of the phenylhydrazones of a series of simple α-dicarbonyl compounds was designed to determine unambiguously the structures of some model phenylhydrazones.

Results and Discussion

The compounds (I, $R_1 = CH_3$, $R_2 = H$; II, $R_1 = R_2 = CH_3$; III, $R_1 = C_6H_5$, $R_2 = H$; IV, $R_1 = R_2 = C_6H_5$) were prepared by condensation of phenylhydrazine hydrochloride with the appropriate α-dicarbonyl compound in water or aqueous ethanol. Compounds I, II, and III were also prepared by the Japp–Klingemann reaction of diazotized aniline with acetoacetic acid, ethyl α-methylacetoacetate, and potassium benzoylacetate, respectively. The ^{15}N isotopomers of II, III, and IV were obtained by the condensation reaction, while that of I was made by the Japp–Klingemann method. The physical and spectroscopic properties of the compounds prepared by both the condensation and Japp–Klingemann methods were identical; however, the condensation product of I required careful purification.

The melting points of the compounds were determined on both a melting point block and by differential scanning calorimetry (DSC). The endotherms observed were found to be reversible and reproducible for all compounds. For compound III the melting point varied with the method used to purify the compound, and it ranged from 101–102 °C for material recrystallized from benzene to 152–153 °C after repeated recrystallization from ethanol. Moreover, the DSC scans for unrecrystallized samples of III showed two endotherms at 101 and 118 °C. However, the IR spectra (Nujol) of all samples of III were identical, as were the NMR spectra in $CDCl_3$ (vide infra). The melting points of the ^{14}N and ^{15}N isotopomers were identical. Melting points and NMR chemical shifts for both ^{14}N and ^{15}N isotopomers are reported in Table I.

The NMR spectrum of compound I in $CDCl_3$ contained two peaks of unequal intensity at 2.2 and 2.4 ppm due to the CH_3 groups, a multiplet centered at about 7.3 ppm attributable to the phenyl proton resonance (and also containing the C–H resonance), and two fairly broad low field resonances at 8.7 and 13.8 ppm, which together integrate to 1 proton relative to 3 for the combined CH_3 resonances. The low field resonances could be ascribed to either OH or NH protons, but not to the CH protons of form C. Since the ^{15}N isotopomer contains the ^{15}N isotope ($I = ½$) directly attached to the benzene ring (the probability of scrambling during diazotization and condensation is low[5]), a proton directly attached to this isotope in the hydrazone form (A) will give rise to a doublet in the absence of fast exchange. As indicated in Table I, both low field resonances in the NMR spectrum of the isotopomer of I are split into doublets with separations characteristic of one-bond ^{15}N–^{1}H couplings.[6] Therefore, the two methyl resonances and the two low field resonances must be assigned to the two geometric isomers of the hydrazone from A. In one isomer the NHC_6H_5 group is oriented toward the carbonyl (hereafter referred to as the cis form) and the NH proton is very likely hydrogen bonded to the carbonyl. Hydrogen bonding generally results in downfield shifts, as previously documented for phenylazopyrazolones[7] and phenylhydrazones of pyruvic ester,[8] and hence the less abundant isomer, which has the low field peak at 13.8 ppm, is probably the cis form.

The infrared spectrum of I in $CHCl_3$ offers support for these assignments. Two peaks appear in the NH regions: a relatively sharp absorption at 3326 cm^{-1} and a broader absorption at 3260 cm^{-1}. In the ^{15}N isotopomer these absorptions appear at 3320 and 3250 cm^{-1}, respectively, due to the effect of the ^{15}N on the reduced mass of the NH group. The sharp absorption can be attributed, therefore, to the stretching vibration of the non-hydrogen-bonded NH group in the trans isomer, and the broader peak is a result of the NH stretch in the hydrogen-bonded cis form. The infrared spectrum also contains a medium intensity absorption at 1660 cm^{-1} with a high frequency shoulder, which can be attributed to C=O stretching vibrations. These peaks are insensitive to isotopic substitution. Two other peaks in the spectrum shift by more than 5 cm^{-1} on substitution with ^{15}N. These sharp peaks appear at 1513 and 1180 cm^{-1} in the ^{14}N derivative and at 1502 and 1172 cm^{-1} in the ^{15}N derivative. The IR spectrum of I in

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Table I. Melting Points and Chemical Shifts

Compd	Recrystallized from	Melting point, °C Obsd.	Lit.	Solvent	Chemical shifts, ppm (J, Hz) ^{14}N	^{15}N[a]
I	Methanol	153–154	148–150[10]	$CDCl_3$	2.23, 2.41, 6.8–7.8, 8.7,[b] 13.8	8.7 (d, J = 92), 13.8 (d, J = 95)
				Me_2SO-d_6	2.33, 6.7–7.9, 11.15	11.15 (d, J = 94)
II	–	135–136	133[11]	$CDCl_3$	1.96, 2.46, 6.7–7.5, 7.8	7.8 (d, J = 90)
				Me_2SO-d_6	1.98, 2.38, 6.5–7.5, 9.9	9.9 (d, J = 95)
III	95% ethanol	152–153	116–118,[2] 146[2]	$CDCl_3$	6.7–8.2, 8.7, 14.35[b]	8.7 (d, J = 94), 14.3 (d, J = 94)
	Benzene	101–102		Me_2SO	6.7–8.2, 11.3,[b] 14.1	11.3 (d, J = 94), 14.1 (d, J = 94)
				C_5H_5N	c, 11.1,[b] 14.5	11.1 (d, J = 95), 14.5 (d, J = 95)
IV	95% ethanol	136–137	135[12]	$CDCl_3$	6.6–8.1, 8.2,[b] 12.1	8.2 (d, J = 92), 12.1 (d, J = 95)
				Me_2SO-d_6	6.6–8.2, 10.0	10.0 (d, J = 94)

[a] Spectra of ^{15}N derivatives are identical to those of ^{14}N except for peaks noted d (doublet). [b] The more intense low field peak. [c] Phenyl region observed by solvent.

Nujol exhibits only one sharp peak in the NH region. This may indicate the existence of only the trans form in the solid state.

If the NMR spectrum of I is taken within several minutes of preparing the solution in $CDCl_3$, the relative intensity of the methyl peaks and the low field NH peaks are different than the relative intensities after several hours (when equilibrium has been established). During this time the higher field methyl resonance and the lower field NH resonance increase until at equilibrium the relative intensities of the higher to lower field NH resonance are about 2:1, respectively. Thus, dissolution in $CDCl_3$ produces a relatively slow conversion from the trans isomer in the solid state to a mixture of about 65% trans isomer, 35% cis isomer in solution.

The NMR spectrum of I in Me_2SO contains only one methyl and one NH resonance (a doublet in the ^{15}N isotopomer). Because the NH proton would hydrogen bond more strongly to Me_2SO than to $CDCl_3$, the NH resonance, which appears at a lower field than the trans isomer in $CDCl_3$ (but at higher field than the cis isomer in $CDCl_3$), can be assigned to the trans form since the resonance for the intramolecularly hydrogen-bonded cis form should be relatively insensitive to solvent effects. Thus, compound I exists solely in the trans-hydrazone form in the solid state and Me_2SO and as a mixture of the trans and cis forms in $CDCl_3$.

The NMR spectra of the other derivatives can be similarly analyzed. In each case there is no evidence for the CH form (C). Moreover, the low field resonance(s) observed for the ^{14}N derivatives splits into doublets on substitution of ^{15}N. Each compound therefore exists in solution only in the hydrazone form. Compound II in both $CDCl_3$ and Me_2SO exists as only the trans geometric isomer, as evidenced by the single relatively high field (7.84 ppm) NH peak which shifts to a lower field in Me_2SO. Compound III exists as a mixture of cis and trans forms in $CDCl_3$, Me_2SO, and pyridine. In $CDCl_3$ the cis form predominates in a ratio of about 12:1, in Me_2SO the trans form predominates in a ratio of 10:1, and in pyridine the ratio of cis to trans is approximately 1:3. The compound was also examined in mixtures of $CDCl_3$ and Me_2SO, and the ratio of cis to trans isomers was found to be dependent on the ratio of $CDCl_3$ to Me_2SO. For example, in a 25% by volume solution of Me_2SO in $CDCl_3$ the ratio of cis to trans was 1:1, in a 50% solution the ratio was 1:3, and in a 75% solution the ratio was 1:9. Compound IV exists primarily in the trans form in $CDCl_3$ and only in the trans form in Me_2SO.

The infrared spectra of compounds II and IV are in general agreement with the structural assignments above. The IR spectrum of the ^{14}N derivative of II in $CDCl_3$ contains two peaks in the NH region: a sharp peak at 3353 cm^{-1} and a broader peak at 3300 cm^{-1}. These peaks shift to 3348 and 3291 cm^{-1} in the ^{15}N isotopomer. A very broad carbonyl peak appears at 1665 cm^{-1} in the spectrum of both isotopomers. Two other peaks shift by more than 5 cm^{-1} on substitution of ^{15}N; these occur at 1497 and 1178 cm^{-1} in the ^{14}N derivative and at 1490 and 1169 cm^{-1} in the ^{15}N derivative. The appearance of two NH absorptions in the IR but only one NH resonance in the NMR may be indicative of exchange between two NH forms. The IR of II in Nujol exhibits only a single sharp NH peak.

The IR spectrum of III in $CDCl_3$ contains two very weak absorptions in the NH region: at 3323 and 3190 cm^{-1} in the ^{14}N isotopomer and at 3308 and 3180 cm^{-1} in the ^{15}N isotopomer. The region from 1635 to 1558 cm^{-1} contains a series of peaks: two shoulders at 1635 and 1608 cm^{-1} and sharp peaks at 1598 and 1588 cm^{-1}. Absorptions at 1428 (weak) and 1146 cm^{-1} (sharp) in the ^{14}N derivative shift to 1417 and 1132 cm^{-1} in the ^{15}N isotopomer. The NH absorptions are not readily apparent in the spectrum of III in Nujol.

The IR spectrum of IV in $CDCl_3$ contains an intense sharp peak at 3315 cm^{-1} and a very weak broad peak at 3268 cm^{-1}. The carbonyl absorption occurs at 1635 cm^{-1}. In the ^{15}N derivative of IV the sharp NH absorption appeared at 3304 cm^{-1}. A shift in the weak peak was difficult to discern. The spectrum of IV in Nujol contained two sharp almost equally intense peaks at 3310 and 3280 cm^{-1}.

Thus, the spectroscopic evidence strongly suggests that only the hydrazone form exists in solution for each of the compounds studied. All but III in $CDCl_3$ exist solely or primarily in the trans geometric isomer. For those that exist as mixtures in $CDCl_3$ (I, III, and IV), the trans form is favored by more basic solvents (Me_2SO, pyridine), presumably because of hydrogen-bonding interactions with the solvent that are unlikely in the cis form. The trans form is also apparently favored in the solid state. Since the equilibrium between the geometric isomers in solution is apparently established rather rapidly for all but I, it is not surprising that the spectroscopic solution data indicate that the same forms or mixtures are obtained by both synthetic routes. Moreover, since this equilibrium is clearly solvent dependent, it is likely that reaction conditions, solvents, and recrystallization media are more influential on product composition than on synthetic route. Clearly, the conditions used for the condensation and Japp–Klingemann reactions reported here resulted in compounds with identical physical properties.

Experimental Section

All condensation reactions were carried out by the reaction of phenylhydrazine hydrochloride with the appropriate α-dicarbonyl compound in aqueous ethanol (except for compound I which was prepared from hot water, thoroughly washed with cold 95% ethanol, and then recrystallized from absolute methanol). Recrystallization solvents for the other compounds are given in Table I. For the preparation of the ^{15}N isotopomers by the condensation method the phenylhydrazine-^{15}N hydrochloride was prepared[9] from 98% isotopically pure aniline-^{15}N (Prochem, Inc.). The Japp–Klingemann procedures described by Reynolds and Van Allan[10] were used for the preparation of I and II, while the method of Bamberger and Schmidt[2] was followed for III.

Solvents for spectroscopic studies were dried over molecular sieves, except for chloroform which was shaken with alumina. Compounds were vacuum-dried. Solution concentrations for both NMR and IR studies were 10–20% by weight.

NMR spectra were obtained on a Varian A-60D spectrometer. Infrared spectra were taken on a Perkin-Elmer 621 spectrophotometer. Melting points were obtained under nitrogen on a Perkin-Elmer DSC-1 differential scanning calorimeter and on a Fisher-Johns melting point block.

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Registry No.—*cis*-I, 64840-28-4; *trans*-I, 27843-96-5; *trans*-II, 15385-07-6; *cis*-III, 15823-87-7; *trans*-III, 15808-13-6; *trans*-IV, 64840-29-5; 2-oxopropanal, 78-98-8; 2,3-butanedione, 431-03-8; α-oxobenzeneacetaldehyde, 1074-12-0; benzil, 134-81-6; phenylhydrazine hydrochloride, 59-88-1.

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Analysis of Carbon-13 Nuclear Magnetic Resonance for Monohydroxy Steroids Incorporating Geometric Distortions[1a]

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For a given molecule, deviations between its observed ^{13}C NMR spectrum and its spectrum predicted from a set of empirical ^{13}C NMR rules is often explained in terms of geometric distortions. Allinger's[2,3] molecular force field is used to study geometric distortions in monohydroxy-5α,14α-androstanes. The net effect of many types of slight geometric distortions on the ^{13}C shift are examined in terms of the nonbonded interactions. The Δ_α and Δ_β effects could be characterized in a few terms suggested by the nonbonded interactions. Caution should be used in explaining ^{13}C chemical shifts with geometric distortion arguments without obtaining some evidence of existing geometric changes and exploring other substructural arrangements which might be important.

Introduction

Within the past decade considerable effort has focused upon deriving empirical ^{13}C NMR rules. One of the standard methods for rationalizing a ^{13}C nuclear magnetic resonance spectrum has been to equate the C-13 shift of a particular carbon atom to contributions from structural features in the molecule.[4–9] The structural features chosen are presumed to give linearly independent contributions to the shift. The subject of some recent work[9] has focused on systems which are skeletally rigid and thus provide ideal systems to study the influence of geometrical and stereochemical features.

The method of structural parameterization has been applied to monohydroxy steroids by Eggert et al.[9] The steroids considered in this work consisted of all trans ring junctions and thus could be classified as rigid systems. Deviations between the observed shifts and shifts calculated by the structural parameterization method have been observed. For instance, C-1 in 5α,14α-androstan-1β-ol has an observed substituent effect, Δ_α, of 40.1 ppm compared to the calculated value of 45.0 ppm. The structural parameters considered in the work of Eggert[9] for the explanation of Δ_α were the number, n, of γ gauche carbons possessing hydrogen atoms able to interact with the hydroxyl group and the number of skew pentane interactions, p, of the hydroxyl group with carbon atoms. The Δ_α substituent effect is given as Δ_α (ppm) = $45.0 + 3.5p - 3.5n$. The explanation of Δ_β was given in terms of q, the number of γ-gauche interactions of the hydroxyl group with the γ carbon atom connected to the β carbon atom in question. The equation for Δ_β is Δ_β)ppm) = $9.3 - 2.4q$.

Geometric distortions in a structural framework leading to changes in local electronic environments of the nuclei have been advanced as one possible explanation of the deviations between observed and calculated shifts. Kollman et al.[10] have looked at long-range effects in cortisol by molecular-orbital calculations and have shown that conformational changes were accompanied by changes in charge densities which often outweigh direct inductive electronic effects. Charge densities have been related to C-13 shifts by various authors.[11,12] Geometric distortions can result in other effects which might influence the C-13 shift. Changes in distances between atoms in the molecule can result in varying steric and electric-field

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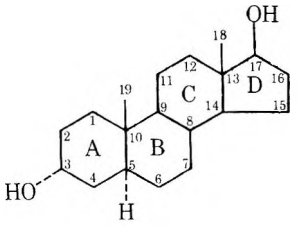
effects. The later is associated with through space influences that polarized regions exert on the local electronic distribution. The steric effect relates to closely spaced structural groups which cause perturbations.

One likely cause of deviations between predicted and observed shifts could be due to geometric distortions; however, it is also feasible that the wrong structural features were chosen or that they are not linearly independent or even that the model which characterizes a shift in terms of structural parameters is not adequate. For example, Dalling and Grant[5] rationalized shifts of methylcyclohexane using substituent parameters. The parameters were used[5] on 1,1,2-trimethylcyclohexane with poor agreement regardless of the equilibrium constant used. Two possible explanations are that the molecule is distorted or that the parameter set was not appropriate.

Confirmation of structural changes is usually difficult due to the labor involved in obtaining x-ray data. In many instances molecular force-field calculations can be used to obtain the information within reasonable time limits. The purpose of this work is to explore the use of molecular force-field calculations to determine the relevance of suggesting specific geometric distortions in monohydroxy 5α,14α-androstanes as explanations for the C-13 shift observed. The influences of geometric distortions on the ^{13}C NMR spectra will have to be restricted to changes due to steric effects. Steroids were chosen because of the availability of earlier work[9] from our laboratory; furthermore, 10-methyl-*trans*-decalols[13] can also be used for comparison of the appropriate bicyclic environment.

Method

In order to establish the ability of Allinger's force field[2,3] to distinguish differences between the monohydroxy steroids, a study of the following compounds was made: (1) 5α-androstane-3α,17β-diol; (2) 5α-androstane-3β,17β-diol; (3) 3α-hydroxy-5α-androstan-17-one; (4) 3β-hydroxy-5α-androstan-17-one.



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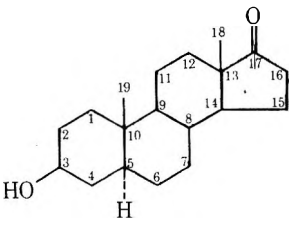


(4)

Allinger[14] recently reported a calculation on 3α-hydroxy-5α-androstan-17-one and concluded that the calculated geometry and the x-ray structure were in good agreement. For the purpose of this work it is necessary to ascertain if geometry changes between closely related structures are also in good agreement with geometry changes that would be predicted from x-ray data.

A force-field calculation was made on each of the four compounds. The torsional angles for the A ring of compounds 1–4 from the force-field and x-ray determinations are shown in Table I. By comparing 3α-hydroxy-5α-androstan-17-one to 3β-hydroxy-5α-androstan-17-one it is seen that the A ring is more puckered (the average torsional angle is larger) in both the force field and x-ray for the 3β structure. Comparing the force-field determinations for 5α-androstane-3α,17β-diol given in column 1 and 5α-androstane-3β,17β-diol it is seen that the A-ring angles are nearly identical for both compounds. The crystal structure for 5α-androstane-3α,17β-diol is nearly identical to 3α-hydroxy-5α-androstan-17-one. The crystal structure for 5α-androstane-3β,17β-diol is more puckered than the 5α-androstane-3α,17β-diol but it's ring is no longer as symmetrical (greater difference between torsional angles within ring) as it was in the keto structure. The crystal structure for 5α-androstane-3β,17β-diol is that of a monohydrate crystal while the other crystal structures were nonhydrated. This could account for some of the differences between the force-field and x-ray structure for 5α-androstane-3α,17β-diol.

Table I. Comparison of the Torsional Angles in Ring A

C atoms	3α-Hydroxy-5α-androstan-17-one[c]		3β-Hydroxy-5α-androstan-17-one[d]	
	Force field	X ray[15]	Force field	X ray[16]
10-1-2-3	54.3	55.6	55.7	57.7
1-2-3-4	49.6	51.9	53.8	55.1
2-3-4-5	49.6	52.3	53.6	54.5
3-4-5-10	54.3	56.3	55.4	56.7
4-5-10-1	53.9	55.3	52.7	55.7
2-1-10-5	53.8	55.3	52.9	56.2
Average	52.6	54.5	54.0	56.0

C atoms	5α-Androstane-3α,17β-diol[e] Force-Field C-1	C-2[a]	X ray[17]	5α-androstane-3β,17β,diol[f] Force field	X ray[18] [b]
10-1-2-3	56.7	54.5	55.9	55.5	54.4
1-2-3-4	53.5	49.7	51.8	53.1	51.9
2-3-4-5	52.7	49.7	51.1	53.0	54.1
3-4-5-10	54.6	54.3	54.7	55.5	58.6
4-5-10-1	52.7	53.7	54.8	53.3	57.9
2-1-10-5	54.0	53.8	54.8	53.2	55.6
Average	54.0	52.6	53.9	53.9	55.4

[a] Local minimum slightly higher in energy. [b] Monohydrate crystal. [c] Registry no.: 53-41-8. [d] Registry no.: 481-29-8. [e] Registry no.: 1852-53-5. [f] Registry no.: 42366-37-0.

Further calculations were made on 5α-androstane-3α,17β-diol and a local minimum was found lying slightly above the minimum given in Table I. The torsional angles for the local minimum are given in Table I, column 2. The conformation corresponding to the local minimum of 5α-androstane-3α,17β-diol is more flattened and thus in better agreement with its x-ray result.

The difference between the results for 5α-androstane-3α,17β-diol and 3α-hydroxy-5α-androstan-17-one could imply that the long-range effects of the keto group are different from those of the hydroxyl group. It should also be noted that the x-ray structures showed differences in the B, C, and D rings between the diols and between the keto structures, while the force field did not show any substantial differences. The ^{13}C NMR spectra of 5α-androstane-3α,17β-diol and 5α-androstane-3β,17β-diol[15] gave nearly identical results for the B, C, and D rings. The differences in the B, C, and D rings given in the x-ray structure could be attributed to artifacts of the crystal packing forces and are thus not a property of the isolated molecule. The inability of the force field to reproduce the changes in the B, C, and D rings is not felt to be a restriction upon their use for analysis of the ^{13}C NMR spectra.

Force-field calculations were made on the monohydroxy 5α-androstanes with the hydroxyl group positioned at one of the following locations: 1α, 1β, 2α, 2β, 3α, 3β, 4α, 4β, 6α, 6β, 7α, 7β, 11α, and 11β. In order to determine the nature of the steric effects which are present, the nonbonded interactions with an energy contribution greater than 0.1 kcal were tabulated. Allinger's program calculates the van der Waals (nonbonded) interaction energy between all pairs of atoms not bonded to each other or to a common atom. The differences between the nonbonded interactions which were present in

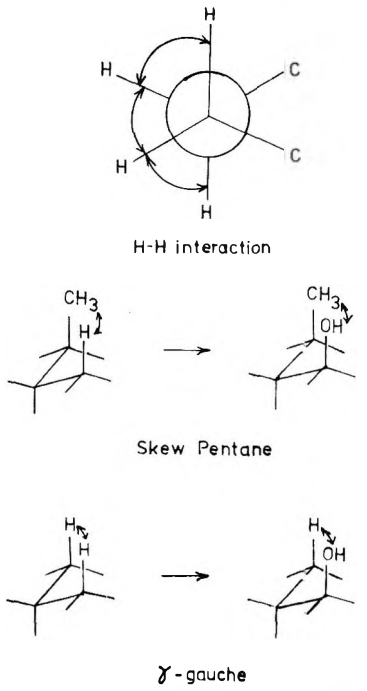


Figure 1. Three types of non-bonded interactions found for monohydroxy steroids. To the left of the arrow is the interaction present in androstane and to the right is the interaction introduced with substitution of the hydroxyl group.

the parent androstane and those of the monohydroxy androstane were then considered. This incorporates steric effects which are introduced when a substituent is added as well as when the steric effects are removed.

Results

The α-Substituent Effect. There were three major types of nonbonded interactions that were either present in androstane and not in the monohydroxy androstane or present in the monohydroxy androstane and not in androstane. Each of the interactions is illustrated in Figure 1. The first type of interaction is a 1,4 nonbonded interaction between hydrogens present in androstane which is removed with substitution of the hydroxyl group. An axial hydrogen will have a nonnegligible 1,4 nonbonded interaction with the equatorial hydrogen on the adjacent carbon removed. An equatorial hydrogen with a secondary neighboring carbon atom will have two 1,4 nonbonded interactions removed. A hydrogen in the equatorial position is more sterically hindered than in the axial position. Therefore, both the orientation of the hydrogen removed and the degree of the neighboring carbon atom contribute to the number of 1,4 nonbonded H–H interactions. A correlation between the orientation of the hydroxyl group has been drawn in earlier works.[20–22] A recent study by Grover and Stothers[13] of the ^{13}C NMR spectra of 10-methyl-*trans*-decalols showed the axial vs. equatorial arrangement to be inapplicable when there is a syn-diaxial OH–CH_3 interaction. Eggert et al.[9] also concluded that the carbinyl carbon shift was not primarily dependent on the axial or equatorial orientation of the hydroxyl group.

The second type of nonbonded interaction which was of importance involved the methyl groups C-19 or C-18. In androstane there was a nonbonded interaction between a methyl group and an axial hydrogen on the same face of the ring as the methyl group. When the hydrogen is substituted with a hydroxyl group, the hydrogen–methyl group interaction is replaced with an interaction between the methyl group and the lone pairs on the oxygen. This is the type of interaction referred to by Eggert et al.[9] as a skew pentane interaction.

Table II. Number of Occurrences of Various Nonbonded Interactions in Monohydroxy Androstanes

Registry no.	OH position	H–H	Skew pentane	γ-gauche	Δ_α, $\delta^{RH} - \delta^{ROH}$, ppm Exptl	Calcd
2287-84-5	1α	1	0	2	32.7	36.6
2287-91-4	1β	2	0	1	40.1	39.6
20707-85-1	2α	4	0	0	45.7	44.5
1225-47-4	2β	2	1	0	45.7	45.2
7657-50-3	3α	2	0	1	39.6	39.6
1224-92-6	3β	4	0	0	44.4	44.6
20707-77-1	4α	3	0	1	41.2	41.5
20707-78-2	4β	1	1	0	43.2	43.3
20311-10-8	6α	3	0	1	40.8	41.5
32215-75-1	6β	1	1	0	43.3	43.3
19037-31-1	7α	1	0	2	36.0	36.6
19037-33-3	7β	3	0	0	43.0	42.6
2872-91-5	11α	3	0	0	48.3	42.6
25814-80-6	11β	1	2	0	47.7	47.9

The third type of interaction involves γ-gauche carbons having hydrogens that can interact. When one of the hydrogens is replaced with a hydroxyl group, the hydrogen–hydrogen interaction of androstane is replaced with an interaction between the lone pairs on oxygen and the other hydrogen. The number of occurrences of the three types of interactions for the compounds in this study are given in Table II. It should be noted that the number of occurrences of each effect does not correspond to what one would expect from a fixed skeletal frame model but represents the distorted molecule.

The nonbonded interactions for 2β, 3α, 3β, 4β, 6β, and 11β were almost entirely represented by the three types of interactions which have been given. These molecules were fitted to a linear form giving $\Delta_\alpha = 36.9 + 1.9n_1 + 4.5n_2 - 1.1n_3$, where n_i represents the number of occurrences of the ith effect, as given in Table II. The resulting expression was then applied to the remaining monohydroxy androstanes and the results are given in Table II. Except for 1α and 11α the calculated α-carbon effect was within 1.2 ppm of the experimental value.

To examine the 1α-monohydroxyandrostane which showed considerable disagreement between the calculated and observed Δ_α effect, the force fields of 10-methyl-*trans*-decalin, *trans*-decalin, and their corresponding 1α OH derivatives were calculated. The nonbonded interactions were tabulated for the 10-methyl-*trans*-decalin compounds and for the *trans*-decalin compounds. The nonbonded interactions for 1α,10-methyl-*trans*-decalol, 1α-*trans*-decalol, 5α,14α-androstan-1α-ol, and 5α,14α-androstan-12α-ol were essentially the same. The substituent effect at the α carbon for the 1α-*trans*-decalol obtained by Grover and Stothers[13] was 36.1 ppm which is in good agreement with the calculated value of 5α,14α-androstan-1α-ol given in Table II. The α-carbon substituent effect for 1α,10-methyl-*trans*-decalol given by Grover and Stothers[13] is 33.1 ppm. Eggert et al.[9] obtained an α-carbon substituent effect for 5α,14α-androstan-1α-ol and 5α,14α-androstan-12α-ol of 32.7 and 33.7 ppm, respectively. These results seem to indicate a direct inductive effect on the α carbon from the 1,2 trans diaxial methyl group.

The difference between the experimental and calculated Δ_α effect for 5α,14α-androstan-11α-ol have not been captured in the simple interactions discussed. A measure of flattening of the C ring at the C-11 position is obtained by the difference between 5α,14α-androstan-11α-ol and 5α,14α-androstane of the sum of the dihedral angles C(8)–C(9)–C(11)–C(12) and C(9)–C(11)–C(12)–C(13). The C ring in 5α,14α-androstan-11α-ol is flattened by 14.1° relative to androstane. It would

Table III. Correlation between Δ_β and Nonbonded Interactions

Category		Androstanol		
Deg of β carbon	Type and no. of interactions	OH position	β C no.	Δ_β, $\delta^{RH} - \delta^{ROH}$, ppm
2	1 H–H	1α	2	6.6
		2β	3	7.0
		3α	2	6.8
		4β	3	7.0
		6β	7	7.4
2	2 H–H	2α	1	9.4
		2α	3	9.1
		3β	2	9.3
		3β	4	9.1
		4α	3	9.4
		6α	7	9.5
		7β	6	9.5
		1β	2	11.0
		11α	12	11.5
2	1 H–H	3α	4	6.7
	1 γ-gauche	7α	6	7.6
2	1 H–H	2β	1	6.4
	1 skew pentane	11β	12	8.8
3	1 H–H	4α	5	7.1
	1 γ-gauche	6α	5	6.7
3	1 H–H	7β	8	8.0
		11α	9	14.7
3	1 γ-gauche	7α	8	4.1
3	1 skew pentane	4β	5	3.0
		6β	5	2.7
		11β	9	3.9
4	2 γ-gauche	1α	10	3.7
4		1β	10	6.2

be impossible to attribute the differences at C-11 in 5α,14α-androstan-11α-ol to any given effect due to the complexity of the geometry changes involved.

The β-Substituent Effect. The explanation power of the nonbonded interactions for the hydroxyl substituent effect on the chemical shift of β carbon atoms was examined. The β carbon situations present in the androstanols studied were divided into catagories according to the degree of the β carbon atom and the number of occurrences of the types of steric interactions described earlier. The categories which result are summarized in Table III. For those categories which showed a range of 1 ppm, there were no additional steric effects which could narrow the range and there did not seem to be any simple correlation between bond distance in particular C^β–C^γ or torsional angle which could explain the deviations.

Three categories showed a deviation of at least 2 ppm between the examples given for each category. The first such category was a secondary β carbon with two H–H interactions. For most of the examples in this category a shift in the range 9.1–9.5 ppm was observed. The shifts of C-2 in 5α,14α-androstan-1β-ol and C-12 in 5α,14α-androstan-11α-ol had Δ_β values of 11.0 and 11.5 ppm, respectively. The work of Eggert et al.[9] also pointed out these exceptions and an explanation was given in terms of compression of the C^β–C^γ bond distance giving rise to a greater downfield shift. The modeled calculations showed a compressed C^β–C^γ bond distance but they were not substantially different from the other bond distances in the group. However, there were present nonbonded interactions between the hydroxyl group and either C-2 or C-12. This nonbonded interaction was not present in the other examples in this category.

The other two categories which showed deviations greater than 2 ppm were a secondary carbon with 1 H–H and 1 skew pentane and a tertiary carbon with 1 H–H interaction. The 5α,14α-androstan-11α-ol and 5α,14α-androstan-11β-ol in these categories showed a nonbonded interaction between the hydroxyl group and the β carbon which did not occur in the other example of each category.

One suggested explanation for the difference in β-substituent effects between axial and equatorial hydroxyl groups is that γ-gauche interactions of the axial hydroxyl group produce an elongation of the C^β–C^γ bond.[3] The proposed elongation should give rise to an upfield shift at the β carbon atom. The examination of C^β–C^γ bond distances for the molecules studied showed a compression of the C^β–C^γ bond distance with substitution of the hydroxyl group. Axial substitution gave longer C^β–C^γ bond distances for 4β-androstanol with carbon 3 and for 6β-androstanol with carbon 7 than the corresponding equatorial 4α and 6α substitutions. However, there were also examples in which there was no difference in C^β–C^γ resulting from orientation such as 2α and 2β with carbon 3 and 3α and 3β with carbon 2 or 4.

The γ-Substituent Effect. Eggert et al.[9] analyzed the γ-substituent effect of the hydroxyl group in six-membered rings in terms of γ-gauche and γ-trans shifts. A γ-gauche shift occurs when the γ-carbon atom is gauche to the hydroxyl group and γ-trans is defined analogously. The magnitude of each of these effects further depends upon whether the γ-carbon atom is secondary or tertiary. Valence and torsional angle deformations from 1,3-syn-diaxial interactions are given as one possible explanations for deviations in the trends expected.

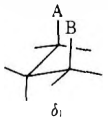
Methylene carbons that have a γ-gauche interaction and a skew pentane have Δ_γ substituent effects of −5.3 ppm for 5α,14α-androstan-2β-ol with carbon 4 and 5α,14α-androstan-4β-ol with carbon 2. A substituent effect of −3.1 ppm is observed under the same constraints for 5α,14α-androstan-4β-ol with carbon 6 and 5α,14α-androstan-6β-ol with carbon 4. The values −5.3 and −3.1 are averaged to give −4.5 ppm, reported in the work of Eggert et al.[9] The Δ_γ of a methylene carbon with a γ-gauche and no skew pentane was −6.4 ppm. The difference in the first group is greater than the difference attributed to the addition of a skew pentane. Eggert et al.[9] used valence angle distortions to describe the differences between those molecules having a skew pentane and those without that interaction. The γ shift of carbon 4 in 10-methyl-*trans*-decal-2β-ol and carbon 2 in 10-methyl-*trans*-decal-4β-ol were −5.2 and −5.3 ppm, respectively. The shift of carbon 6 in 10-methyl-*trans*-decal-4β-ol was −3.3 ppm. These results are in remarkable agreement with the steroids, considering the force field showed considerable differences in their skeleton geometry.

The results indicate the necessity of examining fully a wide scope of substructure parameters before using geometry distortions to explain errors in the parameter set. One method for exploring the full range of structural arrangements is given in the work of Mitchell and Schwenzer.[23]

The δ-Substituent Effect. Grover and Stothers[13] examined various δ-substituent effects and showed that the δ carbon is significantly deshielded in compounds with syn-diaxial δ_{OH-CH_3} interactions with the generalization that more rigid systems give larger shifts. In the work of Eggert[9] it was concluded that the steroid data did not support this generalization.

The δ_1 orientation (notation of Grover and Stothers[13]) of a hydroxyl group to its δ carbon atom is shown in Table IV in addition to the shifts which have a δ_1 orientation. The δ_1 effect was examined in detail, since it was the only one which showed substantial effects. The force field showed 10-methyl-*trans*-decal-4β-ol to be only slightly more torsionally hindered with respect to 10-methyl-*trans*-decal-2β-ol and similarly for the steroids. Examination of the energy contributions from

Table IV. δ_1 Hydroxyl Substituent Effects (in ppm)



Hydroxyl Group (A or B) δ carbon (A or B)

Registry no.	OH position	δ_1 shift, $\delta^{RH} - \delta^{ROH}$, ppm	δ_1 C	Total Nonbonded interaction, kcal
		5α-Steroids		
	2β	2.5	C-19	0.17
	4β	2.4	C-19	0.23
	6β	3.5	C-19	0.07
	11β	3.2	C-19	0.12
		10-Methyl-*trans*-decalols		
25578-06-7	2β	2.1	C-Me	0.22
42280-82-0	4β	3.4	C-Me	0.12

bending indicated that both the 2β- and 4β-10-methyl-*trans*-decalols showed increased bending strain compared to the steroids, but there was an opposite effect on the shift. The only comparison which seemed to give insight into the changes was the total nonbonded interactions. The total nonbonded interactions computed at C-19 for the steroids and at C-11 for 10-methyl-*trans*-decalols are given in Table IV. The results in Table IV indicated that increased nonbonded interactions caused smaller shifts. The interactions between the lone pairs on oxygen and the methyl group contribute to the steric interactions. This work showed the unlikelihood of drawing a direct correlation between specific types of distortions and the observed shifts. Eggert et al.[9] advanced a similar argument that the δ_1 effect was a function of steric hinderance and proposed types of distortions which could be related to relieving the steric hinderance.

Conclusion

The selection of a set of structural parameters which correlate with a C-13 shift is a difficult decision. While the chosen parameter set may duplicate observed shifts within experimental error, there is no guarantee that they represent the correct terms in the model which correlates structural fragments to contributions of a C-13 shift. Various terms can be selected which are not necessarily independent of one another. This is one possible reason for the discrepancy over the importance of equatorial vs. axial orientation in the explanation of Δ_α. The determination of a set of coefficients for the parameters chosen depends on the completeness of the set of parameters as well as the functional form chosen and their values are not necessarily unique.

The use of the force field to determine the important nonbonded interactions and the number of occurrences of each type of interaction in the molecules studied allows the model to drive the correlations between structure and C-13 shift. This procedure is contrasted to an approach in which the C-13 data drives the selection of a set of parameters within a fixed skeletal frame model.

The examination of the differences in the nonbonded interactions between the androstane and monohydroxy androstanes calculated by the force field could be characterized by a few terms. The terms included interactions which had been removed as well as interactions introduced by the addition of the hydroxyl group. The terms were fitted to a linear functional form to obtain coefficients for each of the types of interactions.

Refinements of the shift prediction was not always possible even within the force-field model. However, the force field was valuable in ascertaining if there was sufficient reason for suggesting geometric distortions as explanations for deviations between parameter set predicted shifts and observed shifts. Refinement of the model of representing contributions to the total C-13 shift in terms of structural relationships may rest in looking for larger substructure units to act as parameters rather than suggesting geometric distortions in terms of specific torsional and valence angles and bond distances as the cause of observed deficiencies.

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Synthesis of 3′-*N*-Methylbiotin

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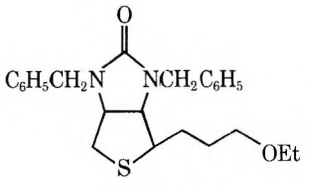
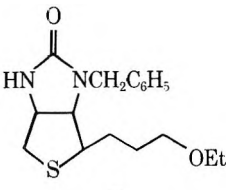
Treatment of *N,N′*-dibenzylurea VII with sodium in liquid ammonia removed the benzyl group in the sterically more crowded environment to give the monobenzyl derivative VIII. The benzyl group which was removed was defined by conversion of VIII to an aldehyde derivative IX, in which the NH group formed had interacted with an aldehyde group generated in the side chain. The monobenzyl derivative VIII methylated on nitrogen and converted to 3′-*N*-methylbiotin by reactions analogous to those used in the synthesis of biotin itself.

A singular observation made by Goldberg and Sternbach during their synthesis of biotin[2] was that treatment of the *N,N′*-dibenzylurea **I** with sodium in liquid ammonia removed only one of the benzyl groups. Furthermore, the reaction was regiospecific in that only one product was obtained. Specifically, this product might be either **II** or **III** depending on which benzyl group is more readily cleaved. Its actual structure was of no consequence to their synthesis, since another cycle of treatment with sodium in liquid ammonia and workup removed the other benzyl group and gave a fully deprotected intermediate. However, the first intermediate **II/III** would be useful for preparing biotin derivatives specifically alkylated on only one of the nitrogens. Of course, in this context, it is now essential to know which benzyl group was removed. The objective was to see if such a compound might be a biotin inhibitor which might have antibiotic activity.



I



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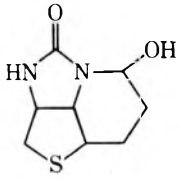

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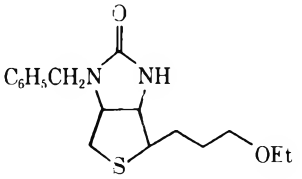
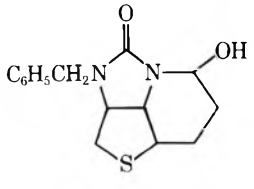
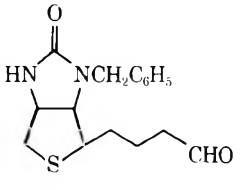


III



V



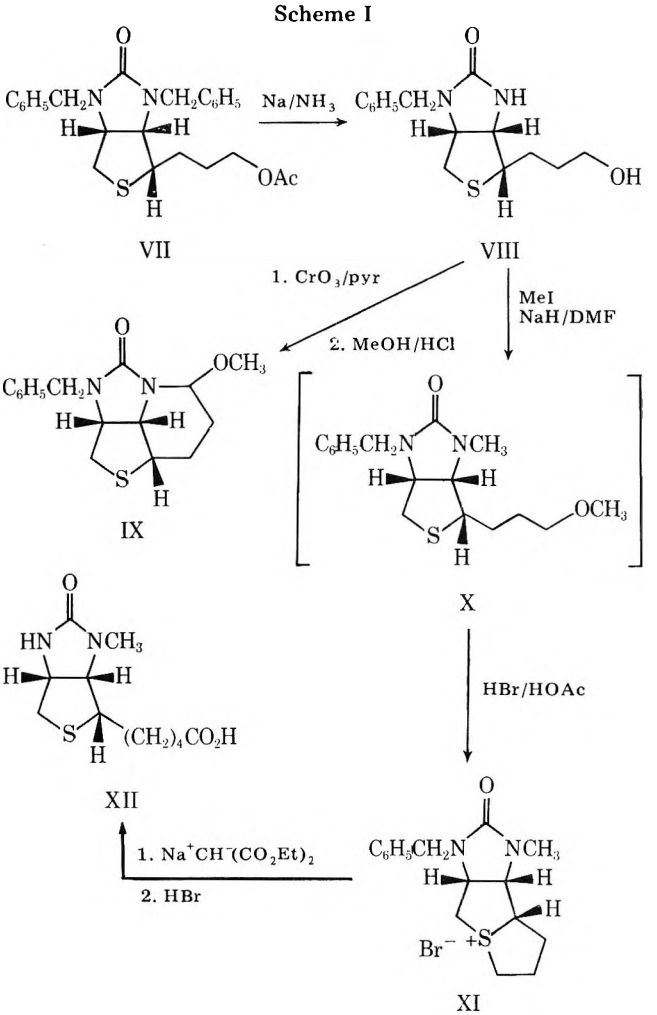
VI

Another observation made during the synthesis of α-dehydrobiotin[3] suggested how a decision between structures **II** and **III** might be made. In that work a fully deprotected intermediate with a propionaldehyde side chain was shown to exist entirely in the hemiaminal form **IV**. By analogy, the monobenzyl aldehyde related to **III** should exist in the cyclic hemiaminal form **V**; inspection of models gave no reason to suppose that the aldehyde related to **II** would have a particularly favored hemiaminal form and therefore should exist in the open aldehyde form **VI**. Consequently, the properties of the monobenzyl aldehyde should permit a decision as to which benzyl group is removed first by sodium in liquid ammonia.

The decisive aldehyde was obtained as shown in Scheme I. We chose to debenzylate the acetate **VII**[3] rather than the ethyl ether **I**, since the acetate was available in optically active form. Treatment of the dibenzyl acetate **VII** with sodium in liquid ammonia gave a monobenzyl alcohol to which structure **VIII** was assigned based on the following evidence. Oxidation with chromium trioxide in pyridine[4] gave a noncrystalline product which when treated with methanolic hydrogen chloride gave the crystalline methyl ether **IX** clearly derived from a cyclic form of the aldehyde. Therefore, sodium in liquid ammonia first removes the benzyl group in the more congested environment in this urea derivative.

Compound **VIII** was then converted to 3′-methylbiotin. Methylation of **VIII** with sodium hydride and methyl iodide gave an oil whose NMR spectrum indicated that the alcohol group had also been etherified to give **X**. Without further characterization, **X** was converted to the thiophanium salt **XI** by treatment with hydrogen bromide in acetic acid. Treatment

Scheme I



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of XI with sodiomalonic ester and then hydrobromic acid as in the synthesis of biotin[2] gave the *N*-methylbiotin **XII**.[5]

Experimental Section[6]

3-Benzyl-2-oxohexahydrothieno[3,4-*d*]imidazole-6-propanol (VIII). To a suspension of 10 g of **VII**[3] in 200 mL of liquid ammonia was added sodium in small pieces until the blue color persisted for 5 min. Ammonium chloride was added to decolorize the suspension, and the ammonia was allowed to evaporate. Water and hydrochloric acid were added to the residue until it was neutral. The solid was collected and recrystallized from ethanol to give 3.5 g of **VIII**, mp 142–145 °C. Further recrystallization from aqueous ethanol gave colorless plates, mp 143–145 °C.

Anal. Calcd for $C_{15}H_{20}N_2O_2S$: C, 61.62; H, 6.89; N, 9.58. Found: C, 61.43; H, 6.90; N, 9.58.

3-Benzylhexahydro-5-methoxy-1-thia-3,4a-diaza-2*H*-cyclopent[*cd*]inden-4(3*H*)-one (IX). To 1.25 L of pyridine was added 60 g of chromium trioxide with stirring during 2 h so that the temperature did not go above 30 °C. Then 29.25 g of *l*-3-benzyl-2-oxohexahydrothieno[3,4-*d*]imidazole-6-propanol (**VIII**; unnatural antipode) was added and the mixture stirred for 1.2 h at room temperature. A solution of 100 g of sodium pyrosulfite in 500 mL of water was added dropwise over ca. 20 min so that the temperature of the reaction mixture did not rise above 30 °C. The reaction mixture was concentrated in vacuo to ca. 0.5 L and diluted with 500 mL of methylene chloride. Then 900 mL of 3 N sulfuric acid was added followed by 150 mL of concentrated hydrochloric acid until the mixture was acidic. A further 500 mL of methylene chloride was added and the organic phase separated. The aqueous phase was washed with a further 500 mL of methylene chloride. The organic phases were combined, washed with 500 mL of 2 N hydrochloride acid and then 500 mL of water, dried over sodium sulfate, and concentrated in vacuo to give 32 g of dark-green oil. This was dissolved in 70 mL of methanol with 3 drops of 3 N hydrochloric acid and allowed to stand overnight. This solution was neutralized at room temperture with sodium bicarbonate solution and diluted to 200 mL with water to precipitate 25.9 g of crude green solid. This was combined with 2.7 g from a similar experiment and dried by azeotropic distillation of benzene. A methylene chloride solution was placed on a column of 100 g of alumina. The column was eluted with methylene chloride. The first 200 mL contained 0.3 g of green material. The next 1.5 L of eluate was concentrated in vacuo. The residues were combined and dissolved in 100 mL of methanol. Water was added to the solution until cloudy to give 17 g of **IX**: mp 113–117 °C; IR ($CHCl_3$) 1700 cm^{-1}; NMR ($CDCl_3$) δ 3.33 (s, 3, $-OCH_3$) and 5.1 ppm (m, 1, CH_3OCHN).

Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.22; N, 9.20. Found: C, 62.86; H, 6.59; N, 9.13.

(3a*R*,8a*S*,8b*S*)-3-Benzyldecahydro-1-methyl-2-oxoimidazo[4,5-*c*]thieno[1,2-*a*]thiolium Bromide (XI). To a stirred solution of 18 g (61.6 mmole) of *d*-**VIII** in 200 mL of tetrahydrofuran at 60 °C was added, in portions, 6 g (0.12 mol) of 50% sodium hydride in mineral oil. The reaction mixture was stirred at this temperature for 1 h and then 10 mL (0.16 mol) of methyl iodide was added dropwise so that the temperature did not go above 65 °C. The reaction mixture was then stirred at 65 °C for 2 h, cooled to room temperature, carefully diluted with 100 mL of water, and extracted with 3 × 250 mL of ether. The combined organic extracts were washed with 100 mL of water, dried over sodium sulfate, and concentrated in vacuo to leave 20 g of oil. A mixture of this oil with 200 mL of 30% hydrogen bromide in acetic acid was stirred and heated to 60 °C for 3 h, cooled to room temperature, and concentrated to dryness in vacuo. The residue was partitioned between 200 mL of water and 150 mL of benzene. The benzene phase was washed with water; the combined aqueous phases were washed with benzene and concentrated to dryness in vacuo. The residue was stirred with 100 mL of acetone and the solid was collected to give 12.5–17 g (55–77%) of **XI**: mp 230–231 °C; IR (KBr) 1680 cm^{-1}.

Anal. Calcd for $C_{16}H_{21}BrN_2OS$: C, 52.03; H, 5.73; N, 7.58. Found: C, 51.71; H, 5.69; N, 7.41.

(3a*S*,8a*R*,8b*R*)-3-Benzyldecahydro-1-methyl-2-oxoimidazo[4,5-*c*]thieno[1,2-*a*]thiolium Bromide (XI; Unnatural). This compound was prepared in the same manner as its antipode, except that dimethyl sulfoxide was used as solvent for the methylation. An NMR spectrum of the oil before hydrogen bromide treatment showed singlets at δ 2.9 and 3.3 ppm in $CDCl_3$. This was taken to indicate that the hydroxyl group had been etherified. The final product had mp 230–231 °C.

Anal. Calcd for $C_{16}H_{21}BrN_2OS$: C, 52.03; H, 5.73; N, 7.58. Found: C, 51.62; H, 5.71; N, 7.39.

(3a*R*,4*R*,6a*S*)-(−)-Hexahydro-3-methyl-2-oxo-1*H*-thieno[3,4-*d*]imidazole-4-valeric Acid (XII; Unnatural). To a solution of 1.38 g (60 mmol) of sodium in 300 mL of freshly distilled diethyl malonate was added 13.2 g (47.3 mmol) of **XI**. The reaction mixture was heated to 140–150 °C for 2 h, cooled, and partitioned between 250 mL of water and 250 mL of ethyl acetate. The organic phase was separated, washed with water, dried over sodium sulfate, and concentrated in vacuo (water pump) to 290 g; the excess malonic ester was distilled off at 100 °C under oil pump vacuum to leave 16.1 g of dark oil. This oil was stirred with 136 mL of 36% hydrobromic acid. The mixture was heated slowly to 90–100 °C for 0.5 h while the distillate was collected. Then the temperature was raised to 125 °C (inside temperature) for 1 h while 25–30 mL of distillate was collected. The reaction was then heated under reflux for 3 h, cooled, and concentrated in vacuo to leave 19.1 g of dark oil, which was heated under reflux with 40 mL of water for 10 min. The aqueous solution was decanted and allowed to stand in the refrigerator to give 6.6 g of crude product. Recrystallization from alcohol gave 5.2 g (43%) of **XII**: mp 211–212 °C; $[\alpha]^{25}_D$ −10.95 (*c* 2, 0.1 N NaOH); IR (KBr) 1740, 1676, and 1642 cm^{-1}; NMR (Me_2SO) δ 11.84 (m, 1, $-CO_2H$), 6.54 (s, 1, $-NH$), 4.28 (m, 1, CHN), 4.00 (m, 1, CHN), 3.20 (m, 1, $-CH_3$), 2.84–2.60 (m, 2, $-SCH_2$), 2.70 (s, 3, $-NCH_3$), 2.20 (t, 2, $-CH_2CO$), and 1.80–1.30 ppm (m, 6, $-(CH_2)_3-$); mass spectrum *m/e* (rel intensity) 258 (1.5, M^+), 241 (0.6), 225 (0.2), 211/212 (0.5), 199 (0.3), 193 (0.2), 184 (4), 166 (0.8), 160 (0.7), 125 (0.7), 111 (100), 99 (25), 87 (6), 85 (6), 75 (45), 45 (5), and 42 (10).

Anal. Calcd for $C_{11}H_{18}N_2O_3S$: C, 51.14; H, 7.02; N, 10.84. Found: C, 50.95; H, 7.06; N, 10.62.

(3a*S*,4*S*,6a*R*)-(+)-Hexahydro-3-methyl-2-oxo-1*H*-thieno[3,4-*d*]imidazole-4-valeric Acid (XII; Natural). This compound was obtained in the same way as its optical antipode in 40% yield: mp 211–212 °C; $[\alpha]^{25}_D$ +12.55 (*c* 2, 0.1 N NaOH).

Anal. Calcd for $C_{11}H_{18}N_2O_3S$: C, 51.14; H, 7.02; N, 10.84. Found: C, 50.92; H, 7.11; N, 10.66.

Registry No.—VII, 27368-82-7; VIII natural, 64871-79-0; VIII unnatural, 64912-41-0; IX, 64871-80-3; XI natural, 64871-81-4; XI unnatural, 64912-42-1; XII natural, 64871-82-5; XII unnatural, 64912-43-2; diethyl malonate, 105-53-3.

References and Notes

(1) Work done at F. Hoffmann-La Roche and Co., A. G. Basel, Switzerland.
(2) M. W. Goldberg and L. H. Sternbach, U.S. Patents 2 489 232; 2 489 235, and 2 489 238, Nov. 22, 1949. This work is outlined by L. H. Sternbach, *Compr. Biochem.*, **11**, 66 (1963).
(3) G. F. Field, W. J. Zally, L. H. Sternbach, and J. Blount, *J. Org. Chem.*, **41**, 3853 (1976).
(4) G. I. Poos, G. E. Arthur, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).
(5) S. E. Polakis, R. B. Guchhait, E. E. Zwergel, M. D. Lane, and T. G. Cooper, *J. Biol. Chem.*, **249**, 6657 (1974), have described the methylation of *d*-biotin methyl ester with diazomethane, but they did not fully characterize their product.
(6) All compounds are optically active. Those designated "natural" are the antipodes shown in the formula scheme. This distinction is, of course, immaterial for synthetic purposes. Melting points are corrected. Alumina used was Woelm grade I. Elemental analyses were performed under the direction of Dr. A. Dirscherl. Spectra were determined in the Physical Chemistry Department. I thank Dr. P. Zeller for the hospitality of his laboratory and Mr. A. Senn for his skillful technical assistance.

Stereocontrolled Total Synthesis of α- and β-Santonin

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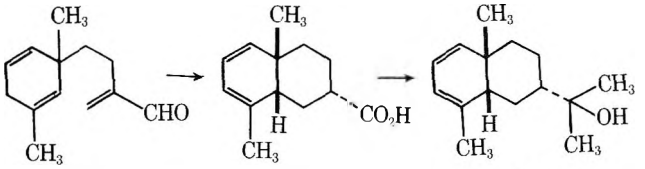
A total synthesis of racemic α- and β-santonin is described. The synthetic sequence involves reduction–alkylation of *m*-toluic acid with lithium in ammonia followed by methyl iodide. Homologation of the resulting 1-methyl-1,4-dihydro-*m*-toluic acid was effected by reduction using lithium aluminum hydride, oxidation with *N*-chlorosuccinimide–dimethyl sulfide reagent, and condensation of the resulting aldehyde with triethyl phosphonoacetate to give the acrylic ester derivative. Reduction with lithium in ammonia–ethanol yielded the propanol-substituted 1,4-dihydro-*m*-xylene, which was transformed to the bromide and alkylated with the lithium salt of the monosulfoxide of formaldehyde diethyl thioacetal. Treatment with acid effected cyclization via the butanal, affording 4a,8-dimethyl-1,2,3,4,4a,8a-hexahydronaphthalen-1-ol (**9**). Oxidation to the ketone and alkylation using ethyl iodoacetate gave the expected keto ester **11**, which was reduced to a mixture of diols. These were separated and the trans isomer was oxidized to the trans lactone **14** using silver carbonate on Celite. Alkylation with methyl iodide yielded the β-methyl isomer **15**, which could be epimerized to the more stable α isomer **16**. Photooxygenation of each of these isomers afforded β-santonin (**17**) and α-santonin (**18**), along with the corresponding endoperoxides **19** and **20**.

We recently described an efficient synthetic sequence leading to cis-fused hexahydronaphthalene derivatives such as IV (Scheme I).[1] The approach involved reduction–alkylation of *m*-toluic acid to the 1,4-dihydrotoluic acid derivative I, reduction to the 1,4-dihydroxylene II, oxidation to the butyraldehyde III, and acid-catalyzed cyclization to the bicyclic product IV.

A variant of the ring-closure step employing the α-methylene butyraldehyde V resulted in a total synthesis of racemic occidentalol VII via the acid VI.[1]

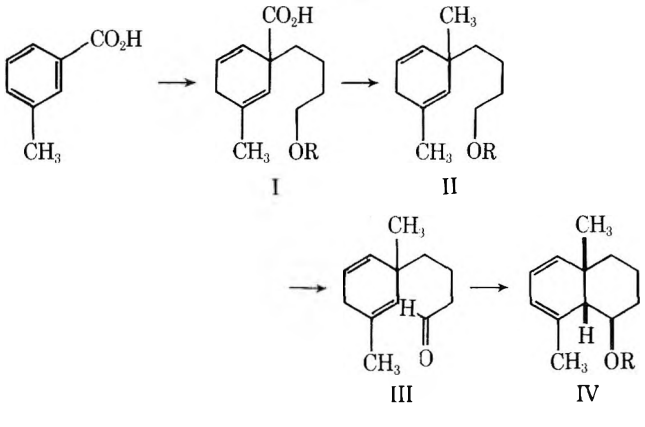


V VI VII

We now describe extensions and variations of this basic synthetic approach as applied to a new stereocontrolled total synthesis of the historically important eudesmanolide α-santonin (**18**) and its less stable epimer β-santonin (**17**).[2]

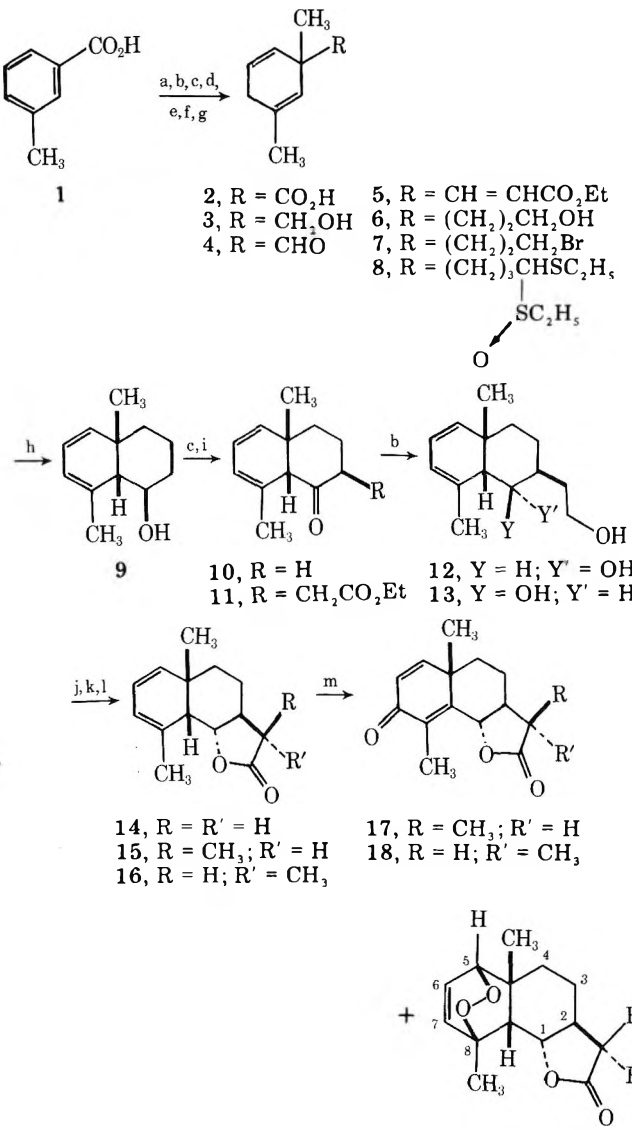
Our first departure from the previous synthesis of the key intermediate, alcohol **9**, involved reduction–*methylation* of *m*-toluic acid to the 1,4-dihydrotoluic acid **2** followed by side-chain introduction via the carboxylic acid substituent. The most satisfactory sequence examined thus far involves reduction with lithium aluminum hydride to the alcohol **3** followed by oxidation with dimethyl sulfide–*N*-chlorosuccinimide to aldehyde **4**.[3] Condensation with triethyl phosphonoacetate gave the acrylate **5** which was reduced to the alcohol

Scheme I



I II III IV

Chart I[a]



1

2, R = CO_2H
3, R = CH_2OH
4, R = CHO
5, R = $CH=CHCO_2Et$
6, R = $(CH_2)_2CH_2OH$
7, R = $(CH_2)_2CH_2Br$
8, R = $(CH_2)_3CHSC_2H_5$ (O, SC_2H_5)

9

10, R = H
11, R = CH_2CO_2Et

12, Y = H; Y′ = OH
13, Y = OH; Y′ = H

14, R = R′ = H
15, R = CH_3; R′ = H
16, R = H; R′ = CH_3

17, R = CH_3; R′ = H
18, R = H; R′ = CH_3

19, R = CH_3; R′ = H
20, R = H; R′ = CH_3

[a] (a) Li, NH_3, CH_3I; (b) $LiAlH_4$; (c) Me_2S,NCS, Et_3N; (d) NaH, $(EtO)_2POCH_2CO_2Et$; (e) Li, NH_3, EtOH; (f) Ph_3P, NBS; (g) $EtSCH_2S(\rightarrow O)Et$, BuLi, (h) $HClO_4$, H_2O; (i) $(i\text{-Pr})_2$-NLi, ICH_2CO_2Et; (j) Ag_2CO_3–Celite, (k) $(i\text{-Pr})_2NLi$, CH_3I; (l) $(i\text{-Pr})_2NLi$; (m) O_2, hematoporphyrin, *hν*.

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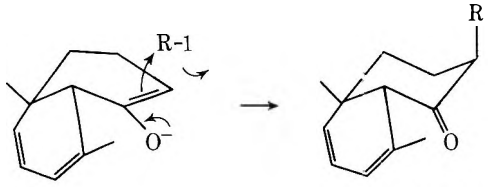
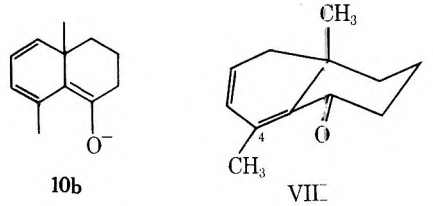
6 with lithium in ammonia–ethanol. The derived bromide 7 afforded the thioacetal monosulfoxide 8 upon treatment with the lithio derivative of ethyl thioethoxymethyl sulfoxide.[4] Treatment of this sulfoxide derivative with perchloric acid led directly to alcohol 9, presumably via the derived butyraldehyde. The entire sequence to this point can be effected in 40% overall yield.[5]

Oxidation of alcohol 9 using dimethyl sulfide–*N*-chlorosuccinimide gave ketone 10. This ketone, upon treatment with lithium diisopropylamide and ethyl iodoacetate, yielded the expected kinetic alkylation product, keto ester 11.

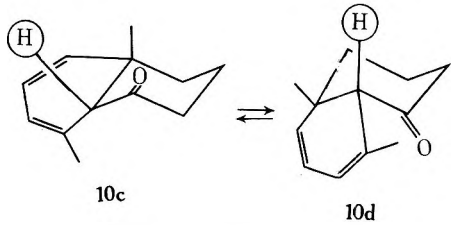
Our expectation of this reaction outcome was based on steric and stereoelectronic considerations. Accordingly, the concave geometry of dienone 10 and any intrinsic preference for axial alkylation should favor attack on the enolate 10a from the convex (top) face as shown below.[6] We were not particularly concerned about formation of the bridgehead enolate 10b and/or isomerization of ketone 10 for two reasons. In the first place, the ring fusion α-hydrogen of dienone 10 cannot assume a favorable perpendicular orientation to the β,γ double bond *and* the ketone carbonyl simultaneously (see 10c ⇆ 10d). Hence, we would not expect any enhanced kinetic acidity for this hydrogen.[7] Secondly, the *cis*-fused dienone 10 should be more stable than the corresponding trans-fused isomer or the possible conjugated enone isomers. In the trans-fused dienone, compression of the diequatorial dihedral angle by the planar butadiene bridge would introduce considerable strain to the cyclohexanone ring. Conjugation of the double bond(s), on the other hand (e.g., VIII), would force the angular methyl group into an axial orientation and would also bring the C-4 vinyl methyl and ketone oxygen into close proximity.[8]



10a 11 (R = CH_2CO_2Et)



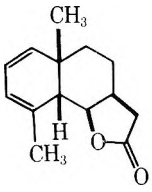
10b VII



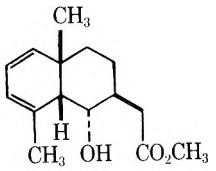
10c 10d

Concordant with the foregoing analysis, we found that treatment of dienone 10 with potassium *tert*-butoxide in *tert*-butyl alcohol gave mainly unchanged dienone and a small amount of conjugated ketone(s).

Attempts at selective reduction of the ketonic carbonyl of keto ester 11 using borohydride reagents met with limited success. Product mixtures consisting of cis lactone 21 and, presumably, hydroxy ester 22 were contaminated by difficultly separable by-products. While these appeared to arise from ester reduction, positive identification could not be made. Reductions with lithium aluminum hydride, on the other hand, gave only the two easily separable diols 12 and 13. At −96 °C the desired trans isomer 12 predominated, whereas at 0 °C the cis isomer 13 was slightly favored. Oxidation of diol 12 with silver carbonate on Celite yielded the trans lactone 14.[9]



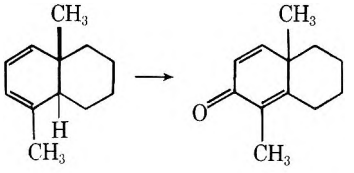
21



22

Molecular models indicate that lactone 14 should undergo enolate methylation from the convex face, leading to the thermodynamically less stable epimer 15. In fact, treatment of lactone 14 with 1 equiv of lithium diisopropylamide followed by methyl iodide gave a single product (15) subsequently converted through sensitized photochemical oxygenation to β-santonin (17).[10] Epimerization of lactone 15 with lithium diisopropylamide afforded a new lactone (16) which was similarly oxidized to α-santonin (18). In each case, a significant amount of endoperoxide (19, isolated; 20, presumed) was produced. Changes in solvent and sensitizer did not markedly influence the ratio of the two product types.[10]

Interestingly, oxygenation of the trans-fused diene 23 affords the cyclohexadienone product 24 in high yield.[11] Evidently, the ring fusion hydrogen possesses the ideal geometric orientation for abstraction in this case. We had hoped that the trans-fused lactone would constrain the cis-fused dienes 15 and 16 into a similar conformational arrangement. However, the alignment would appear less favorable here, judging from the lowered efficiency of the ene vs. 4 + 2 addition process. As expected, the cis-fused diene lactone 21 gave only the endoperoxide product upon sensitized oxygenation. Here the ring fusion hydrogen is nearly coplanar with the diene system and ene participation is thereby rendered unfavorable. Thus, the *trans*-fused lactone of dienes 15 and 16 exerts some conformational control in the desired sense, but the degree falls short of expectation.



23 24

Experimental Section[12]

1-Carboxy-1,3-dimethylcyclohexa-2,5-diene (2). A solution of 50.0 g (0.368 mol) of *m*-toluic acid in 1.5 L of ammonia and 100 mL of tetrahydrofuran was treated with lithium wire until the blue color persisted. When lithium addition was complete the reaction was stirred for 15 min and then 33.0 mL (0.525 mol) of methyl iodide was added. At this point, the mixture underwent a color change from red to white. Stirring was continued for 15 min and then ammonium chloride was added to quench the reaction. Evaporation of ammonia, acidification with concentrated hydrochloric acid, and isolation with ether afforded 57.0 g (101%) of the dienic acid 2 as a viscous oil: IR (film) 1705, 1260, 1115, 930, 735 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.72 (br s, vinyl H, 2 H), 5.46 (m, vinyl H, 1 H), 2.51 (br s, allylic CH_2–), 1.72 (s, vinyl CH_3), 1.29 (s, quaternary CH_3) ppm.

1-Hydroxymethyl-1,3-dimethylcyclohexa-2,5-diene (3). To a slurry of 28.0 g (0.736 mol) of lithium tetrahydridoaluminate in 1.0 L of ether at 0 °C was slowly added a solution of 48.0 g (0.318 mol) of the dienic acid 2 in 400 mL of ether. The reaction was allowed to stir for an additional hour after the addition was complete. After the successive addition of 28.0 mL of water, 56.0 mL of 10% sodium hydroxide, and 56.0 mL of water, the precipitated salts were filtered and the solvent was removed to afford, after distillation, 36.5 g (83%) of the alcohol 3: bp 48.5 °C (0.5 Torr); IR (film) 3400, 1690, 1645, 1040,

930, 910, 835, 720 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 5.83 (half of AB q, split into t, $J_{5,6}$ = 10 Hz, $J_{4,5}$ = 3.5 Hz, vinyl H), 5.41 (half of AB q, split into q, $J_{5,6}$ = 10 Hz, J_q = 2 Hz, 1 H), 5.12 (m, vinyl H, 1 H), 3.27 (s, $-CH_2O-$), 2.56 (br s, allylic $-CH_2-$), 1.72 (d, J = 1.2 Hz, vinyl CH_3), 0.96 (s, quaternary CH_3) ppm.

1-Formyl-1,3-dimethylcyclohexa-2,5-diene (4). To a flask fitted with a low-temperature thermometer was added 600 mL of methylene chloride and 144 g (0.109 mol) of *N*-chlorosuccinimide. The slightly turbid solution was cooled to 0 °C and treated with 10.6 mL (0.145 mol) of dimethyl sulfide which resulted in the formation of a flocculent white precipitate.[3] The mixture was cooled to −25 °C and a solution of 10.0 g (0.072 mol) of the alcohol **3** in 50.0 mL of methylene chloride was slowly added to maintain the temperature below −22 °C. The mixture was stirred at −25 °C for an additional 2 h, and then 18.0 mL of triethylamine was added. The mixture was poured into water and isolated with methylene chloride to afford 9.0 g (92%) of the aldehyde **4** after distillation: bp 72 °C (17.0 Torr); IR (film) 2700, 1725, 1380, 1020, 930, 910, 825, 715 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 5.95 (half of AB q, split into t, $J_{5,6}$ = 10 Hz, $J_{4,5}$ = 3 Hz), 5.41 (half of AB q, split into q, $J_{5,6}$ = 10 Hz, J_q = 2 Hz), 5.12 (m, 1 H), 2.62 (br s, allylic CH_2-), 1.76 (s, vinyl CH_3), 1.18 (s, quaternary CH_3) ppm. The 2,4-dinitrophenylhydrazone, mp 145–146 °C, was prepared.

Anal. Calcd for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.10; N, 17.71. Found: C, 56.8; H, 5.10; N, 17.92.

Ethyl (*E*)-3-(1,3-Dimethylcyclohexa-2,5-dienyl)propenoate (5). To a slurry of 2.6 g (61.5 mmol, 51% oil dispersion) of sodium hydride in 250 mL of dimethoxyethane was slowly added 12.0 mL (61.0 mmol) of triethyl phosphonoacetate.[13] When the addition was complete, the mixture was stirred for an additional 15 min. A solution of 8.0 g (58.5 mmol) of aldehyde **4** in 50.0 mL of dimethoxyethane was then slowly added. The reaction was then brought to reflux for 1 h. Isolation with ether after addition of water afforded 11.9 g (93%) of the propenoate **5**: bp 130 °C (0.6 Torr); IR (film) 1720, 1645, 1310, 1250, 1160, 1175, 1040, 990, 935, 860, 835, 720, 705 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 6.83 (half of AB q, $J_{1,2}$ = 16 Hz, 1 H), 5.66 (half of AB q, $J_{1,2}$ = 16 Hz, 1 H), 5.76 (half of AB q, split into t, $J_{5,6}$ = 10 Hz, $J_{4,5}$ = 3 Hz, 1 H), 5.44 (half of AB q, split into m, $J_{5,6}$ = 10 Hz), 4.15 (t, J = 7.5 Hz, $-OCH_2-$), 2.50 (br s, allylic CH_2-), 1.69 (s, vinyl CH_3), 1.26 (t, J = 7.5 Hz, ethyl CH_3), 1.16 (s, quaternary CH_3) ppm.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.96; H, 8.84.

1-(3-Hydroxypropyl)-1,3-dimethylcyclohexa-2,5-diene (6). A solution of 10.9 g (50.0 mmol) of propenoate **5** in 1.0 L of ammonia, 100 mL of ether, and 150 mL of ethanol was treated with lithium wire until the blue color persisted. Ammonium chloride was then added and the ammonia was allowed to evaporate. Isolation with ether and distillation (bp 70–71 °C, 0.1 Torr) afforded 7.5 g (90.7%) of alcohol **6**: IR (film) 3350, 1690, 1645, 1060, 930, 890, 835, 720 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.65 (half of AB q, split into t, $J_{5,5}$ = 10 Hz, $J_{4,5}$ = 3 Hz), 5.32 (half of AB q, split into q, $J_{5,6}$ = 10 Hz, $J_{4,6}$ = 2 Hz), 5.05 (m, vinyl H), 3.45 (m, $-CH_2O-$), 2.48 (m, allylic $-CH_2-$), 1.18 (s, vinyl $-CH_3$), 0.98 (s, quaternary $-CH_3$) ppm.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.42; H, 10.91. Found: C, 79.69; H, 10.82.

1-(3-Bromopropyl)-1,2-dimethylcyclohexa-2,5-diene (7). To a mechanically stirred solution of 2.0 g (12.0 mmol) of alcohol **6**, 3.4 g (13.0 mmol) of triphenylphosphine, and 20.0 mL of benzene was slowly added 2.22 g (12.5 mmol) of *N*-bromosuccinimide (exothermic).[14] When the addition was complete, stirring was continued for 15 min, 100 mL of hexane was added to precipitate succinimide and triphenylphosphine oxide, and the mixture was filtered. Removal of solvent and distillation (bp 105 °C, 0.15 Torr) afforded 2.52 g (91.5%) of the bromide **7**: IR (film) 1275, 1240, 1210, 1090, 1015, 925, 740, 720, 690 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.65 (half of AB q, split into t, $J_{5,6}$ = 10 Hz, $J_{4,5}$ = 3 Hz), 5.20 (half of AB q, split into q, $J_{5,6}$ = 10 Hz, J_q = 2 Hz), 5.05 (m, vinyl H), 3.25 (t, J = 7 Hz, $-CH_2Br$), 2.48 (m, allylic $-CH_2-$), 1.69 (s, vinyl $-CH_3$), 0.98 (s, quaternary CH_3) ppm.

1-(4-Ethylthio-4-ethylsulfinylbutyl)-1,3-dimethylcyclohexa-2,5-diene (8). A solution of 4.70 g (31.3 mmol) of ethylthioethylsulfinylmethane in 40.0 mL of dimethoxyethane at 0 °C was treated with 13.8 mL of 2.29 M *n*-butyllithium in hexane.[4] After the reaction had stirred for 30 min, 7.0 g (31.3 mmol) of the bromide was added. The ice bath was removed and the solution was stirred overnight at room temperature. Isolation with ether afforded 8.67 g (97.7%) of a viscous yellow oil as a mixture of two diastereomers as evidenced by LC and GC. This material was used without further purification since it could not be distilled: IR (film) 1830, 1260, 1050, 1015, 965, 925, 835, 720 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.70 (H-5, d of t, $J_{5,6}$ = 10 Hz, $J_{4,5}$ = 3 Hz), 5.35 (H-6, br d, $J_{5,6}$ = 10 Hz), 5.10 (H-2, br s), 1.69 (vinyl CH_3), 0.99 (angular CH_3) ppm.

1β-Hydroxy-4aβ,8-dimethyl-1,2,3,4,4a,8aβ-hexahydronaphthalene (9). Perchloric acid was added to a solution of 8.67 g (28.8 mmol) of the sulfoxide **8** in 125 mL of ethyl acetate at room temperature. After stirring for 30 min, the mixture was poured into sodium bicarbonate solution and isolated with ether to afford 3.87 g (76.5%) of the alcohol **9** after short-path distillation (bp 100 °C, 0.1 Torr). An analytical sample, mp 66–68 °C, was secured by recrystallization from hexane: IR (film) 3355, 1650, 1590, 1365, 1060, 1050, 1015, 935, 885, 720 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.70 (H-5, H-6, m), 5.26 (H-7, d, J = 9.7 Hz), 3.56 (H-1, d of t, J = 10.5, 3.0 Hz), 1.99 (vinyl CH_3, br s), 0.88 (angular CH_3) ppm.

4aβ,8-Dimethyl-3,4,4a,8aβ-tetrahydro-1(2*H*)-naphthalenone (10). To a flask fitted with a low-temperature thermometer and nitrogen inlet was added 200 mL of dichloromethane and 6.30 g (47.3 mmol) of *N*-chlorosuccinimide. The solution was cooled to 0 °C and treated with 4.63 mL (63.0 mmol) of dimethyl sulfide which resulted in the formation of a flocculent white precipitate.[3] The mixture was cooled to −25 °C, and a solution of 5.30 g (31.5 mmol) of the alcohol **9** in 20 mL of dichloromethane was slowly added to maintain the temperature below −20 °C. The mixture was stirred an additional 2.0 h, and then 5.0 mL of triethylamine was added. After stirring an additional 5 min, the mixture was poured into water and extracted with chloroform. This material consisted of a mixture of succinimide and the desired ketone. The succinimide was conveniently removed by filtration through 15 g of silica gel with 5% ethyl acetate–hexane. Removal of the solvent gave 5.22 g (94%) of the ketone **10** which readily crystallized. An analytical sample, mp 61–62 °C, was secured by recrystallization from methanol–water: IR (film) 1705, 1640, 1595, 1340, 1305, 1150, 1070, 1005, 930, 890, 860, 800, 720 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.81 (H-4 and H-5, m), 5.27 (br d, H-6, J = 9.7 Hz), 2.49 (H-8a, s), 1.82 (vinyl CH_3), 1.06 (angular CH_3) ppm.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.94; H, 9.09.

Ethyl 4aβ,8-Dimethyl-3,4,4a,8aβ-tetrahydro-1(2*H*)-naphthalenon-2β-ylacetate (11). To a solution of 0.24 mL (1.20 mmol) of diisopropylamine in 4.0 mL of tetrahydrofuran at −78 °C was added a solution of 0.60 mL (1.20 mmol) of 2.0 M *n*-butyllithium in hexane. The reaction mixture was stirred for 20 min at −78 °C, at which time 200 mg (1.13 mmol) of ketone **10** in 1 mL of tetrahydrofuran and 1.0 mL of hexamethylphosphoroustriamide was added. Stirring at −78 °C was continued for an additional 20 min, and then 0.15 mL (1.36 mmol) of ethyl iodoacetate was added. After 30 min at −78 °C, the reaction mixture was poured into 5% hydrochloric acid, and the product was extracted with ether to afford 218 mg (74%) of keto ester **11** after preparative layer chromatography with 25% ethyl acetate–hexane. An analytical sample, mp 54–55 °C, was secured by recrystallization from hexane: IR (KBr) 1740, 1710, 1650, 1590, 1350, 1300, 1260, 1220, 1160, 1140, 1030, 910, 855, 790, 730 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.70 (H-5, H-6, m), 5.35 (H-7, m), 4.05 ($-CH_2O-$, q, J = 7 Hz), 1.75 (vinyl CH_3, br s), 1.21 (CH_3CH_2-, t, J = 7 Hz), 1.01 (angular CH_3) ppm.

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.41; H, 8.54.

2-(1-Hydroxy-4aβ,8-dimethyl-1,2,3,4,4a,8aβ-hexahydronaphthalen-2β-yl)ethanol (12, 13). A solution of 200 mg (0.71 mmol) of the keto ester **11** in 15 mL of anhydrous ether at 0 °C was treated with 68 mg (1.8 mmol) of lithium aluminum hydride and stirred at 0 °C for 1.5 h. The addition of 0.35 mL of water resulted in the precipitation of aluminum salts which were filtered. Removal of solvent afforded 158 mg of the diol mixture. This mixture (1:1) was separated into its two components by preparative liquid chromatrography on a Porasil column with 50% ethyl acetate–hexane.

cis-Diol **13**, mp 113–114 °C, from hexane: IR (film) 3350, 1640, 1590, 1195, 1135, 1080, 1030, 1020, 910, 875, 850, 800, 720 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.80 (H-5, H-6, m), 5.22 (H-7, d, J = 7 Hz), 3.70 (>CHO–, $-CH_2O-$, m), 1.95 (vinyl CH_3), 0.90 (angular CH_3) ppm.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63 H, 9.97. Found: C, 75.81; H, 10.18.

trans-Diol **12**, mp 57–58 °C, from hexane: IR (CCl_4) 3400, 1640, 1590, 1205, 1180, 1130, 1100, 1025, 1000, 985, 935, 880, 840, 815, 700 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.80 (H-5, H-6, m), 5.43 (H-7, d, J = 7 Hz), 3.69 ($-CH_2O$, >CHO–, m), 1.84 (vinyl CH_3, br s), 0.94 (angular CH_3) ppm.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.72; H, 10.19.

2-(1α-Hydroxy-4aβ,8-dimethyl-1,2,3,4,4a,8aβ-hexahydronaphth-2β-yl)acetic Acid Lactone (14). To a flask fitted with a Dean–Stark trap, condenser, and mechanical stirrer was added 620 mg (2.78 mmol) of trans diol **12**, 40 g (0.51 g/mmol) of silver carbonate on Celite, and 250 mL of benzene.[9] The mixture was heated to reflux

for 8 h, cooled, and filtered. Removal of solvent and purification by preparative layer chromatography with 10% ethyl acetate–hexane gave 318 mg (52.5%) of the trans lactone **14**. An analytical sample, mp 90–91 °C, was secured by recrystallization from hexane: IR (film) 1785, 1650, 1590, 1385, 1300, 1220, 1200, 1185, 1135, 1050, 1020, 1000, 980, 905, 875, 810, 740 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.67 (H-5, H-6, m), 5.18 (H-7, m), 4.21 (H-1, m), 1.86 (vinyl CH_3), 1.20 (angular CH_3) ppm.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.07; H, 8.37.

2β-Methyl-2-(1α-hydroxy-4aβ,8-dimethyl-1,2,3,4,4a,8aβ-hexahydronaphth-2β-yl)acetic Acid Lactone (15). To a solution of 0.069 mL (0.45 mmol) of diisopropylamine in 3 mL of tetrahydrofuran at −78 °C was added a solution of 0.18 mL (0.40 mmol) of 2.29 M *n*-butyllithium in hexane and 0.05 mL of HMPA. The reaction mixture was stirred at −78 °C for 20 min at which time 68 mg (0.40 mmol) of the lactone in 1.0 mL of tetrahydrofuran was introduced. The reaction was stirred at −78 °C for 45 min and a 0.1-mL portion of methyl iodide was added. Stirring was continued for 1 h. The mixture was poured into water and extracted with ether to afford 90 mg (97%) of the methylated lactone **15**, which crystallized upon cooling. An analytical sample, mp 96–97 °C, was secured by recrystallization from hexane: IR ($CHCl_3$) 1780, 1650, 1590, 1195, 1175, 1140, 1110, 1010, 980 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.70 (H-5, H-6, m), 5.30 (H-7, m), 4.43 (H-1, d of d, $J_{1,8a}$ = 11.5 Hz, $J_{1,2}$ = 5 Hz), 1.85 (vinyl CH_3) 1.20 (angular CH_3), 1.11 (lactone CH_3, d, J = 7 Hz) ppm.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.64; H, 8.61.

2α-Methyl-2-(1α-hydroxy-4aβ,8-dimethyl-1,2,3,4,4a,8aβ-hexahydronaphth-2β-yl)acetic Acid Lactone (16). A solution of 0.084 mL (0.60 mmol) of diisopropylamine in 4.0 mL of tetrahydrofuran at −78 °C was treated with 0.30 mL of 2.0 M *n*-butyllithium in hexane solution. Stirring at −78 °C was continued for 20 min, at which time 120 mg (0.517 mmol) of the trans lactone **15** was added with the aid of 1.0 mL of tetrahydrofuran. After 30 min at −78 °C, the mixture was poured into water and the product was extracted with ether to give 120 mg (100%) of material which was recrystallized from hexane to give 100 mg of lactone **16**: mp 78–79 °C; IR (CCl_4) 1785, 1590, 1240, 1170, 1140, 1125, 1015, 950 cm^{-1}; NMR δ_{Me_4Si} 5.75 (H-5, H-6, m), 5.30 (H-7, m), 4.25 (H-1, d of d, $J_{1,8a}$ = 10 Hz, $J_{1,2}$ = 5 Hz), 1.85 (vinyl CH_3, br s), 1.20 (angular CH_3), 1.18 (lactone CH_3, d, $J \approx 6$ Hz) ppm.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.34; H, 8.80.

(±)-β-Santonin (17). A solution of 150 mg (0.65 mmol) of the lactone **15** in 200 mL of pyridine and a small amount of hematoporphorin was irradiated with a 150-W flood lamp for 12 h while oxygen was slowly bubbled through the solution.[10] The mixture was kept cool with running water. Removal of solvent and filtration through 15 g of alumina with ether gave 84 mg of the endoperoxide **19** as a crystalline solid, mp 190–191 °C, and 29 mg (19%) of β-santonin (**17**), mp 184–185 °C (lit. mp 186 °C),[15] purified by preparative layer chromatography on silica gel using 50% ethyl acetate–hexane. The NMR spectrum was identical to a published spectrum.[16]

Endoperoxide 19: IR (film) 1770, 1375, 1230, 1215, 1180, 1100, 1005, 980, 945, 925, 850 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 6.70 (H-6, d of d, $J_{6,7}$ = 10 Hz, $J_{5,6}$ = 4 Hz), 6.34 (H-7, d of d, $J_{6,7}$ = 10 Hz, $J_{1,2}$ = 5 Hz), 4.12 (H-5, d of d, $J_{5,6}$ = 4 Hz, $J_{5,7}$ = 1 Hz), 1.39 (CH_3), 1.42 (CH_3), 1.12 (lactone CH_3, d, J = 5 Hz) ppm.

Anal. Calcd for $C_{15}H_{19}O_4$: C, 68.42; H, 7.65. Found: C, 68.15; H, 7.79.

(±)-α-Santonin (18). A solution of 200 mg (0.86 mmol) of the α-methyl lactone **16** and a small amount of methylene blue in 150 mL of pyridine was irradiated with a 150-W flood lamp while oxygen was slowly bubbled through the solution overnight. Removal of solvent, filtration through 15 g of alumina with ether, and preparative layer chromatography with 50% ethyl acetate–hexane gave 60 mg of α-santonin (**18**) which was spectroscopically identical with an authentic sample, mp 180–181 °C (lit. mp 181 °C).[15]

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Registry No.—**1**, 99-04-7; **2**, 64872-57-7; **3**, 64872-58-8; **4**, 64872-59-9; **4** DNP, 64872-60-2; **5**, 64872-61-3; **6**, 64872-62-4; **7**, 64872-63-5; **8**, 64081-54-5; **9**, 64912-44-3; **10**, 648-72-50-0; **11**, 64872-51-1; **12**, 64872-53-3; **13**, 64872-52-2; **14**, 64872-54-4; **15**, 64912-45-4; **16**, 64912-46-5; **17**, 64912-47-6; **18**, 64912-48-7; **19**, 64872-55-5; methyl iodide, 74-88-4; triethyl phosphonoacetate, 867-13-0; *N*-bromosuccinimide, 128-08-5; ethylthiolthylsulfinylmethane, 37032-97-8; ethyl iodoacetate, 623-48-3.

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(12) The apparatus described by W. S. Johnson and W. P. Schneider ("Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 132) was used to maintain an argon atmosphere. The isolation procedure consisted of thorough extractions with the specified solvent, washing the combined extracts with water and saturated brine solution, and drying the extracts over anhydrous sodium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Nuclear magnetic resonance spectra were recorded with Varian CFT-20 or Perkin-Elmer R20B spectrometers. Signals are reported as the chemical shift downfield from tetramethylsilane (Me_4Si) in parts per million of the applied field. Coupling constants are reported in hertz. Melting points were determined on a calibrated Thomas capillary melting point apparatus. Melting points are not corrected.
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New Approaches to the Synthesis of 3-Deoxy-3-fluoro-D-glucose[1]

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The diisopropylidene hexose derivatives 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) and 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**4**) react with diethylaminosulfur trifluoride (DAST) to give stable but labile intermediates which can undergo further nucleophilic attack at sulfur rather than fluorination. Distillation of the reaction mixtures of **1** and DAST gives 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*gluco*-hex-3-enofuranose (**3**), while **5** and DAST gave 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**). The formation of **6** is shown to be an S_N2 displacement by labeling experiments with the radioisotope ^{18}F. In a rapid and simple reaction, **6** can also be prepared from the trifluoromethanesulfonate of **5** and cesium fluoride.

There is considerable interest in the fluorinated sugars as probes for the normal and abnormal metabolism of glucose and other carbohydrates.[2,3] 3-Deoxy-3-fluoro-D-glucose (**7**) appears an attractive compound, as in experimental animals it is phosphorylated, transported across cell membranes, and enters the metabolic cycle in a similar fashion to glucose[3] but does not complete the cycle.[4] However, present synthetic reactions[5] are somewhat lengthy, and our interest in ^{18}F ($t_{1/2}$ = 110 min)[6] labeled compounds made a faster procedure necessary.

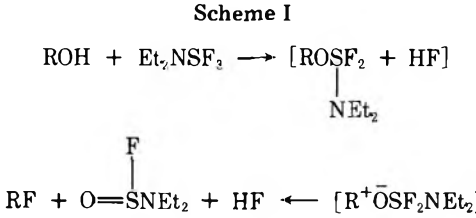
Diethylaminosulfur trifluoride (DAST) has recently been introduced as a mild and rapid reagent for effecting the F for –OH conversion with retention of configuration at the reaction center[7] (Scheme I) and has been used for the synthesis of 6-deoxy-6-fluorohexoses.[8] The reaction between DAST and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[9] (**1**) appeared a simple, rapid route for the synthesis of **7**.

Results and Discussion

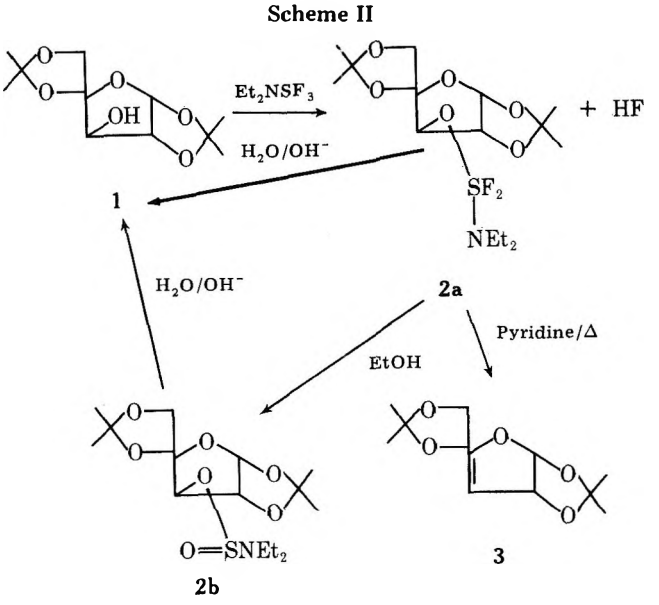
When **1** was reacted with DAST under conventional conditions (CH_2Cl_2 solution, 0 °C, aqueous workup)[7] the starting material was isolated in excellent yield, but with the introduction of 2 equiv of pyridine followed by direct distillation of the reaction mixture (80 °C, 0.05 mmHg) the olefin[10] **3** was isolated in 75% yield. Control experiments with **1** in the absence of DAST established that it did not eliminate under these conditions, so establishing that an intermediate was being formed but not undergoing spontaneous decomposition to give the fluorinated product. Attempts to isolate this intermediate failed, either the starting material **1** or the olefin **3** being the only isolated products, but the ^{19}F NMR spectrum of an equimolar mixture of DAST and **1** in methylene chloride showed no signal at −40 ppm for DAST[11] but a poorly resolved five-line signal at −59 ppm (J = 2 Hz), suggesting long-range coupling in an intermediate such as **2a**.

Treatment of this intermediate with ethanol gave a major product and a minor product on GC, but once again attempts at isolation led only to starting material **1**. The GC/MS of the major product gave a highest mass ion at 306, with $M^+ + 2$ 5% of M^+, characteristic of sulfur-containing compounds and is probably due to the loss of Et_2NH from **2b**. Therefore, the most likely course of reaction is as shown in Scheme II, and in the intermediate a second nucleophilic displacement is more favored at sulfur than at carbon.[12]

Scheme I



Scheme II



This is compatible with the observations that **1** does not give the 3-chloro compound on treatment with phosphorus pentachloride but rearrangement products[13] and that the tosylate of **1** only gives simple nucleophilic displacement reactions with "soft" nucleophiles in dipolar aprotic solvents[14-16] and does give elimination products.[10]

Nucleophilic displacement on 1,2:5,6-di-*O*-isopropylidene-3-tosyl-α-D-allofuranose is a reasonably facile process, giving the product with inversion of configuration at the 3 position.[5] Therefore, the reaction between 1,2:5,6-*O*-isopropylidene-α-D-allofuranose[9] (**4**) and DAST was performed to determine whether the intermediate, if formed, could undergo nucleophilic displacement to give the 3-fluorogluco derivative **6**. With an aqueous workup the only product was the starting material, but on direct distillation of the reaction mixture (0.05 mmHg, 60 °C) 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**)[5] was isolated in 90% yield.

The intermediates in the allose series were more labile than with the glucose compounds, but the ^{19}F NMR spectrum showed a poorly resolved multiplet at −58 ppm with more complex coupling than was shown in the glucose compound, suggesting an intermediate **5**.[10] The products from the addition of ethanol were not observed in this case. If the intermediate **5** is added to a solution of $H^{18}F$[17] in pyridine and heated to 150 °C, the product **6** is isolated, incorporating the ^{18}F activity. This provides additional evidence that there is a discrete S_N2 displacement rather than an ion pair or cyclic transition state (Scheme III).

As the DAST is apparently reacting to give a very good leaving group which is then rapidly displaced by fluoride ion,

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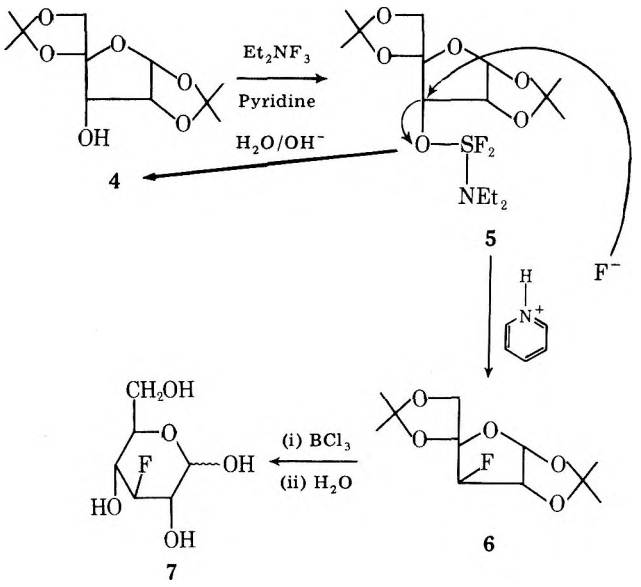
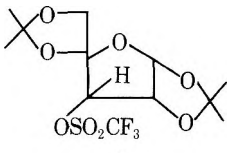
Scheme III



the alternative of a very good leaving group and an external source of fluoride ion appeared attractive.

The trifluoromethane sulfonate of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (8)[18] was refluxed with a 10% excess of cesium fluoride in DMF for 25 min and after workup and evaporation of the solvent gave **6** as a chromatographically pure liquid in 95% yield. Distillation (0.05 mmHg, 50 °C) reduced the yield somewhat, depending on the scale of the reaction. No precautions were taken to exclude air and water, with the exception of using freshly distilled DMF. In order to remove the protecting groups and convert **6** to **7**, **6** was dissolved in methylene chloride and treated with an excess of boron trichloride[17] for 2 min, followed by an aqueous workup. This gave a syrup that was chromatographically identical both quantitatively and qualitatively with **7** obtained from the sulfuric acid hydrolysis, but neither sample has yet been induced to crystallize.[5] However, on forming the tetraacetate,[5] the sample from the boron trichloride hydrolysis was considerably harder to crystallize than that from the sulfuric acid procedure, and finally had to be seeded to obtain clean, sharp, melting crystals. Thus, it could represent a different anomeric mixture.



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These experiments establish that in these compounds DAST reacts with the alcohols to give intermediates rather than transition states, which can have reaction pathways other than simple fluorination. The isolation of both the allo and gluco isomers, unchanged from the aqueous hydrolysis of their reactions with DAST, establishes that solvolysis is occurring at sulfur rather than at carbon. The experiments with $H^{18}F$ make it very probable that a S_N2 displacement is involved, as the alternative reaction of fluoride exchange at sulfur followed by a cyclic transition state or tight ion pair carbenium ion[7] would give a maximum incorporation of 50% of the ^{18}F activity rather than the 90% observed. The difference in reaction between the two isomeric furanose derivatives could be ascribed either to the difference in stability of the two olefins that would be formed by transdiaxial elimination (i.e., the $\Delta^{2,3}$ isomer is a more strained structure than the $\Delta^{3,4}$ isomer **3**) or to the steric effects of the 1,2-isopropylidene ring blocking the approach of the nucleophile to the α face of the ring. Of the two reactions to give **6** the second is less hazardous and more convenient than the first, especially if **6** is hydrolyzed directly without distillation, which is a necessary step in the first reaction. However, the reagents in the second reaction are much more expensive and so may be less suitable for a large-scale synthesis.

Experimental Section

NMR spectra were recorded on a T-60 NMR spectrometer at 60 and 56.4 MHz with Me_4Si and $CFCl_3$ as internal standards. IR spectra were recorded on a Perkin-Elmer 297 spectrometer as liquid films or in $CHCl_3$ solutions. Melting points are uncorrected.

Reactions of DAST with 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (1). (a) DAST (0.9 g, 5.5 mmol) in methylene chloride (20 mL) was cooled to 0 °C under nitrogen, and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) (1.3 g, 5 mmol) in methylene chloride (20 mL) and pyridine (2 mL) was slowly added. The solution was stirred for 30 min, warmed to room temperature, and after removal of the volatile components distilled at 80 °C (0.05 mmHg) to give 1 g of brown oil homogeneous on TLC. Chromatography on silica gel and elution with methylene chloride, followed by crystallization from petroleum ether (40–60 °C), gave 0.75 g of 1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-*gluco*-hex-3-enefuranose (**3**): [mp 50–52 °C (lit. mp 50 °C);[10] IR 1670 cm^{-1} (m, unsaturated ether); NMR δ 6.35 (1 proton doublet J = 5 Hz, H-1), 5.5 (1 proton singlet overlapping 1 proton doublet, H-3, H-2), 4.9 (2 proton triplet, J = 6 Hz, H-5), 4.30 (1 proton multiplet H-6), 1.7 (12 proton singlet methyl groups).

(b) DAST (0.9 g) and **1** (1.3 g) were reacted together as above and then treated with ethanol (2 mL). GC analysis showed a major (~90%) and a minor (~10%) peak, and the GC/MS showed a high mass for the major peak of 306 (with 308 being 5% of 306) assigned to **4b**, while the minor peak showed a high mass of 323 (325 is 5% of 323) and is as yet unidentified. On attempted aqueous workup of these solutions, starting material was isolated (1.2 g, 90% recovery).

Preparation of 3-Deoxy-3-fluoro-1,2:5,6-di-*O*-propylidene-α-D-glucofuranose (6). (a) DAST (3.5 g, 22 mmol) was dissolved in methylene chloride (50 mL) and pyridine (5 mL), and the solution was cooled to 0 °C under nitrogen. **4** (5.2 g, 20 mmol) was added slowly and the solution warmed to room temperature. The solvent was removed under vacuum and the residue distilled at 60 °C (0.05 mmHg) to give 5.1 g of **6** as a light yellow oil that was ~90% pure by GC. A second distillation gave 3.2 g of 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**) as a pure colorless liquid: ^1H NMR[18] δ 6.0 (1 proton doublet, J = 3 Hz, H-1), 5.1 (1 proton double doublet, J = 48, 1 Hz, H-3), 4.6 (1 proton double doublet, J = 20, 3 Hz, H-4), 4.6–4.0 (unresolved 5 proton multiplet, H-2, H-5, and H-6), 1.5 (four 3 proton singlets, methyl groups); ^{19}F NMR +208 ppm (double double doublet, above $CFCl_3$, J = 48, 28, and 10 Hz).

(b) The reaction was repeated as above except that before distillation a solution containing 1.1 mCi of $H^{18}F$ in 0.5 mL of pyridine was added. GC analysis of the product showed that >90% of the ^{18}F activity was incorporated into **6**.

Preparation of 1,2:5,6-di-*O*-Isopropylidene-3-*O*-trifluoromethanesulfonyl-α-D-allofuranose (8).[18] **4** (5.2 g, 20 mmol) was dissolved in methylene chloride (300 mL) and pyridine (10 mL) and cooled to −15 °C under nitrogen. Trifluoromethanesulfonic anhydride (3.8 mL, 23 mmol) in methylene chloride (20 mL) was slowly added and allowed to react for 90 min. The solution was washed with saturated bicarbonate and the solvents were removed under vacuum. Crystallization from petroleum ether (40–60 °C) gave 6.9 g (88%) of 1,2:5,6-di-*O*-isopropylidene-3-*O*-trifluoromethanesulfonyl-α-D-allofuranose (**8**) as colorless needles, mp 46–47 °C (lit. mp 40 °C).[18]

Preparation of 3-Deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (6). **8** (0.79 g, 2 mmol) was dissolved in DMF (25 mL) (distilled from CaH_2), and cesium fluoride (0.34 g, 2.2 mmol) was added. The solution was refluxed for 25 min, poured into water (200 mL), and extracted (3 × 100 mL) with methylene chloride. Evaporation of the solvent gave 0.51 g of a pale yellow, chromatographically pure oil **6**. Distillation (60 °C, 0.05 mmHg) gave 0.37 g (71%) of pure 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **6**.

Preparation of 3-Deoxy-3-fluoro-D-glucose (7) and Its Tetraacetate (5). **6** (1.4 g, 4 mmol) was dissolved in methylene chloride (20 mL), and boron trichloride (10 mL of a 1 M solution in methylene chloride) was added. The solution was stirred for 2 min at room temperature, water was added, and the methylene chloride was removed under vacuum. The solution was neutralized with AG501-X8

ion-exchange resin and the water removed under vacuum to give 0.8 g of a syrup identical on a Waters carbohydrate column to that obtained from the sulfuric acid catalyzed hydrolysis of **6**.

This syrup (0.36 g) was dissolved in acetic anhydride (7 mL) with sodium acetate (0.6 g) and boiled for 10 min. Workup and crystallization (petroleum ether 60–80 °C) gave 0.2 g of 1,2,4,6-tetra-*O*-acetyl-3-deoxy-3-fluoro-α-D-glucose: mp 116–120 °C (lit. mp 119–120 °C).[5]

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Antineoplastic Agents. 55. Isolation and Structure of Multigilin and Multistatin[1]

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Two new cytotoxic and antineoplastic pseudoguaianolides designated multigilin (**2b**) and multistatin (**2d**) have been isolated from *Baileya multiradiata* Harv. and Gray. The related sesquiterpene lactone fastigilin A (**1c**) was also found to be a constituent of this plant. With the x-ray crystal structure of radiatin (**1a**) serving as a valuable reference, complete structural and stereochemical assignments were made for fastigilin A (**1c**), multigilin (**2b**), and multistatin (**2d**). Interpretation of the ^{13}C nuclear magnetic resonance spectra provided a firm basis for these assignments and allowed further confirmation of structures previously proposed for fastigilin B (**1b**), fastigilin C (**2a**), and multiradiatin (**2c**).

A detailed investigation of *Baileya multiradiata* Harv. and Gray (Compositae) cytotoxic and antineoplastic constituents begun in 1966 led to the isolation of six sesquiterpene lactones displaying such physiological activity.[2] Of these growth inhibitory substances radiatin (**1a**), fastigilin B (**1b**), fastigilin C (**2a**), and multiradiatin (**2c**) appeared most promising. Until 1973, requirements for these compounds were met through re-collections of the plant made in June within a 40-mile radius in Mohave County, Arizona. In April 1975 when it became necessary to increase supplies of radiatin and fastigilin C for further biological evaluation, re-collection of the plant was made at lower elevations some 100–150 miles south of previous collections. Sesquiterpene fractions from these specimens of *Baileya multiradiata* expected to contain primarily radiatin were found instead to be largely fastigilin B (**1b**) and fastigilin A[3,4] (**1c**), and those fractions presumed to contain fastigilin C and multiradiatin were found to also contain two new pseudoguaianolides that we have designated multigilin (**2b**) and multistatin (**2d**). The terpene assumed to be fastigilin A (**1c**) was confirmed by comparison with authentic fastigilin A provided by Professor W. Herz. A summary of the compelling spectral evidence supporting structural assignments for sesquiterpene lactones **1c**, **2b**, and **2d** and further confirmation for the structures previously assigned to fastigilin B[2,4] (**1b**), fastigilin C[3,4] (**2a**), and multiradiatin[2] (**2c**) now follow.

On casual inspection fastigilin A, multigilin, and multistatin could readily be mistaken for the isomeric and known constituents of *Baileya multiradiata* lactones **1b**, **2a**, and **2c**. The mass spectra by electron impact and thin-layer chromatographic behavior were indistinguishable from the known constituents. However, inspection of the ^1H NMR spectra revealed that the ester side chain methyl group resonances were shifted from the expected δ 1.80 and 2.12 (typical of a senecioate ester[4]) to δ 1.72 and 1.82, respectively (typical of an angelate). Eventually this observation served as a useful qualitative method for distinguishing between mixtures of multigilin with fastigilin C and fastigilin A with fastigilin B and the pure substances. Indeed certain compositions of multigilin with fastigilin C behaved in other respects as a pure substance and resisted all attempts at complete separation. A further challenge was presented by the quantities available, with fastigilin A and multigilin obtainable in approximately 0.002% yield while multistatin was isolated in only trace amounts. Both the ^1H NMR and infrared spectra of multigilin and multistatin suggested that they bore the same relationship

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Table I. ^{13}C NMR Spectra of *Baileya multiradiata* Components

	Radiatin (1a)	Fastigilin A (1c)	Fastigilin B (1b)	Fastigilin C (2a)	Multigilin[c] (2b)	Multiradiatin (2c)	Multistatin (2d)
C-1[a]	49.48	49.71	49.32	49.71	50.10	51.56	51.40
C-2	161.67	161.51	161.51	161.60	161.86	159.07	158.91
C-3	130.01	129.97	130.01	129.88	129.81	132.38	132.41
C-4	209.00	209.17	209.17	208.65	208.87	207.61	207.54
C-5	54.52	54.49	54.36	55.33	55.43	55.43	55.56
C-6	72.17	71.55	70.61	77.00[b]	79.19	70.06	71.07
C-7[a]	47.04	47.17	47.24	45.71	45.68	46.52	46.85
C-8	84.72	84.78	84.82	83.45	83.39	78.32	78.22
C-9	78.06	77.96	77.93	77.83	77.70	205.59	205.43
C-10	32.83	32.74	32.80	33.06	33.00	44.67	44.63
C-11	40.54	40.47	40.51	137.71	137.55	132.61	132.41
C-12	177.96	178.15	178.09	169.02	169.31	167.94	167.81
C-13	10.79	10.79	10.83	126.27	126.23	121.68	121.88
C-14	15.80	15.70	15.73	15.86	15.90	16.35	16.42
C-15	17.30	17.30	17.36	18.21	18.11	17.88	17.85
C-1′	166.03	166.32	165.02	165.15	166.51	164.66	165.90
C-2′	136.02	127.27	115.34	115.31	127.14	114.69	126.72
C-3′	126.20	139.34	158.48	159.13	139.95	160.17	140.77
C-2′-Me	18.14	20.38[a]			20.45[a]		20.25[a]
C-3′-Me		15.70[a]	20.35	30.45	15.90[a]	20.48	15.83[a]
C-3′-Me			27.34	27.47		27.54	

[a] Assignments for C-2′ methyl groups and C-3′ methyl groups may be reversed. In addition C-1 and C-7 values may be reversed in each example except for fastigilin C (see text). [b] This value is approximate, since the resonance is obscured by a $CDCl_3$ resonance. [c] This spectrum was obtained from a solution of **2b** contaminated with **2a**. Some resonances of these two substances overlapped.

as fastigilin C and multiradiatin. Confirmation of this assumption was obtained by chromium trioxide oxidation of alcohol **2b** to ketone **2d** and this interconversion was employed to obtain larger quantities of multistatin.

After uncovering the preceding relationships a ^{13}C NMR study was undertaken to confirm the skeletal assignments and where feasible the stereochemical relationships among this group of pseudoguaianolides. Completion[5] of an x-ray crystal structure analysis of radiatin (**1a**) provided a valuable benchmark structure for comparison purposes. Most probable ^{13}C NMR assignments for radiatin (**1a**) and the six related sesquiterpene lactones are given in Table I. Carbon atoms C-2, C-3, C-4, C-5, C-12, C-1′, and C-2′ of radiatin were assigned on the basis of shifts observed with model compounds[6,7] and off-resonance decoupling experiments. The same means and the downfield shift seen upon introduction of a double bond were used to assign C-11. In addition to chemical shift and off-resonance decoupling experiments, single-frequency proton decoupling was used to assign C-6, C-8, C-9, C-10, C-13, C-14, C-15, C-3′, and the C-2′ methyl group. The ^1H NMR frequencies corresponding to the hydrogens attached to each of these carbons were obtained from assignments recorded by Yoshitake and Geissman.[8] The only uncertainty resides with the assignments for C-1 and C-7, since these notations are based on single-frequency proton-decoupling experiments carried out with fastigilin C (see below) and may be reversed for radiatin.

With the ^{13}C NMR resonance assignments for radiatin in hand, interpretation of the corresponding spectra of fastigilin A (**1c**) and fastigilin B (**1b**) was readily achieved and this allowed the first complete structural proposal for fastigilin A[4] and removed any uncertainties in the fastigilin B stereochemistry.[2] With fastigilin A the only resonances which differed appreciably from those of radiatin were those at C-6 bearing the ester linkage and the ester side chain. The side-chain resonances were characteristic of a substituted acrylic acid ester bearing methyl groups on both the α and β carbons, rather than the methacrylic ester system of radiatin. Since the C-2′ and C-3′ methyl resonances were further downfield than expected for a tiglate ester[9] the angelate ester was confirmed. In view of the relatively high degree of steric crowding in fastigilin A, changes in relative configuration at any of the eight chiral centers would be expected to result in large chemical-shift changes. Therefore, radiatin and fastigilin A differ only in the ester side chain and bear the same relative configuration at each asymmetric carbon. Accordingly, the skeletal system and relative positioning of substituents proposed by Herz[4] for fastigilin A were quite correct.

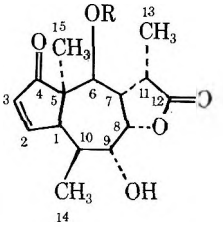
Analogous off-resonance decoupling experiments and model compound shifts were employed in the assignment of structure **1b** to fastigilin B. The chemical shifts for fastigilin B were found nearly identical with those of radiatin and fastigilin A with the exception of those for C-6 and the ester side chain. The latter shifts were characteristic of a senecioate ester[9] and this confirms the structural features proposed by Herz and co-workers.[4] In addition, we were able to complete the configurational notation as shown for the C-11 methyl group.

In conjunction with determining the structures of multigilin and multistatin, it became necessary to study fastigilin C and multiradiatin. Application of the ^{13}C NMR techniques applied to pseudoguaianolides **1a–c** led to the carbon shift assignments in Table I for fastigilin C. The spectrum of α,β-unsaturated lactone **2a** when compared with that of saturated lactone **1a** shows the expected upfield shift of C-12 and the downfield shifts of C-11 and C-13. The chemical shifts for C-1, C-7, C-8, C-9, C-14, and C-15 were assigned on the basis of proton single-frequency decoupling experiments using the proton values reported by Herz.[4] The resonance for C-6 was found shifted downfield to approximately 77 ppm and under conditions of broadband decoupling this resonance was obscured by deuteriochloroform. The ^{13}C NMR resonance assignments for fastigilin C coupled with the fact that lactones **2a** and **1b** have been hydrogenated to a common intermediate[4] leave no doubt that fastigilin C (**2a**) has the structure originally proposed by Herz and co-workers.[4,10]

We have interrelated fastigilin C and multiradiatin by a chromium trioxide oxidation step[2] (**2a** → **2c**) and the ^{13}C NMR spectrum of multiradiatin was easily interpreted. The resonances at C-6, C-8, C-10, C-14, and C-15 were verified using proton single-frequency decoupling techniques. The proton values were consistent with those made by Herz and co-workers[10] for the oxidation product of linearifolin A, a

closely related terpene. The major changes observed in the spectrum after oxidation of alcohol **2a** to multiradiatin were the downfield shift of C-9 and C-10 and the upfield shift of C-8. All were consistent with oxidation of C-9 to a carbonyl group. Evidently the carbonyl group of multiradiatin results in a significant conformational change as compared to fastigilin C. This was indicated by shift changes observed for C-2, C-3, C-6, C-8, C-11, and C-13, and to a lesser extent with other resonances relatively remote from the carbonyl group. On the assumption that oxidation of fastigilin C with Jones reagent does not change any configuration except that of C-9, multiradiatin must have the same relative configuration as fastigilin C and structure **2c** was substantiated.

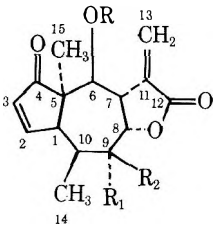
A comparison of the ^{13}C NMR spectrum of multistatin (**2d**) with that of multiradiatin (**2c**) shows clearly that the only resonance positions that differ significantly are those for C-6 and the ester side chain. The ester side chain of multistatin corresponded to an angelate and this completed structure **2b** for multistatin. Since multistatin was obtained from multigilin by oxidation, structure **2b** was proposed for multigilin. This structure was confirmed by the ^{13}C NMR spectrum, which differed significantly from that of alcohol **2a** only in the resonances of C-6 and the angelate side chain.



1a, R = —C(=O)—C(CH$_3$)=CH$_2$ (Radiatin)

b, R = —C(=O)—CH=C(CH$_3$)$_2$ (Fastigilin B)

c, R = —C(=O)—C(CH$_3$)=CH— (Fastigilin A)



2a, R = —C(=O)—CH=C(CH$_3$)$_2$ (Fastigilin C)

R_1 = OH; R_2 = H

b, R = —C(=O)—C(CH$_3$)=CH— (Multigilin)

R_1 = OH; R_2 = H

c, R = —C(=O)—C(CH$_3$)=CH— (Multiradiatin)

$R_1 = R_2$ = O

d, R = —C(=O)—C(CH$_3$)=CH— (Multistatin)

$R_1 = R_2$ = O

Preliminary biological evaluation of fastigilin A (P388 ED_{50} 2.1 and KB ED_{50} 3.9), multigilin (P388 T/C 164 at 12.5 mg/kg), and multistatin (P388 ED_{50} = 0.37 and T/C 131 at 32 mg/kg) in the National Cancer Institute's lymphocytic leukemia P388 cell line and in vivo screen indicates that all three of the pseudoguaianolides are capable of inhibiting neoplastic cell growth. Apparently, *Baileya multiradiata* has a very versatile mechanism for synthesizing cytotoxic and antineoplastic agents of the pseudoguaianolide type. The present study also indicates that minor changes in the plant's environment or growth period can markedly affect biosynthesis of the ester side chains. Alternatively the latter observation might reflect a hitherto unknown species variation of *Baileya multiradiata* and be of further interest from a taxonomic standpoint.

Experimental Section

All solvents were redistilled. Column chromatography unless otherwise noted was performed with silica gel (70–230 mesh and 30–70 mesh) or with prepacked silica gel 60 columns sizes B and C, both from E. Merck, Darmstadt. The material to be chromatographed was first adsorbed[11] on silica gel and when the prepacked column technique was employed the preadsorbed material was placed in a precolumn.[12] Thin-layer chromatography was performed with silica gel GF Uniplates supplied by Analtech Inc. and with precoated TLC plates (5 × 20 cm) of silica gel F254 supplied by E. Merck. The very careful fractionation performed with the precolumn/prepacked silica gel columns was partially automated using a Gilson microfractionator. Visualization of the plates was conducted as previously described.[2]

The mutual identity of authentic and isolated specimens was confirmed by thin-layer chromatographic and infrared spectral (KBr) comparisons. All melting points are uncorrected and were observed utilizing a Koefler-type melting point apparatus. The circular dichroism data (methanol solution) was obtained by Mr. J. Holler using a JASCO ORD/UV-5 instrument. The infrared (KBr) and ^1H NMR spectra (deuteriochloroform solution, tetramethylsilane internal standard) were nicely provided by Dr. J. Witschel, Jr., using a Beckman Model 12 infrared equipment and the Varian A-60 or XL-100 NMR instruments. The ^{13}C NMR spectra were measured at 22.6 MHz using a Bruker WH-90 NMR spectrometer and are reported in parts per million downfield from tetramethylsilane. Tetramethylsilane was used as an internal standard in 10-mm sample tubes containing approximately 0.08 M solutions of sesquiterpene in deuteriochloroform. Mass spectra were obtained by Messrs. E. Kelley and R. Scott employing the Atlas CH-4B and SM-1B (equipped for field ionization or electron impact) instruments. Elemental analyses were determined at the Spang Microanalytical Laboratory, Ann Arbor, Mich.

Collection and Extraction of *Baileya multiradiata*. In April 1975, a large scale re-collection of *Baileya multiradiata* Harv. and Gray aerial portion was made (G.R.P. assisted by Dr. Richard H. Ode, Messrs. Lawrence D. Vanell, Gregory C. Bryan, Russell Myers, and Miss Robin K. Pettit) near Wickenberg on the Yavapai/Maricopa County border, Arizona. The plant was in the flowering stage and upon air drying a 48.6-kg amount was extracted with chloroform as previously described.[2] The 800 g of crude green gummy extract was dissolved in ethanol (7.5 L) and hot water (22.5 L) was added. The solution was filtered through Celite and extracted with chloroform. Removal of solvent from the chloroform extract led to 212 g of amber-colored oil. Two 106-g portions of this oily fraction were each chromatographed on 2.85 kg of silica gel. The column was packed dry and the fractions eluted by 9:1 benzene–ethyl acetate led to 27-g amounts each of mixtures containing fastigilin A (**1c**), multistatin (**2d**), and multigilin (**2b**).[15]

Multigilin (2b). A 7.0-g aliquot of the benzene–ethyl acetate fractions noted in the preceding experiment was chromatographed on a column of silica gel (200 g). Careful elution with 9:1 benzene–ethyl acetate led to a fraction (1.65 g) containing primarily multigilin. Final purification was achieved employing chromatography on a size C prepacked silica-gel column with the enriched fraction preadsorbed on 4 g of silica gel. Elution (6-mL fractions) with 95:5 benzene–ethyl

acetate allowed multigilin to be concentrated in fractions 330–355. Removal of solvent gave 0.53 g of oily solid which crystallized from ethyl acetate–hexane as oily crystals (0.15 g): NMR ($CDCl_3$) δ 1.01 (3 H, s), 1.43 (3 H, d, J = 7 Hz), 1.78 (3 H, m, J = 2 Hz), 1.96 (3 H, dq, J = 7, 2 Hz), 2.2 (2 H, m), 3.10 (1 H, m), 3.68 (2 H, m), 5.07 (1 H, dd, J = 7, 3 Hz), 5.38 (1 H, s), 6.15 (2 H, dd, J = 6, 4 Hz), 6.38 (1 H, d, J = 2 Hz), 6.57 (1 H, d, J = 2 Hz), 7.80 (1 H, dd, J = 6, 3 Hz); MS m/e 360 (M^+), 342 (M − 18), 277 (M − 83), 261 (M − 99), 260 (M − 100), and 83 base peak.

Multistatin (2d). Method A. From *Baileya multiradiata*. Column chromatography on silica gel (200 g) of a fraction (7 g) containing multigilin provided a multigilin-rich fraction (4 g) which eluted with 9:1 benzene–ethyl acetate. Attempted crystallization of this fraction from acetone–hexane afforded approximately 10 mg of multistatin. Characterization was completed as summarized in Method B.

Method B. By Oxidation of Multigilin (2b). To a cold (ice-bath) solution of multigilin (**2b**, 0.467 g) in dry acetone (20 mL redistilled from potassium permanganate) was added (dropwise) excess 8 N Jones reagent.[13] Approximately 5 min later isopropyl alcohol (10 mL) was added followed by dilution with water (100 mL). The mixture was extracted with methylene chloride (3 × 10 mL) and the combined extracts were washed successively with 5% potassium carbonate (10 mL), saturated sodium chloride solution (10 mL), and water. Removal of solvent gave a pale yellow solid residue (0.39 g). Examination by thin-layer chromatography with benzene–ethyl acetate (3:1) as mobile phase indicated the presence of ketone **2d** (R_f 0.33) as the major product accompanied by some unreacted multigilin (R_f 0.18). The total product was chromatographed on a column of CC-4 SilicAR silica gel (20 g, supplied by Mallinckrodt). Elution with methylene chloride–ethyl acetate (9:1) provided in the first 65 mL a minor quantity of oily products and in the next 70 mL a 0.16-g (34%) yield of multistatin. The next 300 mL of solvent eluted 0.15 g of unreacted multigilin. The multistatin was pure as evidenced by thin-layer chromatography and recrystallized from heptane–acetone as colorless crystals melting at 257–260 °C: NMR ($CDCl_3$) δ 0.89 (s, 3, C_5-CH_3), 1.50 (d, J = 7 Hz, 3, C_{10}-CH_3), 1.77 (d, J = 2 Hz, 3, 2′-angelate Me), 1.94 (d of d, J = 2 and 6 Hz, 3, 4′-CH_3), 2.72 (m, J = 7 and 14 Hz, 1, C_{10}-H), 3.40 (m, 1, C_1-H), 3.72 (m, 1, C_7-H), 5.60 (d, J = 8 Hz, 1, C_{10}-H), 5.73 (s, 1, C_6-H), 5.93 (d, J = 3 Hz, 1, *exo*-C_{13}-H), 6.16 (d of d, J = 2 and 7 Hz, 1, 3′-H), 6.32 (d of d, J = 2 and 6 Hz, 1, C_3-H), 6.42 (d, J = 3 Hz, 1, *exo*-C_{13}-H), 7.70 (d of d, J = 2 and 6 Hz, 1, C_2-H); IR (KBr) 1773 (C=O), 1720–1705 (br band, C=O) cm^{-1}; MS m/e 358 (M^+), 340 (M − 18), 330 (M − 28), 275 (M − 83), 259 (M − 99), 258 (M − 100), 83 (M − 275) base peak. The isolated multistatin and the multigilin oxidation product were identical by IR, MS, TLC, and NMR.

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.18; O, 26.78. Found: C, 67.03; H, 6.21; O, 26.88.

Fastigilin A (1c). Method A. From *Baileya multiradiata*. The careful chromatographic separation of multigilin described above gave fractions containing fastigilin A and this substance was isolated in pure form by rechromatography on a size C prepacked silica gel column (2.03 g). Elution with 9:1 to 4:1 hexane–acetone afforded 0.35 g of fastigilin A, identical by NMR, TLC, and MS comparisons with fastigilin A described in method B.

Method B. From *Baileya pleniradiata*. Chromatographic fractions from *Baileya pleniradiata* kindly provided by Professor Geissman[3] were found to contain as principal components radiatin (**1a**) and fastigilin A (**1c**). A mixture (0.68 g) of this approximate composition was carefully chromatographed employing a size B prepacked silica gel column. Fractions (6 mL each) 184–193 eluted by 9:1 to 4:1 heptane–acetone afforded 0.06 g of fastigilin A. Recrystallization from acetone–hexane yielded colorless needles: mp 179–183 °C; CD λ_{max} 326 nm ($[\theta]$ −4022); NMR ($CDCl_3$) δ 1.02 (3 H, s), 1.40 (3 H, d, J = 7 Hz), 1.57 (3 H, d, J = 6 Hz), 1.71 (3 H, m, J = 2 Hz), 1.90 (3 H, dq, J = 7, 2 Hz), 2.2 (2 H, m), 3.06 (3 H, m), 3.52 (1 H, m), 4.92 (1 H, dd, J = 6, 3 Hz), 5.46 (1 H, s), 6.09 (2 H, dd, J = 6, 4 Hz), and 7.72 (1 H, dd, J = 6, 3 Hz); IR (KBr) 3460, 1760, 1715–1730 cm^{-1}; MS m/e 362 (M^+), 344 (M − 18), 334 (M − 28), 279 (M − 83), 263 (M − 99) base peak, and 262 (M − 100).

The compound was identical with an authentic sample of fastigilin A[4] by infrared and NMR comparisons.

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Registry No.—**1a**, 25873-31-8; **1b**, 6995-11-5; **1c**, 6995-10-4; **2a**, 6995-12-6; **2b**, 64937-25-3; **2c**, 58262-52-5; **2d**, 64937-26-4.

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Dehydroaporphines. An Acylation Study

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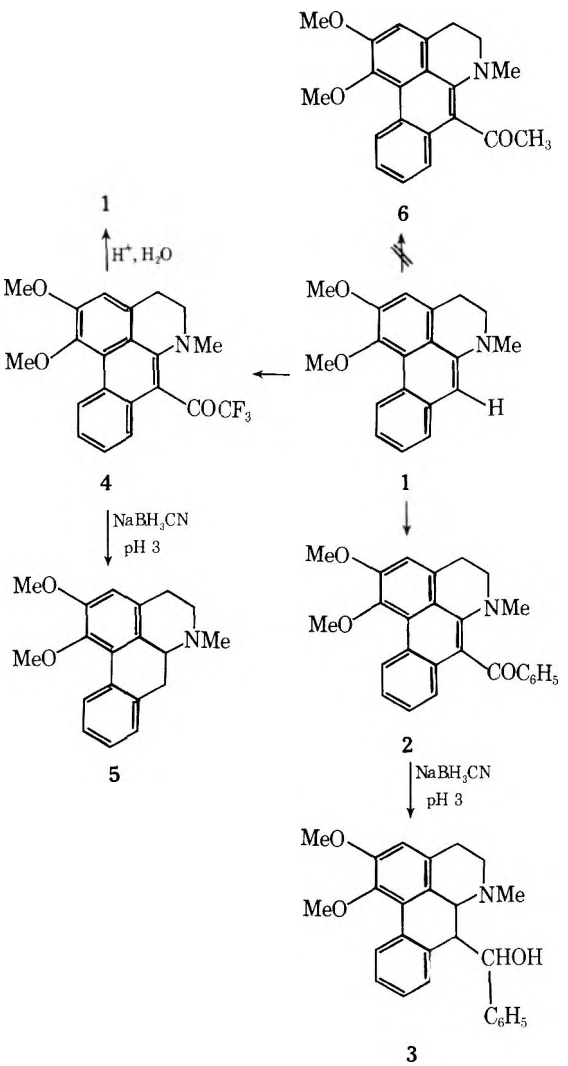
The representative dehydroaporphine, dehydronuciferine (**1**), is acylated by benzoyl chloride and by trifluoroacetic anhydride to give the 7-benzoyl and 7-trifluoroacetyl derivatives **2** and **4**, respectively. Dehydronuciferine (**1**) and dehydroapomorphine dimethyl ether (**13**) undergo direct acylative cyclization on treatment with oxalyl chloride to give the condensed isatins **8** and **14**, respectively. Some chemical transformations of the acyl derivatives **2** and **4** and the isatins **8** and **14** are described.

Previous studies from our laboratory have shown that dehydroaporphines possess a certain degree of enamine-type character, as evidenced by their behavior on protonation,[1] as well as their participation in a Reimer–Tiemann type formylation reaction.[2] We now report the first examples of dehydroaporphine acylations, and a simple route to some previously unavailable and pharmacologically interesting 7-substituted aporphine derivatives.

Results

Dehydronuciferine (**1**) was found to react smoothly with benzoyl chloride in pyridine at room temperature to give the yellow crystalline 7-benzoyldehydronuciferine (**2**) (Scheme I). Attempts to convert **1** into 7-acetyldehydronuciferine (**6**) in a similar manner failed, however, the starting material being converted into a complex mixture, as evidenced by TLC analysis. This failure was attributed to the possibility that **6** was in fact initially formed, but subsequently converted into secondary reaction products by way of reactions involving the acetyl methyl group. In accord with this idea, dehydronuciferine (**1**) was found to react cleanly with trifluoroacetic anhydride in pyridine to give 7-trifluoroacetyldehydronuciferine (**4**) as an orange oil.

Scheme I



The two ketones **2** and **4** differed markedly in their behavior toward acids as well as sodium cyanoborohydride. Whereas the benzoyl compound **2** was stable under both basic and acidic conditions (solutions or adsorbants), the trifluoroacetyl compound **4** was stable only in the absence of acid. A dilute acid wash, or even chromatography on ordinary silica, brought about a reverse acylation with the formation of dehydronuciferine (**1**). Sodium cyanoborohydride reduction of the benzoyl compound **2** took place readily at pH 3 to give an apparently homogeneous 7-(α-hydroxybenzyl)nuciferine (**3**), characterized as its crystalline hydrochloride. Under the same experimental conditions, the trifluoroacetyl compound **4** afforded only nuciferine (**5**).

Dehydronuciferine (**1**) reacted readily with oxalyl chloride under mild conditions (Scheme II). Unlike the case of the corresponding reaction with indole,[3] the initially formed glyoxalyl chloride **7** was not isolable, and cyclized with the loss of methyl chloride to give the wine-red isatin derivative **8**. In accord with the assigned structure, isatin **8** showed two carbonyl bands in the infrared at 5.75 and 5.90 μm, and no *N*-methyl singlet in its NMR spectrum.

Isatin **8** was used as the starting material for the synthesis of several unusual representative dehydroaporphines. Reaction of **8** with excess diazomethane gave the condensed pyridone **9**, a process analogous to the known conversion of isatin itself into 3-methoxycarbostyril.[4] The infrared spectrum of **9** showed a single carbonyl band at 6.10 μm, while its NMR spectrum showed the presence of three aromatic methoxyls (δ 3.86, 3.91, and 3.98) and two aromatic singlets (δ 7.01 and 7.51). Oxidation of **8** with *m*-chloroperbenzoic acid gave the isatoic anhydride **10**, characterized by its anhydride carbonyl doublet in the infrared at 5.59 and 5.88 μm. Finally, reduction of **8** with lithium aluminum hydride in tetrahydrofuran[5] afforded the indole derivative **11** as the major product (ca. 60%); a minor reaction product (12%) was lysicamine (**12**), which may have been formed from **11** as a photooxidation product during workup.

In a similar manner, dehydroapomorphine dimethyl ether (**13**) was successfully transformed into the corresponding isatin (**14**), pyridone (**15**), and anhydride (**16**). In view of the considerable pharmacological interest in apomorphine and its derivatives,[6] these compounds should be of value for the synthesis of various novel C-7 substituted apomorphines.

Discussion

The striking difference in the chemical behavior of the two ketones **2** and **4** must be attributed to the contrasting elec-

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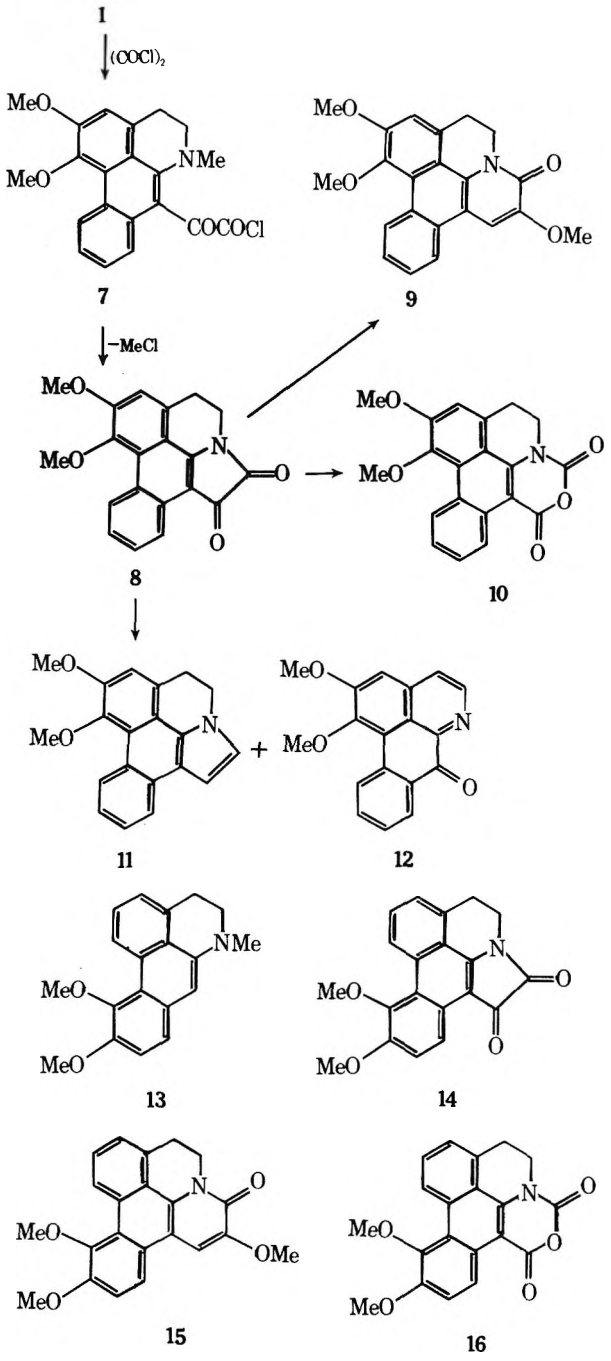
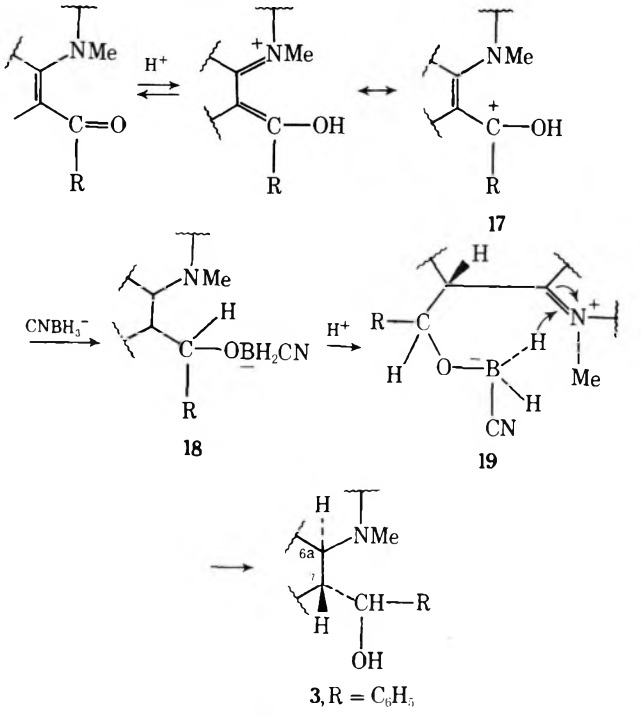
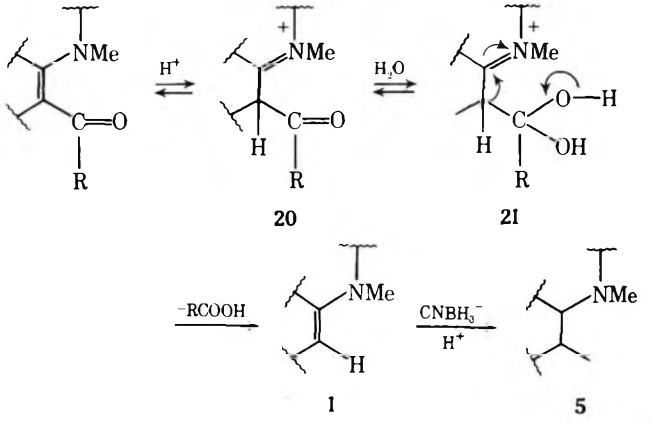
Scheme II



Scheme III



Scheme IV



tronic nature of their acyl substituents. In the case of the benzoyl compound **2**, a reversible protonation would be expected to occur readily at the carbonyl oxygen (Scheme III), the resulting cation being resonance stabilized by the phenyl substituent (R = C_6H_5). The rapid reduction of **2** to alcohol **3** by sodium cyanoborohydride in an acid medium is in accord with this view, since the reagent is known to be almost inert to ketonic carbonyls, but a good reducing agent for immonium ions.[7] 1,4-Reduction of the conjugated immonium ion **17** would give the dehydroaporphine borate ion **18**, protonation of which would give a new immonium ion **19**. If the latter process is followed by a rapid intramolecular hydride transfer as shown below, the ring hydrogens at C-6a and C-7 would be in a trans-diaxial arrangement, and the C-7 hydroxybenzyl substituent of **3** would have the more stable equatorial configuration.

In the case of the trifluoroacetyl compound **4**, carbonyl protonation on oxygen would be unfavorable, since the above ion **17** (R = CF_3) would be destabilized by the strongly electron-withdrawing trifluoromethyl substituent. As a result, the alternative process shown below (Scheme IV) could take place. Protonation of the ketone at C-7 would result in an immonium ion (**20**), which could be in equilibrium with its ketone hydrate **21**, especially if R is a strongly electron-withdrawing group. Rapid collapse of **21** would afford the deacylated dehydroaporphine (**1**). In the case of ketone **4**, collapse of the immonium ion **21** to **1** must occur more rapidly than its attack by cyanoborohydride ion, since treatment of **4** with acidic cyanoborohydride yields only nuciferine (**5**), shown to be the reduction product of dehydroaporphine **1** under the same experimental conditions.

Experimental Section

Melting points are uncorrected. Chromatography was carried out using silica. NMR spectra ($CDCl_3$ containing tetramethylsilane as internal standard), ultraviolet spectra (ethanol), infrared spectra (KBr), and mass spectra were determined using JEOL-JNH-PS-100 and Perkin-Elmer 202, 137, and 270 spectrometers, respectively. Microanalyses were performed by Midwest Microlab, Indianapolis, Indiana.

7-Trifluoroacetyldehydronuciferine (4). Excess trifluoroacetic anhydride (0.3 mL) was added to a cooled solution of dehydronucif-

erine[8] (1, 0.400 g) in dry pyridine (4 mL). After standing overnight at room temperature the orange solution (which showed the absence of 1 by TLC) was poured into water. The mixture was made slightly acidic and quickly extracted with chloroform, and the extract was washed with 5% $NaHCO_3$ followed by water. Evaporation of the extract gave crude 4 (~0.4 g) as an oil which was purified by chromatography over basic alumina (grade I), using a benzene–chloroform eluant. The orange oil, which could not be crystallized, showed UV maxima at 260, 321, and 370 nm; NMR δ 2.93 (s, 3 H, NMe), 3.88 (s, 3 H, OMe), 4.01 (s, 3 H, OMe), 7.08 (s, 1 H, C-3), 7.43–7.95 (m, 3 H), 9.48–9.65 (m, 1 H); IR 5.80, 5.85 μm; mass spectrum *m/e* (rel intensity) 389 (M^+, 56) 320 (100), 293 (13), 276 (24), 194.5 (2).

A chloroform solution of 4 (0.100 g) was shaken three times with 5% HCl and then water. Evaporation of the dried solvent gave dehydronuciferine (1, 0.090 g), mp 129–130 °C, identical (IR, UV, NMR, mmp) with authentic material.[8] In contrast, neutral or basic methanolic solutions of 4 were found (TLC) to be stable for weeks.

A freshly prepared solution of 4 (0.100 g) in methanol was acidified to pH 3 with 1% HCl, and excess $NaCNBH_3$ was added. After 15 min, workup (basification and chloroform extraction) afforded, after ethanol crystallization, racemic nuciferine (5), mp 133–135 °C (lit.[9] 134–135 °C), identical (IR, UV, TLC, mmp) with authentic material.

7-Benzoyldehydronuciferine (2). Benzoyl chloride (0.2 mL) was added to a solution of dehydronuciferine (1, 0.200 g) in dry pyridine (1 mL). After standing overnight, the solution was poured into water, the mixture was made slightly acidic, and the product was extracted into chloroform. Chromatography on silica (chloroform eluant) afforded 2 (0.190 g, 71%), which crystallized from EtOH as yellow prisms: mp 154–155 °C; IR 5.97 μm; UV λ_{max} 257 nm (ϵ 46 000), 323 (11 000), 373 sh (3200); NMR δ 2.80 (s, 3 H, NMe), 3.08 (s, 4 H), 3.92 (s, 3 H, OMe), 3.98 (s, 3 H, OMe), 7.06 (s, 1 H), 6.96–9.38 (m, 9 H); mass spectrum *m/e* (rel intensity) 397 (M^+, 100), 380 (90), 198.5 (1). Anal. Calcd for $C_{26}H_{23}NO_5$: C, 78.58; H, 5.79; N, 3.52. Found: C, 78.30; H, 5.93; N, 3.37.

7-(α-Hydroxybenzyl)nuciferine (3). Reduction of ketone 2 (0.200 g) by $NaCNBH_3$ was carried out as in the case of the trifluoroacetyl analogue 4 (see above). The resulting oil (0.150 g, 3) was converted into colorless plates of the hydrochloride: mp 225–227 °C; UV λ_{max} 243 (sh) nm (ϵ 23 000), 275 (32 000); NMR δ 2.68 (s, 3 H, NMe), 3.35 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 5.21 (d, 1 H, J = 5 Hz, CH(OH)-C_6H_5), 5.43 (br, 1 H, OH, vanishes with D_2O), 6.56 (s, 1 H, C-3), 6.60–7.43 (m, 8 H), 8.30–8.50 (m, 1 H, C-11); mass spectrum *m/e* (rel intensity) 391 (M^+, 14), 385 (28), 384 (100), 370 (18), 294 (24), 278 (12), 263 (13), 252 (84). Anal. Calcd for $C_{26}H_{28}NO_5Cl$: C, 71.31; H, 6.40; N, 3.20. Found: C, 71.30; H, 6.24; N, 3.19.

Isatin 8. Oxalyl chloride (3 mL) was added to a solution of dehydronuciferine (1, 2.00 g) in a mixture of dry ether (80 mL) and tetrahydrofuran (30 mL). After stirring for 2 h, the precipitated product was filtered, washed with ether, and crystallized from chloroform to give wine-red needles (2.09 g): silica chromatography of the mother liquors afforded a further 0.22 g of crystalline 8: mp 233–234 °C; IR 5.75, 5.90 μm; UV λ_{max} 257 nm (ϵ 68 000), 324 sh (21 000), 336 (25 000), 357 sh (14 000), 510 (6000); NMR (Me_2SO + $CDCl_3$) δ 3.36 (t, 2 H, J = 6 Hz), 3.90 (t, 2 H, J = 6 Hz), 3.90 (s, 3 H, OMe), 4.09 (s, 3 H, OMe), 7.43 (s, 1 H), 7.53(–9.40 (4 H, m); mass spectrum *m/e* (rel intensity) 333 (M^+, 100), 305 (52), 277 (21), 166.5 (1). Anal. Calcd for $C_{20}H_{15}NO_4$: C, 72.07; H, 4.50; N, 4.20. Found: C, 71.91; H, 4.77; N, 4.15.

Pyridone 9. Excess ethereal diazomethane was added to a solution of isatin 8 (0.050 g) in chloroform–methanol. After standing overnight, the mixture was worked up in the usual manner to give, after crystallization from ethyl acetate, pyridone 9 (0.040 g): mp 152–153 °C; IR 6.10 μm; UV λ_{max} 247 (sh) nm (ϵ 30 000), 267 (50 000), 320 (13 000), 344 (14 000), 360 (14 000), 379 (16 000); NMR δ 3.11 (t, 2 H, J = 6.5 Hz), 4.43 (t, 2 H, J = 6.5 Hz), 3.86 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 3.98 (s, 3 H, OMe), 7.01 (s, 1 H), 7.51 (s, 1 H), 7.45–9.66 (m, 4 H); mass spectrum *m/e* (rel intensity) 361 (M^+, 100), 346 (28), 331 (25), 318 (46), 103.5 (5). Anal. Calcd for $C_{22}H_{19}NO_4$: C, 73.13; H, 5.26; N, 3.87. Found: C, 73.13; H, 5.46; n, 3.81.

Anhydride 10. An excess of *m*-chloroperbenzoic acid in methylene chloride was added dropwise with cooling and stirring to a solution of isatin 8 (1.00 g) in methylene chloride (100 mL) containing an excess of powdered sodium bicarbonate. After 4 h at room temperature, the yellow solution contained no detectable starting material (TLC). The organic phase was shaken with 10% sodium sulfite until a starch-iodide test showed that all peracid was destroyed and was then washed (sodium bicarbonate then water), dried, and evaporated. Crystallization from chloroform–ethanol afforded yellow plates of anhydride 10 (0.750 g): mp 219–220 °C; IR 5.59, 5.88 μm; UV λ_{max} 262 nm (ϵ 38 000), 310 (8900), 324 (9300), 378 (4100); NMR δ 3.30 (t, 2 H, J = 6 Hz), 4.35 (t, 2 H, J = 6 Hz), 3.91 (s, 3 H, OMe), 4.04 (s, 3 H, OMe), 7.13 (s, 1 H), 7.52–9.55 (m, 4 H). Anal. Calcd for $C_{20}H_{15}NO_5$: C, 68.76; H, 4.29; N, 4.01. Found: C, 68.47; H, 4.32; N, 3.93.

Indole 11. Lithium aluminum hydride (0.400 g) was added in small portions to a solution of isatin 8 (1.300 g) in dry tetrahydrofuran (75 mL). After refluxing for 4 h, excess hydride was destroyed by the careful addition of saturated sodium sulfate solution. Evaporation of the filtered solution yielded a gum which was chromatographed on silica ($CHCl_3$ eluant) to give, after crystallization from ethanol, prisms of indole 11 (0.520 g): mp 134–135 °C; UV λ_{max} 254 (sh) nm (ϵ 47 000), 263 (70 000), 296 (13 000), 317 (9300), 360 sh (28 000), 376 (3500); NMR δ 3.43 (t, 2 H, J = 6.8 Hz), 4.31 (t, 2 H, J = 6.8 Hz), 3.97 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 6.91 (d, 1 H, J = 2.8 Hz), 7.03 (d, 1 H, J = 2.8 Hz), 7.16 (s, 1 H), 7.46–9.62 (m, 4 H); mass spectrum *m/e* (rel intensity) 303 (M^+, 100), 288 (54), 260 (24), 151.5 (5). Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.20; H, 5.61; N, 4.62. Found: C, 79.11; H, 5.35; N, 4.83.

A minor reaction product (12%) was isolated by elution of the silica column and proved to be lysicamine (12), as shown by comparison (TLC, IR, mmp) with authentic material.

Isatin 14. Oxalyl chloride (0.600 g) was added dropwise to a solution of dehydroapomorphine dimethyl ether (13, 0.500 g) in a mixture of dry ether (35 mL) and tetrahydrofuran (10 mL). After 90 min, the solvent was evaporated and the residue was taken up in chloroform and washed with 5% sodium bicarbonate and then water. Evaporation of the solvent and crystallization from methanol afforded, in two crops, wine-red prisms of isatin 14 (0.320 g): mp 183–184 °C; IR 5.70, 5.83 μm; UV λ_{max} 215 nm (ϵ 11 000), 255 (33 000), 320 (6600), 525 (1200); NMR δ 3.21 (t, 2 H, J = 6 Hz), 3.78 (t, 2 H, J = 6 Hz), 3.85 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 7.05 (d, 1 H, J = 9 Hz), 7.95 (d, 1 H, J = 9 Hz), 7.31 (m, 1 H), 7.56 (m, 1 H), 9.11 (m, 1 H); mass spectrum *m/e* (rel intensity) 333 (M^+, 100), 319 (20), 305 (92), 290 (32), 277 (14), 262 (32), 234 (21), 219 (35), 190 (25), 166.5 (4). Anal. Calcd for $C_{20}H_{15}NO_4$: C, 72.07; H, 4.50; N, 4.20. Found: C, 71.63; H, 4.60; N, 4.05.

Pyridone 15. Excess ethereal diazomethane was added to a solution of isatin 14 (0.070 g) in chloroform–methanol. After standing overnight, the mixture was worked up in the usual manner and the product chromatographed on silica (chloroform eluant) and crystallized from ethyl acetate–ether to give needles of pyridone 15 (0.060 g): mp 153–154 °C; IR 5.96 μm; UV λ_{max} 257 (sh) nm (ϵ 41 000), 268 (50 000), 302 (16 000), 320 (12 000), 346 (8300), 365 (1900), 384 (10 000); NMR δ 3.28 (t, 2 H, J = 6 Hz), 4.51 (t, 2 H, J = 6 Hz), 3.96 (s, 3 H, OMe), 4.03 (s, 3 H, OMe), 4.08 (s, 3 H, OMe), 7.31 (s, 1 H), 7.13 (d, 1 H, J = 9 Hz), 7.70 (d, 1 H, J = 9 Hz), 7.36 (m, 1 H), 7.20 (m, 1 H), 9.33 (m, 1 H); mass spectrum *m/e* (rel intensity) 361 (M^+, 100), 346 (15), 318 (27), 303 (10), 274 (10), 260 (9), 180.5 (11). Anal. Calcd for $C_{22}H_{19}NO_4$: C, 73.13; H, 5.26; N, 3.86. Found: C, 72.91; H, 5.18; N, 3.77.

Anhydride 16. Isatin 14 (0.060 g) was oxidized by *m*-chloroperbenzoic acid as described above for the oxidation of the isomeric isatin 8. The anhydride 16 (0.050 g) crystallized from acetone as yellow needles: mp 194–195 °C; IR 5.59, 5.87 μm; UV λ_{max} 240 nm (ϵ 17 000), 261 (25 000), 284 sh (8100), 309 sh (7100), 323 (8400), 358 (3900), 387 (3400); NMR δ 3.23 (t, 2 H, J = 6 Hz), 4.25 (t, 2 H, J = 6 Hz), 3.88 (s, 3 H, OMe), 3.98 (s, 3 H, OMe), 7.23 (d, 1 H, J = 9 Hz), 7.78 (d, 1 H, J = 9 Hz), 7.45 (m, 1 H), 7.31 (m, 1 H), 9.25 (m, 1 H); mass spectrum *m/e* (rel intensity) 349 (M^+, 100), 321 (37), 306 (35), 281 (10), 278 (16), 263 (16), 234 (15), 174.5 (1). Anal. Calcd for $C_{20}H_{15}NO_5$: C, 68.76; H, 4.29; N, 4.01. Found: C, 68.10; H, 4.35; N, 3.87.

Cyanoborohydride Reduction of 1. A methanol–tetrahydrofuran solution of dehydronuciferine (1, 0.100 g) was acifified to pH 3 with 1% HCl, and excess $NaCNBH_3$ was added. After 30 min, the usual workup afforded (ethanol crystallization) racemic nuciferine (5, 0.090 g), mp 133–135 °C, identical (IR, UV, TLC, mmp) with authentic material.

Acknowledgment. We thank the National Institutes of Health for a grant (CA-11445) in support of this work and the Fundación Juan March for a supporting fellowship to one of us (J. M. Saá).

Registry No.—1, 7630-74-2; 2, 64938-90-5; 3 HCl, 64938-91-6; 4, 64957-46-6; 8, 64938-92-7; 9, 64938-93-8; 10, 64938-94-9; 11, 64938-95-0; 13, 18605-43-1; 14, 64938-96-1; 15, 64938-97-2; 16, 64938-98-3; trifluoroacetic anhydride, 407-25-0; benzoyl chloride, 98-88-4; oxalyl chloride, 79-37-8; diazomethane, 334-88-3.

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Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. 56. Strychnos Alkaloids[1]

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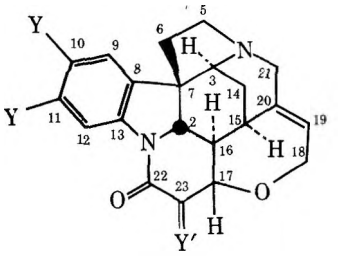
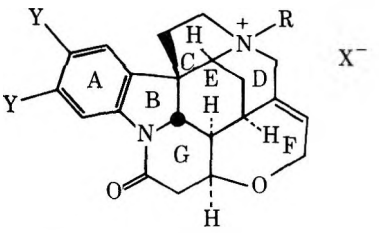
An exhaustive ^1H and ^{13}C NMR analysis of the Strychnos alkaloids strychnine, brucine, Wieland Gumlich aldehyde, diaboline, hemitoxiferin-I, 10-methoxy-*O*-demethyltsilanine, toxiferine-I, and strychnospermine and their derivatives is presented. The data have been used for the solution of a variety of configurational and conformational problems.

The naturally abundant Strychnos alkaloids are characterized by an azabicyclo[3.3.1]nonane system fused to an indoline unit. They vary in structural complexity from the pentacyclic alkaloid tubifolidine (**14** minus the 16β-methyl group) to heptacyclic strychnine (**1a**) and "dimeric" substances such as toxiferine-I (**12**). The present communication presents a composite study of the ^{13}C NMR spectroscopy of the Strychnos and related alkaloids.[3]

The study was initiated by the analysis of the spectra of strychnine (**1a**), its hydrochloride (**2a**), methiodide (**2b**), *N*-oxide (**2c**), and 23-oximino derivative (**1b**), as well as of brucine (**1c**) and its hydrochloride (**2d**).[6] The aromatic carbon resonances of compounds **1** and **2** can be assigned by comparison with indoline shifts of Aspidosperma bases.[7] The aromatic methines can be differentiated from the olefinic ones by the larger residual coupling in the single-frequency off-resonance decoupled (sford) spectra (the decoupler frequency being set at the high-field end of the spectrum and therefore close to the olefinic proton resonances) and the splitting caused by the meta hydrogens ($^3J_{CH}$).[8] Most upfield carbon signals are assigned on the basis of their multiplicities and chemical-shift theory.[9] Being an allylic carbon, C(15) shows larger residual coupling than C(16) and reveals long-range coupling with olefinic H(19). C(18) couples with the same hydrogen. The distinction between the aminomethylenes C(5) and C(21) is founded on the exhibition of second-order coupling by the former but not the latter and unequal residual coupling of the latter to each of its own hydrogens. For further differentiation of the aminomethylenes as well as the methylenes at highest field, C(6) and C(14), individual carbons and their attached hydrogens were related by way of Birdsall plots, a series of sford experiments at various decoupling frequencies.[10] All carbon shifts of compounds **1** and **2** are presented in Table I.

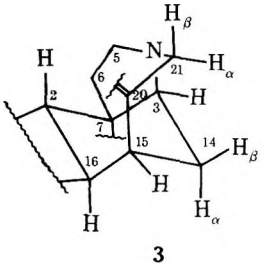


1a, Y = H; Y′ = H_2
b, Y = H; Y′ = NOH
c, Y = OMe; Y′ = H_2



2a, R = Y = H; X = Cl
b, R = Me; X = I; Y = H
c, R = O^-; Y = H
d, R = H; X = Cl; Y = OMe

The above study necessitated a ^1H NMR spectral investigation of the Strychnos alkaloid systems, especially in order to ascertain the conformation of strychnine (**1a**) and its relatives. Even though an analysis of a 250-MHz ^1H NMR spectrum of the alkaloid has been reported,[11] the new measurements (Tables II and III) require a reversal of shift assignment within each pair of geminal hydrogens at C(5), C(14), and C(21). The small vicinal couplings, ca. 2–5 Hz, between the hydrogens of C(3), C(14), C(15), and C(16) and the large H(2)–H(16) coupling, 10.5 Hz, confirm the equatoriality of H(3) and H(15) and the axiality of H(2) and H(16) within a chair conformation of ring E (**3**). It has been shown that H(18α) is coupled with H(15) and H(19) with the low-field hydrogen at C(21).[11] Further double irradiation experiments



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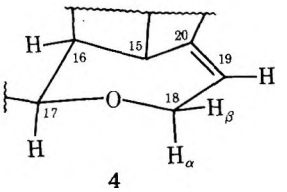

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Table I. Carbon Shifts of Compounds 1 and 2 [a]

	1a [b]	1b [b,c]	1c [b,d]	2a [e]	2b [e,f]	2c [e]	2d [e,g]
C(2)	59.9 [h]	58.7	59.8 [h]	58.4	58.0	58.1	58.8
C(3)	59.8 [h]	59.4	59.3 [h]	60.6	73.8	82.1	60.3
C(5)	50.1	49.3	49.6	50.0	61.3	67.5	49.9
C(6)	42.6	42.6	41.9	40.3	38.4	38.7	39.9
C(7)	51.7	51.4	51.4	51.2	52.4	52.6	51.4
C(8)	132.4	132.1	122.9	129.3	129.1	130.6	120.3
C(9)	121.9	121.7	105.1	122.3	123.4	122.8	107.0
C(10)	123.8	124.7	145.6	123.9	123.4	124.2	146.0
C(11)	128.1	128.3	148.5	128.9	129.1	129.0	149.2
C(12)	115.8	115.5	100.5	115.0	115.0	115.2	100.7
C(13)	141.8	141.4	135.3	141.5	141.3	141.5	135.4
C(14)	26.7	26.3	26.3	24.3	24.0	24.5	24.3
C(15)	31.4	31.5	31.1	29.6	28.6	29.5	29.6
C(16)	48.0	45.2	47.7	46.1	46.0	46.8	46.3
C(17)	77.3	75.0	77.1	75.7	75.4	76.1	76.0
C(18)	64.3	65.5	64.0	63.1	63.1 [h]	63.5	63.1
C(19)	126.8	128.0	126.7	134.3	135.1	132.9	134.3
C(20)	140.2	138.5	139.8	132.7	132.5	135.6	132.7
C(21)	52.4	52.3	52.1	50.9	63.4 [h]	70.3	51.1
C(22)	168.8	159.6	168.2	168.5	168.6	168.9	168.2
C(23)	42.2	148.3	41.8	41.0	40.8	41.5	41.0

[a] In ppm downfield from Me_4Si. [b] In $CDCl_3$, $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [c] Methanol was added to improve the solubility. [d] δ(OMe) = 55.7 and 56.0 ppm. [e] In Me_2SO-d_6, $\delta(Me_4Si) = \delta(Me_2SO\text{-}d_6) + 39.5$ ppm. [f] δ(NMe) = 54.4 ppm. [g] δ(OMe) = 55.8 and 56.2 ppm. [h] Values within any vertical column may be interchanged.

Table II. Proton Chemical Shifts [a]

	1a [b,c]	2c [d,e]	5c [f]	8a [g]	11 [d]	12 [h]	13a	13b [i]	14	15 [j]
H(2)	3.85	4.0	4.30	3.3	3.95	6.1	3.80	3.72	3.32	4.00
H(3)	3.92	4.25	3.94	3.4 [k]	3.55	4.3 [k]	3.34	3.31	3.40	3.47
H(5α)	3.19	3.45	3.30	3.0 [k]	2.9 [k]	4.3 [k]	3.16	3.18	3.14	3.15
H(5β)	2.86	3.8 [k]	2.8 [k]	3.0 [k]	2.9 [k]	4.3 [k]	2.85	2.84	2.84	2.87
H(6α)	1.87	2.4	1.7 [k,l]	1.8 [k]	1.7 [k]	3.1 [l]	1.85	1.80	1.79	1.97
H(6β)	1.87	2.0	1.98 [l]	2.5	2.4	3.3 [l]	2.53	2.51	2.48	2.47
H(9)	7.15	7.5	7.09	7.05	7.4	7.95	7.03	6.90	6.99	*n*
H(10)	7.08	7.15	7.09	6.8	7.1	7.45	6.76	6.29	6.70	*n*
H(11)	7.23	7.3	7.26	7.1	7.2	7.75	7.04		6.99	*n*
H(12)	8.09	7.95	8.00	6.7	7.55	7.1	6.62	6.19	6.57	*n*
H(14α)	1.43	1.5	1.55	1.7	1.7	2.3	1.64	1.65	1.64	1.68
H(14β)	2.34	2.6	2.26	1.95	2.0	2.6	1.93	1.99	1.98	2.17
H(15)	3.13	3.25	2.8 [k]	2.9 [k]	2.7	*n*	1.97	1.77	1.74	2.08
H(16)	1.25	1.4	1.87	1.9 [k]	2.25		1.75	1.80	1.5 [k]	1.5 [k]
H(17α)	4.27	4.35	5.80	3.45 [l]		*o*	3.84	3.59	1.15	3.93
H(17β)				3.5 [l]	5.2	*o*	3.56	3.89	1.15	
H(18α)	4.05	4.1 [k]	4.05	4.0 [m]	3.95	4.8	1.31	1.13	0.95	3.57
H(18β)	4.13	4.1 [k]	4.30	4.1 [m]	3.95	4.8	1.31	1.13	0.95	4.00
H(19)	5.88	6.3	5.85	5.75	5.6	6.4	3.69 (β)	3.54 (α)	1.5 [k]	1.4 [k]
H(20)							1.35	1.35	*n*	2.3 [k]
H(21α)	3.69	3.9 [k]	3.73	3.4 [k]	3.45	4.9	3.03	3.03	3.09	2.3 [k]
H(21β)	2.71	3.9 [k]	2.72	3.1 [k]	2.95	4.1	2.49	2.32	2.15	2.3 [k]

[a] δ values for $CDCl_3$ solutions are at 220 MHz unless stated otherwise. [b] Reinterpreted 250-MHz data of ref 11. [c] δ (H-23α) = 3.11, δ(H-23β) = 2.66 ppm. [d] At 100 MHz in Me_2SO-d_6. [e] At 40 °C, δ(H-23α) = 3.0, δ(H-23β) = 2.6 ppm. [f] δ ($NCOCH_3$) = 2.37, $\delta(OCOCH_3)$ = 2.06 ppm. [g] At 100 MHz in 1:1 $CDCl_3$–CD_3OD. [h] At 100 MHz in D_2O, δ(NMe) = 3.65 ppm. [i] δ(OMe) = 3.75 ppm. [j] δ(H-23α) = 3.02, δ(H-23β) = 2.63 ppm. [k] Approximate shift. [l,m] Signals within a vertical column may be reversed. [n] Unmeasured shift. [o] δ(H-17) = 7.05 ppm.

now establish that H(19) is coupled with H(15). Since this implies that H(15), H(18α), and the deshielded H(21) are well out of the plane of the C(19)–C(20) double bond,[12] the data are in consonance with ring D and F boat and chair conformations (**3** and **4**), respectively, and require the assignment of the low-field H(14) and H(21) multiplets to those hydrogens occupying flagpole positions on the boat ring D, i.e., H(14β) and H(21α), respectively. The chair conformation of the tetrahydrooxepin ring F is supported by the observation of H(15)–H(18α) coupling and by the low magnitude of the H(15)–H(16) and H(16)–H(17) coupling constants.

Protonation of strychnine (**1a** → **2a**) introduces small but significant shift perturbations throughout the carbon framework. The olefinic carbons become greatly polarized, C(19) being deshielded and C(20) shielded each by 7.5 ppm.[13] The carbon shifts of the methiodide (**2b**) are nearly identical with those of the hydrochloride (**2a**) except for large β effects (11–14 ppm) on carbons 3, 5, and 21. The *N*-oxide (**2c**) shows a similar shift pattern, the β shifts being even larger (17–22 ppm) and the double bond less polarized than in **2a** or **2b**.

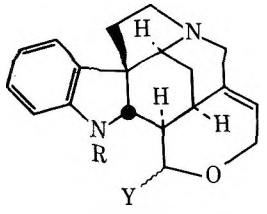
The hexacyclic Wieland Gumlich aldehyde derivatives, substances **5** and **6**, contain an anomeric center at C(17). Thus the 17-hydroxy compounds can equilibrate and present two sets of carbon signals in their ^{13}C NMR spectra. The carbon-

Table III. ^{1}H–^{1}H Coupling Constants of Nonaromatic Hydrogens[a]

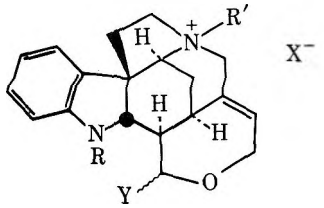
$^3J_{HH}$	1a[b]	2c[c]	5c	8a[d]	11[c]	12[e]	13a	13b	14	15
2–16	10.5	11	10	*f*	13		8.5	8.5	10	11
16–17α	3.1	3	<2	*f*			2.5	2.5	7	4
16–17β				*f*	12		<1	<1	7	
15–16	3.1	3	<2	*f*	3		*f*	*f*	<1	*f*
15–20							*f*	*f*	*f*	*f*
20–21α							5	6	5	*f*
20–21β							12	12	12	*f*
19–20							<1	2.5	*f*	*f*
18α–19	5.7	6.5[g]	5.5	7[g]	6[g]	6.5	6.5	6.5	7	12.5, 3
18β–19	6.9	8[g]	5	7[g]	6[g]	6.5	6.5	6.5	7	6, <1
3–14α	1.8	<1	<2	3	2	3.5[g]	3.5	3.5	3	3
14α–15	2.0	<2	<2	3	3	3.5[g]	3.5	3.5	3	3
14β–15	4.6	4[g]	4.5	4	4	3.5[g]	3.5	3.5	3	3
3–14β	4.1	3	4.5	4	4	3.5[g]	3.5	3.5	3	3
5α–6β	*f*	<1	<1	*f*	*f*	*f*	8.5	8.5	8.5	9
5β–6β	*f*	5.5	6.5	*f*	*f*	*f*	8.5	8.5	8.5	9.5
5β–6α	*f*	14	12.5	*f*	*f*	*f*	2.5	2.5	3	3
5α–6α	*f*	7	7	*f*	*f*	*f*	10	10	10	9
17–23α	8.4	8.5								8
17–23β	3.3	3								5
$^2J_{HH}$										
5–5	*f*	11.5	11	11	*f*	*f*	*f*	11	12	12
6–6	*f*	13	13	13	*f*	*f*	13.5	13.5	13.5	13.5
14–14	14.4	14.5	14	14	13	14	13.5	13.5	13.5	13.5
17–17				*f*			11	11		
18–18	14.2	*f*	14	12.5	*f*	*f*				12.5
19–19										*f*
21–21	14.8	14.5	15	*f*	*f*	*f*	12	12	12	14
23–23	17.4	17.5								16

[a] *J* values in Hz. [b] Reinterpreted 250-MHz data of ref 11. Other coupling constants for **1** are $^4J_{15-19}$ = 2.5, $^4J_{19-21\alpha}$ = 1.2, $^5J_{15-18\alpha}$ = 2.5, and $^4J_{5\alpha-21\alpha}$ = 1.7 Hz. [c] At 100 MHz in Me_2SO-d_6. [d] At 100 MHz in 1:1 $CDCl_3$–CD_3OD. [e] At 100 MHz in D_2O. [f] Unmeasured coupling constant. [g] Approximate coupling constant.

shift analyses of Wieland Gumlich aldehyde (**5a–b**), its N_a,*O*-diacetyl derivative (**5c**), and diaboline (N_a-acetyl Wieland Gumlich aldehyde, **5d–e**), as well as of Wieland Gumlich aldehyde N_b-methiodide (**6a–b**), hemitoxiferin-I (Wieland *Gumlich aldehyde N_b-methochloride*, **6c–d**), and diaboline hydrochloride (**6e–f**), follow closely from the arguments presented for compounds **1** and **2**. The absence of a N_a-acyl substituent, e.g., as in **5a–b**, causes shielding of the ring A



5a, R = H; Y = β-OH
b, R = H; Y = α-OH
c, R = Ac; Y = β-OAc
d, R = Ac; Y = α-OH
e, R = Ac; Y = β-OH



6a, R = H; R′ = Me; X = I; Y = β-OH
b, R = H; R′ = Me; X = I; Y = α-OH
c, R = H; R′ = Me; X = Cl; Y = β-OH
d, R = H; R′ = Me; X = Cl; Y = α-OH
e, R = Ac; R′ = H; X = Cl; Y = α-OH
f, R = Ac; R′ = H; X = Cl; Y = β-OH

carbons ortho and para to N_a, as expected from model data.[9] Aminomethine C(3) is distinguished from C(2) by its shift invariance through the series of compounds. The good correlation of the residual couplings from the sford spectra of **5c** with the actual hydrogen shifts (cf. Tables II and III) confirms the signal assignment presented in Table IV.

Despite the absence of ring G, the δ values of the ring C, D, and E carbons of compounds **5** are similar to those of strychnine (**1a**), indicating maintenance of the ring conformations. Nevertheless, some conformational relaxation occurs, as revealed by the ca. 4-ppm shielding of C(6). The identity of the ring D conformation in **1a** and **5c** is reflected by the similarity of certain regions of their ^{1}H NMR spectra, e.g., the nonequivalence of the geminal hydrogens of C(14) and C(21) as well as allylic and homoallylic coupling of H(21α) and H(18α), respectively (vide supra) (cf. Tables II and III).

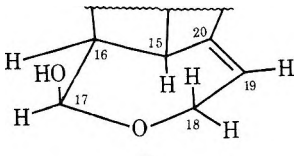
The carbon shifts of N_a,*O*-diacetyl Wieland Gumlich aldehyde (**5c**)[14] are similar to those of strychnine (**1a**) and thus consistent with the presence of an equatorial 17β-acetoxy group within ring F in the chair form, as proposed earlier on the basis of ^{1}H NMR and molecular rotation measurements.[15] Since the ^{13}C NMR data of **5c** are correlatable readily with those of the major components of the anomer mixtures of Wieland Gumlich aldehyde (**5a–b**) and its N_b-metho salts **6a–b** and **6c–d**, the preponderant anomers **5a**, **6a**, and **6c**, respectively, possess an equatorial 17β-hydroxy group. The ca. 7-ppm shielding of C(17) and ca. 3-ppm shielding of C(15) and C(18) of the minor anomers point to an axial 17α-hydroxy group within ring F still in the chair form. The pattern of conformation, however, differs in the cases of diaboline (**5d–e**) and its hydrochloride (**6e–f**). One pair of anomers reveals shifts consistent with an axial 17α-hydroxy structure within conformation **4** (**5d** and **6e**), whereas the other pair exhibits anomalous shifts, e.g., the hemiacetal carbon being shielded

Table IV. Carbon Shifts of Compounds 5 and 6 [a]

	5a [b]	5b [b]	5c [b,c]	5d [d]	5e [d]	6a [e,f]	6b [e,f]	6c [g,h]	6d [g,h]	6e [i]	6f [i]
C(2)	60.5	62.3	63.5	65.4	66.0	61.2	62.0	61.3	62.6	63.6	64.8
C(3)	58.8	58.4	58.6	59.4	59.4	75.5	75.3	75.7	75.5	61.6	61.6
C(5)	50.4	50.4	51.4	51.9	51.9	63.9	63.9	64.1	64.1	52.7	53.5
C(6)	37.9	38.3	38.1	39.0	38.8	36.5	36.5	36.4	36.4	36.4	36.0
C(7)	53.5	53.5	53.5	*j*	54.4	56.1	56.4	56.3	56.6	49.0	*j*
C(8)	130.8	130.1	133.9	137.0	135.6	128.7	128.7	129.1	129.0	132.6	*j*
C(9)	121.2	120.9	121.1	123.4	122.7	123.7	123.7	123.9	123.9	122.9	122.3
C(10)	118.7	118.4	124.1	126.2	126.2	121.3	121.0	121.7	121.6	125.8	126.2
C(11)	127.4	127.8	127.8	128.6	128.6	131.0	131.0	131.1	131.1	129.3	129.3
C(12)	110.6	109.7	118.5	118.8	120.3	112.8	112.5	113.2	113.0	118.6	120.0
C(13)	149.4	149.3	142.1	142.3	142.3	150.5	150.5	150.5	150.5	140.7	140.9
C(14)	25.6	24.4	25.4	25.6	25.8	25.0	24.4	25.1	24.4	22.9	22.9
C(15)	31.3	27.6	33.2	29.4	29.4	30.5	27.6	30.7	27.7	27.6	27.6
C(16)	46.0	50.5	44.7	50.8	47.9	46.9	50.6	47.0	51.2	48.3	46.9
C(17)	104.6	97.6	102.1	97.0	94.0	103.9	96.8	104.3	97.8	95.6	93.1
C(18)	61.6	59.6	64.3	59.4	55.9	62.7	59.2	63.1	60.4	58.4	55.6
C(19)	126.0	124.6	124.8	127.7	127.7	135.8	135.3	135.9	135.3	134.2	134.2
C(20)	139.4	138.7	141.8	139.9	143.0	133.9	133.7	134.1	133.2	131.6	*j*
C(21)	52.7	52.3	53.5	53.2	53.2	65.6	65.6	65.8	65.8	52.7	53.5
C=O			169.8	172.2	172.2					172.8	173.6
Me			23.9	23.2	23.2					22.5	22.5

[a] In ppm downfield from Me_4Si. [b] In 5:1 $CDCl_3$–MeOH, $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [c] $\delta(OAc) = 168.5, 20.8$ ppm., [d] In 1:2:1 MeOH-d_4–MeOH–NH_3 (concd), $\delta(Me_4Si) = \delta(MeOH) + 49.5$ ppm. [e] In 1:1 Me_2SO-d_6–D_2O, $\delta(Me_4Si) = \delta(Me_2SO\text{-}d_6) + 39.5$ ppm. [f] $\delta(NMe) = 55.6$ ppm. [g] In 1:1 D_2O–H_2O; the 150.5-ppm peak was taken as reference. [h] $\delta(NMe) = 55.8$ ppm. [i] In 1:1 D_2O–H_2O, dioxane as internal reference, $\delta(Me_4Si) = \delta(C_4H_8O_2) + 66.6$ ppm. [j] Signal not observed.

even more than C(17) of any of the aforementioned 17-epimeric alcohols. The data are explicable most easily on the basis of a 17β-hydroxy configuration within a ring F boat form (**7**) for the anomers **5e** and **6f**, leading to C(18) being shielded



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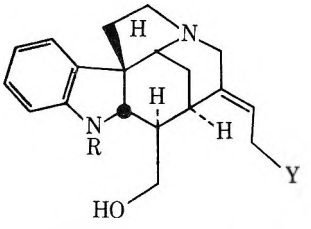


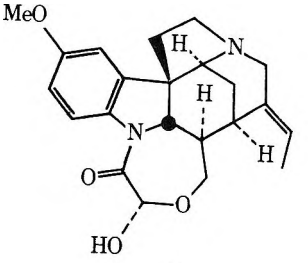
8a, R = H; Y = OH
b, R = Ac; Y = OH
c, R = Y = H
d, R = Ac; Y = H

by the 17β-hydroxy group and the C(15) shift remaining invariant in view of the loss of a γ effect from the hydroxy group being balanced by one from the ring oxygen. The unusual behavior of diaboline (**5d–e**) vis-à-vis the other Wieland Gumlich aldehyde derivatives may reflect the absence of the stabilizing hydrogen bond between the hydroxy group and N_a in **5e**, a small energy difference between chair and boat forms of ring F, and preference of the hemiacetal hydroxy function for axiality in ring compounds, i.e., the equivalent of the "anomeric effect" in the carbohydrate field.[16,17]

The shift assignments for the retuline-like substances **8a–c** and 16-isoretuline (**8d**)[18] parallel those for substances **5–6**. Among the aminomethines the C(3) shift remains unperturbed, whereas the δ value for C(2) shows large variation. Larger residual coupling in the sford spectra distinguished C(18) from the other methylenes of **8a** and **8b**. The differentiation of the aminomethylenes is based on C(5) being expected to show relatively little shift change with respect to compounds **5–6**. The identity of the C(5) and C(21) shifts was confirmed by Birdsall plots on diol **8a**.[10] All shifts of substances **8** are listed in Table V.

A comparison between the shifts of compounds **8** with those of Wieland Gumlich aldehyde (**5a–b**) shows widespread differences, suggestive of conformation changes. The large deshielding of C(2) is most prominent but not explicable fully by assumed modification of the γ effect exerted by the C(17) oxygen. The simultaneous deshielding of C(14) and C(21) points to a change of ring D to that of a chair form, thereby gaining a δ effect for C(2) and C(21) and losing a γ effect by the latter and C(14). This conclusion is corroborated by the ^1H NMR evidence. The olefinic hydrogen of diol **8a** exhibits a well-defined triplet due to vicinal coupling with the hydroxymethyl hydrogens. Thus in contrast to $J_{H(19)\text{-}H(15)} = 2.5$ Hz for strychnine (**1a**), H(19) is relatively free from allylic coupling with H(15) and H(21). Inspection of a model of **8a** shows this to be consistent with a flattened ring D chair. The partial ring D inversion back to that common in bicyclo[3.3.1]nonane systems[19–21] relieves nonbonded interactions between the C(16) and C(20) side chains. The low-field hydrogens of the C(14) and C(21) methylenes are 0.3–0.5 ppm more shielded in the diol (**8a**) than in strychnine (**1a**) or in the Wieland Gumlich aldehyde system (cf. **5c**), wherein they occupy flagpole positions. In view of the change of the hydrogen orientation relative to the double bond and N_b, the shift nonequivalence of the C(14) and C(21) hydrogen pairs is less than 0.25 ppm compared to 0.7–1.0 ppm in **1a** and **5c**. This fact is reflected in the splitting pattern of the sford spectra of compounds **8**, i.e., triplets instead of doublets of doublets.

The alkaloid 10-methoxy-*O*-demethyltsilanine (**9**)[22] is similar to compounds **8**, but contains an additional seven-membered ring G. The lack of shielding of C(2) relative to compounds **8** precludes ring G being in the boat form since in this event the ring oxygen should affect C(2) as it shields C(15) of the diaboline isomer **5e**. This fact, the ca. 10-ppm de-



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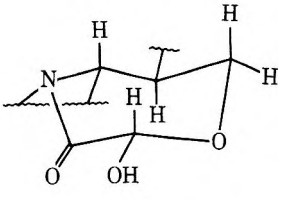

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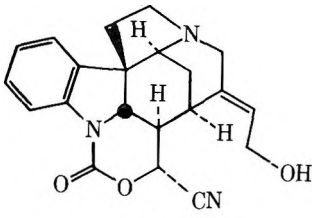
Table V Carbon Shifts of Compounds 8, 9, 11, and 12 [a]

	8a [b]	8a [c]	8b [b,d]	8c [c]	8d [e,f]	9 [e,g]	11 [c,h]	12 [i,j]
C(2)	69.5	69.3	68.3	70.0	70.2	72.5	65.0	70.5
C(3)	61.4	61.4	60.9	61.5	61.6	61.5	60.5	77.2
C(5)	53.1	53.5	53.3	53.5	53.8	53.3	53.0	60.8
C(6)	42.2	43.4	41.4	43.3	42.4	45.0	44.3	38.7
C(7)	52.8	53.0	51.8	52.8	52.3	51.8	50.7	53.6
C(8)	132.3	133.4	138.2	133.5	137.2	137.2	134.2	133.9
C(9)	121.1	121.5	122.1	119.0	122.3	107.3	122.9	124.0
C(10)	118.7	117.1	125.0	117.1	125.0	157.1	124.6	121.3
C(11)	127.4	127.2	127.4	127.1	127.3	112.3	128.1	130.4
C(12)	109.5	108.3	117.0	108.3	117.2	117.0	113.6	109.0
C(13)	148.6	150.0	140.0	150.0	140.4	133.3	139.8	145.6
C(14)	27.4	28.1	27.5	28.0	28.4	27.6	28.3	21.5
C(15)	28.3	28.5	29.9	28.0	31.5	28.8	26.8	30.0
C(16)	48.4	49.1	47.3	49.2	47.3	45.2	46.3	113.4
C(17)	64.0	63.5	62.5	64.0	64.7	74.2	69.0	132.9
C(18)	56.5	56.5	56.7	12.5	12.8	12.6	56.2	57.5
C(19)	125.3	126.0	125.2	121.4	120.2	121.0	128.4	130.4
C(20)	137.4	137.1	138.2	136.2	135.2	132.8	132.8	134.4
C(21)	57.0	57.5	57.9	57.6	58.8	57.1	55.8	65.2

[a] In ppm downfield from Me_4Si. [b] In 7:1 $CDCl_3$–MeOH, $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [c] In Me_2SO-d_6, $\delta(Me_4Si) = \delta(Me_2SO\text{-}d_6) + 39.5$ ppm. [d] δ(NAc) = 170.0, 22.8 ppm. [e] In $CDCl_3$. [f] δ(NAc) = 170.5, 23.0 ppm. [g] δ(OMe) = 55.3, δ(NCOCHOH) = 166.5, 92.0 ppm. [h] $\delta(NCO_2) = 149.1$, δ(CN) = 116.3 ppm. [i] In 1:5 D_2O–MeOH, $\delta(Me_4Si) = \delta(MeOH) + 49.5$ ppm. [j] δ(NMe) = 48.5 ppm.

shielding of C(17), and the β effect of ether formation[9] without an added γ effect indicate the presence of an equatorial and hence α-hydroxy group (cf. **10**). The stereochemistry of this functionality had been unknown heretofore. The chemical shifts of the alkaloid (**9**) are presented in Table V.

Carbon-13 NMR analysis proved useful for the elucidation of the structure of a $C_{21}H_{21}O_3N_3$ byproduct of the degradation of 23-oximinostrychnine (**1b**) to Wieland Gumlich aldehyde (**5a–b**).[23] The compound reveals carbon shifts characteristic of the retuline-like substances **8**. Small upfield shifts relative to **8a** are noted at carbons 2, 7, 15, and 16, as well as deshielding of C(17), and indicate structure changes near carbons 2 and 16. The signals at 149.0 and 116.3 ppm, in conjunction with the infrared absorption bands of 1740 and 2160 cm^{-1}, suggest the presence of carbamate and nitrile functions, respectively. On the basis of these facts and the chemical origin of the substance, structure **11** (as yet without C(17) stereochemical detail) can be proposed for the compound. A high-resolution mass spectrum reveals peaks with *m/e* 363 (M^+), 345 ($M - H_2O$), and 332 ($M - CH_2CH$), characteristic



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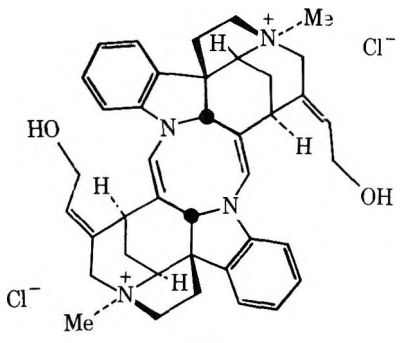


12

of the presence of a ring linking N_a and C(16).[24] The ^1H NMR spectrum shows an olefinic hydrogen without significant allylic coupling, in accord with the presence of a hydroxyethylidene side chain attached to a flattened ring D chair (cf. Tables II and III). The vicinal coupling of 12 Hz exhibited in the 5.15-ppm H(17) signal indicates the C(17) stereochemistry as depicted in formula **11**. All carbon shifts of the hexacycle are listed in Table V.

The symmetrical, "dimeric" alkaloid toxiferine-I (**12**) has features in common with the retuline-like compounds **8**, permitting its shift assignment to be based on the latter. The olefinic methine shifts are designated from Birdsall plots.[10] An interesting facet of the ^{13}C NMR spectrum is the very high-field position of the C(14) signal. This must be due to a γ effect from the N_b-methyl group (even on consideration of the solvent shifts[6]) and is in sharp contrast to the C(14) shift of the N_b-metho salts **2b** and **6a–d** whose ring D is in the boat form. The γ effect is reciprocated, the methyl group being shielded strongly relative to the substances possessing a ring D boat.

All the alkaloids examined thus far possess a C(19)–C(20) double bond. Its saturation makes the allocation of the carbon signals more difficult than heretofore. Hence much use is made of correlations with the hydrogen resonances presented in Table II. Moreover, the latter show that the 19,20-dihydro compounds of the present study fall into two groups. 3-Deoxyisostrychnosplendine (**13a**),[25] deacetylstrychnospermine (**13b**),[25] and 16β-methyltubilfolidine (**14**)[26] are characterized by large chemical-shift nonequivalence of the geminal C(21) hydrogens. Contrastingly, these hydrogens in dihydrostrychnine (**15**) are shielded nearly equally. The carbon shifts of compounds **13–15** are illustrated in Table VI.

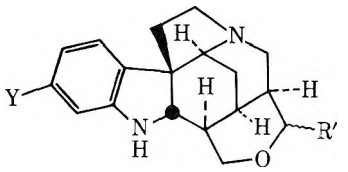
The published 220-MHz ^1H NMR spectra of **13a** and **13b** provide evidence for a cis fusion of rings D and F, both in the chair form.[25] Ring D of **14** is similarly in the chair conformation. In each of these compounds H(20α) is anti ($^3J_{HH}$ = 12 Hz) to the more shielded H(21) and gauche ($^3J_{HH}$ = 5–6 Hz) to the less shielded C(21) hydrogen. The high-field H(21) thus occupies an axial position on a chair piperidine and is shielded strongly (δ = 2.2–2.5 ppm), being anti to the nitrogen lone-electron pair. A chair ring F is evident also from the ^{13}C NMR data. The axial α-methyl group of **13a** is gauche to C(15) and C(17), these carbons being shielded in **13a** relative to **13c**.

Table VI. Carbon Shifts of Compounds 13–15 [a]

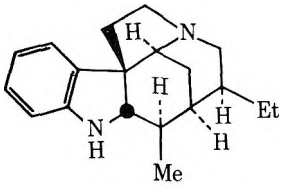
	13a	13c	13d[b,c]	13d[c,d]	13d[c,e]	14	15[f]
C(2)	68.2	68.4	69.2	70.3	70.0	75.0	67.6
C(3)	61.3	61.5	60.7	60.0	60.8	62.3	62.5
C(5)	54.5	54.8	54.2	54.2	54.5	54.0	53.7
C(6)	44.0	44.0	42.4	41.6	42.5	43.3	46.4
C(7)	53.3	g	50.7	51.9	51.8	54.0	51.4
C(8)	134.1	134.1	130.9	128.5	129.8	133.8	134.9
C(9)	121.9	121.9	122.3	121.4	121.8	121.7	121.7
C(10)	119.2	119.2	107.9	110.7	109.8	118.5	124.2
C(11)	127.6	127.6	158.5	158.7	159.1	127.2	127.9
C(12)	109.6	109.6	104.4	104.8	105.0	109.0	115.5
C(13)	149.3	149.3	141.6	141.9	142.3	149.0	140.6
C(14)	27.2	27.4	26.3	26.2	26.7	32.1	31.3
C(15)	23.7	30.7	30.8	31.3	31.8	34.9	30.1
C(16)	43.2	43.0	40.6	40.4	41.2	43.0[h]	53.3
C(17)	63.0	71.5	71.0	69.8	70.7	19.3	76.4
C(18)	16.1	17.6	17.8	17.5	17.5	13.0	68.4
C(19)	71.8	76.1	75.6	76.4	76.2	27.2	32.6
C(20)	37.2	37.2	37.1	37.0	37.7	43.5[h]	34.9
C(21)	53.5	48.8	48.5	49.3	49.3	55.9	57.8
C=O			169.1	168.9	168.7		
Me			23.8	23.4	23.2		

[a] In ppm downfield from Me_4Si, $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] Major rotamer at −26 °C. [c] $\delta(OMe) = 55.4$ ppm. [d] Minor rotamer at −26 °C. [e] At 55 °C. [f] δ(C-22) = 169.3, δ(C-23) = 41.1 ppm. [g] Signal masked. [h] Signals may be interchanged.

Similarly, the equatorial β-methyl group of **13c** is gauche to C(21), the latter being shielded in **13c** relative to **13a.** All other shifts for these two 19-epimers are practically identical.



13a, R = Y = H; R′ = α-Me
b, R = H; R′ = β-Me; Y = OMe
c, R = Y = H; R′ = β-Me
d, R = Ac; R′ = β-Me; Y = OMe



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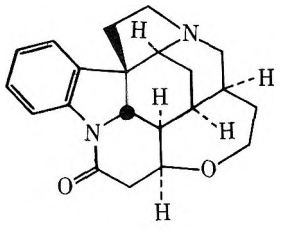

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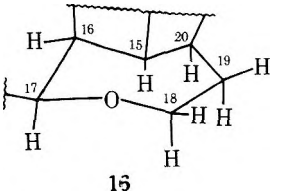
In the absence of an ether bridge and the removal of the gauche interaction between the oxygen and C(2) and C(21) in 16β-methyltubifolidine (**14**),[26] these carbons are deshielded strongly in **14** relative to **13c,** whereas C(15) is deshielded less strongly. Such comparisons with **13c** but not with **13a** being possible indicate that the preferred rotamer for the ethyl side chain of **14** is the one whose methyl group is gauche to C(21) and anti to C(15). The interaction of the ether oxygen with the positions gauche to it are observed also in the ^1H NMR spectra, wherein H(2) and H(21β) of **13a** and **13b** are deshielded by 0.2–0.5 ppm relative to **14.** The ^1H and ^{13}C NMR data of dihydrostrychnine (**15**) establish the conformation of its seven-membered ring F as in formula **16.** This arrangement is indicated by the vicinal coupling between H(16) and H(17) and between the C(18) and C(19) hydrogens (see Table III). The gauche relationship between the ether oxygen and C(2) is shown by the similarity of this carbon's shifts in **15** and compounds **13,** wherein such interaction exists. The nearly equivalent C(15) shifts of **15** and **13c** favor a chair conformation for the seven-membered ring, which also excludes a nonbonded interaction between carbons 18 and 21. The chemical shift of the latter is similar to that of C(21) of **14,** wherein a gauche interaction with C(18) does exist (vide supra). Other anomalies include C(14) being less shielded in **15** than in **13,** the C(21) hydrogens being equivalent (vide supra), and H(14β) being deshielded. All these facts are explicable on the assumption of a lessening of the 1,3-diaxial interaction between C(2) and C(21) and the flattening of ring D to form a intermediate between a chair and a boat. A ring D chair would be disfavored since it involves eclipsing of the C(19) and C(20) substituents.



16

Being the N_a-acetyl derivative of **13b,** strychnospermine (**13d**) reveals a spectrum at 55 °C that is easily interpretable by comparison with that of **13b.** At room temperature, however, some signals begin to broaden, and at −26 °C two sets of signals are apparent. Since the alkaloid contains no epimerizable centers such as Wieland Gumlich aldehyde (**5a–b**) and its derivatives (**5–6**) and since the Δδ values between the two signal sets are too small to imply any significant conformational change, the two groups of signals therefore must reflect the presence of two possible rotamers of the acetyl group.[27] Thus, the rotation barrier of the amide linkage of strychnospermine (**13d**) is higher than that of the acetamides of the Wieland Gumlich aldehyde series, **5c, 5d–e,** and **6e–f.**[28]

Registry No.—**1a,** 57-24-9; **1b,** 24180-59-4; **1c,** 357-57-3; **2a,** 1421-86-9; **2b,** 2131-76-2; **2c,** 7248-28-4; **2d,** 5786-96-9; **5c,** 2871-28-5; **8a,** 900-98-1; **11,** 64754-36-5; **12,** 6696-58-8; **13a,** 22153-1305; **13b,** 6516-44-5; **14,** 34174-79-3; **15,** 15006-14-1; **5a,** 466-85-3; **5b,** 38570-01-3; **5d,** 64783-88-6; **5e,** 509-40-0; **6a,** 64754-37-6; **6b,** 64754-38-7; **6c,** 24180-76-5; **6d,** 64754-39-8; **6e,** 64783-89-7; **6f,** 11032-42-1; **8b,**

13013-60-0; **8c**, 13941-27-0; **8d**, 10388-62-2; **9**, 29028-14-6; **13c**, 22153-12-4; **13d**, 509-45-5.

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Carbon-13 Magnetic Resonance of Cotton Terpenoids: Carbon–Proton Long-Range Couplings

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The ^{13}C NMR spectra of five sesquiterpenoids and three C_{25} terpenoids found in *Gossypium hirsutum* and *G. Barbadense* cottons have been analyzed. Chemical shift assignments for the aryl and carbonyl carbons were made using long-range carbon–proton couplings and single frequency irradiation before and after deuterium exchange. Large deuterium isotope shifts are observed for the exchange of the hydroxy proton that is syn and strongly hydrogen bonded to the aldehyde function.

Some primitive varieties of cotton are more resistant than cultivated cottons toward the cotton bollworm and tobacco budworm (*Heliothis* spp.).[1] This greater resistance has been correlated with higher concentrations of several terpenoids, such as hemigossypolone (**1a**) and its 7-methyl ether derivative (**1b**), and the C_{25} terpenoids, such as heliocides H_1 (**3a**), B_1 (**3b**), and H_2 (**3c**).[2,3] The structures of hemigossypolone and **3c** were determined by mass, proton, and carbon-13 spectra. Compound **3c** was synthesized from hemigossypolone and its stereochemistry determined by x-ray crystal analysis.[4,5] The structures of **3a** and **3b** were based upon syntheses and carbon-13 spectra.[6–8] The carbon-13 spectra were essential in assigning the structures of several of the heliocides. However, it was not possible to make unambiguous shift assignments for carbons 2, 6, 7, or 8 or to distinguish between the bridgehead carbons 9 and 10 or the carbonyl carbons 1 and 4 with proton-decoupled spectra. It was also important to study the carbon-13 spectra of the sesquiterpenoids hemigossypol (**2a**), methoxyhemigossypol (**2b**) (the biosynthetic precursors of **1a** and **1b**[9]), and gossypol (**2c**) because of their biosynthetic relationship to the heliocides and to assist in the analysis of new, structurally related terpenoids.

One-bond couplings and off-resonance decoupling are of little value in uniquely assigning the aromatic and carbonyl carbons because most are quaternary. Shift assignments based upon additivity relationships also fail because of the many ortho interactions.[10] However, proton-decoupled carbon-13 chemical shifts are useful in the structural analysis of polysubstituted aromatic natural products once shift assignment ambiguities are resolved, and chemical shift changes are correlated with substituent changes.[6,7] This is especially important when the quantity isolated from natural sources precludes the use of coupled spectra as an assignment technique.[6]

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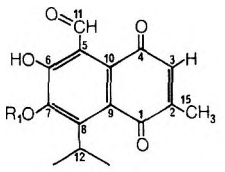
Table I. Carbons 2, 3, and 5: Chemical Shifts and Proton–Carbon Couplings[a]

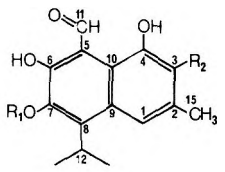
Compd	Registry no.	C-2 Shift, δ	C-2 $^2J_{H15}$	C-3 Shift, δ	C-3 $^1J_{H3}$	C-3 $^3J_{H1}$	C-3 $^3J_{H15}$	C-5 Shift, δ	C-5 $^2J_{H11}$	C-5 $^3J_{OH6}$
1a	35688-47-2	147.9	6.7	132.4	166.5		5.9	114.9	20.3	*b*
b	35839-49-7	149.3	6.3	133.4	166.5		5.4	117.0	19.6	4.2
2a	40817-07-0	132.8	6.0	111.7	156.1	7.3	4.8	110.9	17.8	*b*
b	50399-95-6	132.7	6.0	113.1	156.2	7.5	4.7	112.4	18.2	*c*
c	303-45-7	132.9	5.5	116.8		8.4	4.2	111.1	17.9	*b*
3a	64872-64-6	49.0	*d*	57.3	*d*	*d*	*d*	114.1	20.0	*b*
b	64872-35-1	49.0	*d*	56.9	*d*	*d*	*d*	115.3	19.8	5.2
c	63525-06-4	49.3	*d*	54.8	*d*	*d*	*d*	115.2	19.8	*b*

[a] Chemical shifts are in ppm downfield from Me_4Si using central resonance of $CDCl_3$ as an internal reference; solvent for **1b, 3a, 3b,** and **3c** was deuteriochloroform and solvent for **1a, 2a, 2b,** and **2c** was acetone; coupling constants are in Hz (±0.5 Hz); u, unresolved multiplet. [b] Coupling to C-6 hydroxy proton not observed. [c] Coupling to C-6 hydroxy proton not observed because coupled spectrum was obtained in acetone. [d] Not determined.



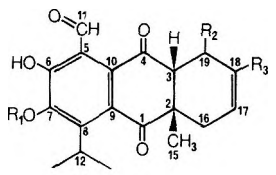
1

a: R_1 = H
b: R_1 = CH_3



2

a: R_1, R_2 = H
b: R_1 = CH_3, R_2 = H
c: R_1 = H, R_2 = γ_2



3

a: R_1 = H, R_2 = $CH_2CH=C(CH_3)_2$, R_3 = CH_3
b: R_1 = CH_3, R_2 = $CH_2CH=C(CH_3)_2$, R_3 = CH_3
c: R_1, R_2 = H, R_3 = $CH_2CH_2CH=C(CH_3)_2$

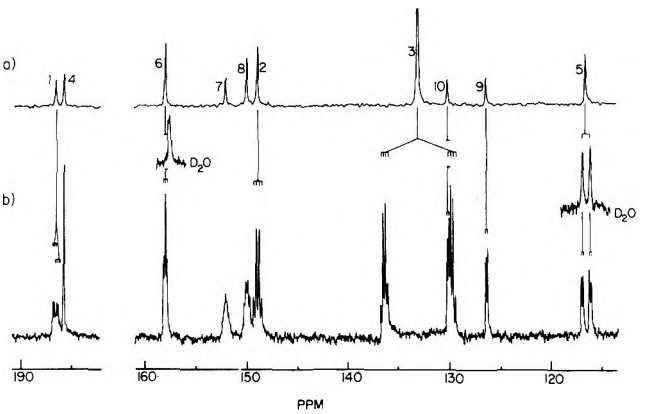


Figure 1. Carbon-13 spectra of the carbonyl and aryl regions of 7-methoxyhemigossypolone (**1b**): (a) proton-decoupled spectrum before deuterium exchange; (b) proton-coupled spectrum before and after deuterium exchange. Upfield change in carbon 6 after deuterium exchange is due to deuterium isotope shift.

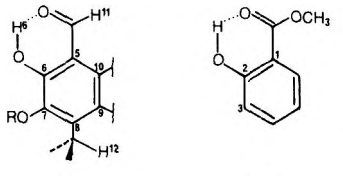
Recent reports for phenols,[11] courmarins,[12,13] flavanones, and flavones[14] have shown the usefulness of long-range proton–carbon couplings in the assignment of quaternary carbon resonances. We report here a detailed analysis of the long-range couplings for hemigossypolone (**1a**), hemigossypolone 7-methyl ether (**1b**), hemigossypol (**2a**), 7-methoxyhemigossypol (**2b**), and gossypol (**2c**). Also, the naturally occuring C_{25} terpenoids **3a** (derived from ocimene and hemigossypolone), **3b** (derived from ocimene and 7-methoxyhemigossypolone), and **3c** (derived from myrcene and hemigossypolone) have been studied. Analysis of the long-range couplings before and after exchange with deuterium oxide combined with single frequency irradiation of various hydrogens allows unequivocal assignments for all quaternary carbons. Further, these long-range coupling patterns give insight into stereochemical features of these molecules in solution.

Results and Discussion

Chemical Shift Assignments for Carbons 2, 3, and 5. In all the sesquiterpenoids, carbon 2 is easily assigned in the proton-coupled spectra because it is a well-resolved quartet due to two-bond coupling to the C-15 methyl hydrogens. In the C_{25} terpenoids, carbon 2 is the only quaternary carbon in the alkyl region (Table I).

Carbon 3 for **1a** and **1b** shows a large one-bond coupling to the directly attached hydrogen and a three-bond coupling to the C-15 methyl hydrogens and is therefore also easily assigned. In **2a** and **2b**, two one-bond doublets are present because of hydrogens at carbons 1 and 3. Carbon 3 is assigned to the upfield doublet because greater shielding is experienced by the carbon ortho to the C-4 hydroxy. For gossypol (**2c**), carbon 3 is a quaternary carbon at δ 116.8. For **3a, 3b,** and **3c,** carbon 3 is a doublet in the alkyl region.

All the compounds displayed an upfield aromatic resonance between δ 110 and 117, assigned to carbon 5 because of the large two-bond coupling to H-11. The shielding of these resonances compared to carbon 1 of benzaldehyde (δ 137.7) is due to intramolecular hydrogen bonding of the aldehyde. A further splitting of the C-5 resonance is observed for the 7-methoxy compounds, **1b** and **3b,** when dissolved in deuteriochloroform. Figure 1 presents the decoupled and coupled spectra of the aryl and carbonyl regions for **1b** which shows this further coupling at carbon 5. The smaller coupling disappears upon dueterium exchange. Since **1b** and **3b** have only one exchangeable proton (R_1 = CH_3) this fine structure must be due to three-bond coupling between the C-6 hydroxy proton and carbon 5 (**4**). The magnitude of this coupling indicates that



4 **5** **6**

the stereochemistry of the C-6 hydroxy function is syn to the aldehyde and strongly hydrogen bonded to it.[15] Similar syn couplings have been observed between the hydroxy proton and C-1 in methyl salicylate (**5**, $^3J_{C1-OH^2}$ = 4.4 Hz)[11] and between the 5-hydroxy proton and C-4 in 5-hydroxyflavones and

Table II. Carbons 6, 7, and 8: Chemical Shifts and Proton-Carbon Couplings[a]

Compd	C-6 Shift, δ	C-6 $^2J_{OH^3}$	C-6 $^3J_{H^{11}}$	C-7 Shift, δ	C-7 $^3J_{H^{12}}$	C-7 $^4J_{H^{11}}$	C-8 Shift, δ
1a	151.3	*b*	4.2	148.5	6.7	2.7	139.9
b	158.4	4.4	4.4	152.4	u	2.5	150.4
2a	154.7	*b*	5.0	142.0	5.8	2.9	133.2
b	159.1	*c*	4.4	145.5	u	u	143.3
c	155.0	*b*	4.2	142.5	6.0	2.9	132.9
3a	152.5	*b*	4.1	148.3	5.9	2.4	140.3
b	158.8	4.2	4.2	151.9	u	u	149.7
c	152.2	*b*	3.9	148.9	~7	~2	140.0

[a] Chemical shifts are in ppm downfield from Me_4Si using central resonance of $CDCl_3$ as an internal reference; solvent for **1b, 3a, 3b,** and **3c** was deuteriochloroform and solvent for **1a, 2a, 2b,** and **2c** was acetone; coupling constants are in Hz (±0.5 Hz); u, unresolved multiplet. [b] Coupling to C-6 hydroxy proton not observed. [c] Coupling to C-6 hydroxy proton not observed because coupled spectrum was obtained in acetone.

5-hydroxyflavanones (**6**, $^3J_{C^4\text{-}OH^5}$ = 4.5 Hz).[14a] The anti three-bond coupling of a hydroxy proton is usually larger (e.g., **5**, $^3J_{C^3\text{-}OH^2}$ = 7.5 Hz).[11] The anti coupling to carbon 7 was not observed for **1b** or **3b** because carbon 7 is an unresolved multiplet due to coupling to other hydrogens.

None of the other compounds displayed this three-bond coupling of the C-6 hydroxy proton to carbon 5. For this coupling to be observed, intramolecular and intermolecular proton exchange must be slow on the carbon-13 time scale. For the compounds studied in deuteriochloroform (**3a** and **3c**), absence of this coupling implies an increase in the rate of proton exchange, perhaps because of the presence of two hydroxy functions. For compounds with low solubility in deuteriochloroform (**1a, 2a, 2b,** and **2c**), coupled spectra were obtained in acetone. In this more polar solvent, the rate of exchange is expected to be more rapid and coupling of carbon 5 to the C-6 hydroxy proton is lost.

Chemical Shift Assignments for Carbons 6, 7, and 8. The resonances due to the oxygen-substituted carbons 6 and 7 and the isopropyl-substituted carbon 8 were the most difficult to distinguish from one another. These resonances are expected between δ 130 and 160. The long-range couplings of carbons 6, 7, and 8 and the chemical shift assignments based upon these couplings are presented in Table II.

The coupled spectrum of **1b** shows four resonances between δ 149 and 159 (Figure 1b). The clearly resolved quartet at δ 149.3 has already been assigned to carbon 2. Carbon 6 may be distinguished from carbons 7 and 8 in **1b** and the other 7-methoxy compounds (**2b** and **3b**) because of long-range coupling to the hydroxy and aldehydic hydrogens. The resonance at δ 158.4 is a "triplet" which becomes a doublet and undergoes an isotope shift upon deuterium exchange. Taken together with the concurrent loss of coupling at carbon 5 upon deuterium exchange, the triplet must be due to two-bond coupling to OH-6 and three-bond coupling to H-11 of the same magnitude.

The two remaining downfield aryl resonances at δ 152.4 and 150.4 must be due to carbons 7 and 8. These unresolved multiplets can not be unequivocally assigned based upon their long-range couplings alone. Simultaneous irradiation of H-12 and the 7-methoxy hydrogens (^1H NMR δ 4.03 and 3.98, respectively) after deuterium exchange causes the downfield resonance to collapse to a doublet ($^4J_{C^7\text{-}H^{11}}$ = 2.5 Hz), while the upfield resonance remains a multiplet due to coupling to the isopropyl methyls. Therefore, the downfield resonance is assigned to carbon 7 and the upfield resonance to carbon 8.

Figure 2 shows the coupled, decoupled, and single frequency decoupled spectra for hemigossypolone (**1a**), typical of the coupling patterns observed after deuterium exchange for compounds with hydroxy groups at both carbons 6 and 7. In the coupled spectrum (Figure 2b), the furthest downfield aryl

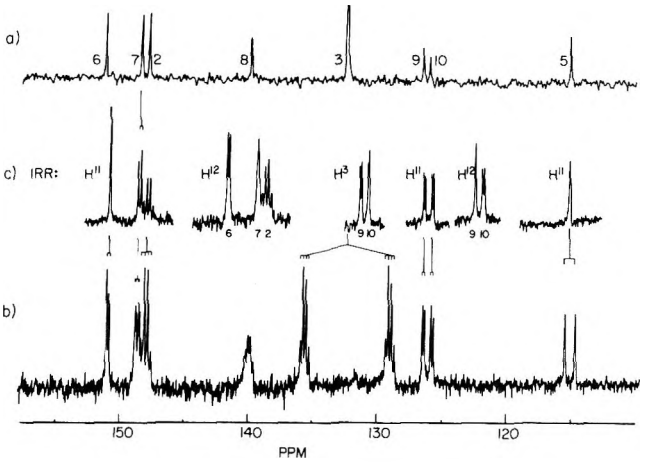
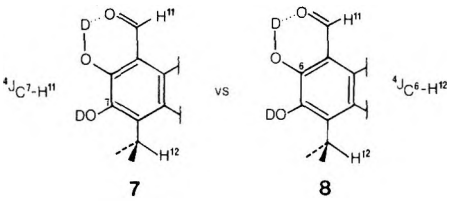


Figure 2. Carbon-13 spectra of the aryl region of hemigossypolone (**1a**): (a) proton-decoupled spectrum before deuterium exchange; (b) proton-coupled spectrum after deuterium exchange (upfield change in carbon 6 is due to deuterium isotope shift); (c) proton-coupled spectra with single frequency irradiation of various hydrogens.

resonance is a doublet due to coupling to H-11 and is therefore assigned to carbon 6. The sharp quartet at δ 147.9 is assigned to carbon 2. The resonance between carbons 2 and 6 is a doublet of doublets and is assigned to carbon 7. This coupling pattern is due to a larger three-bond coupling to H-12 and a smaller four-bond coupling to H-11 (**7**). Similar patterns were found for carbon 7 in the deuterium exchanged spectra of **2a,**



2c, and **3a** (Figures 3, 4, and 5). For **3c,** the four-bond coupling was not resolved and only a broadened doublet was observed.

It might be argued that the assignments of carbons 6 and 7 for **1a** and for the other compounds with hydroxy functions at 6 and 7 should be reversed. If this were the case, carbon 6 would be a doublet of doublets due to three-bond coupling to H-11 and four-bond coupling to H-12 (**8**). To eliminate this possibility, H-11 and H-12 were individually irradiated. Irradiation of H-11 removed the three-bond coupling to carbon 6, the two-bond coupling to carbon 5, and only the smaller four-bond coupling to the doublet of doublets assigned to carbon 7 (Figure 2c). Irradiation of the isopropyl hydrogen,

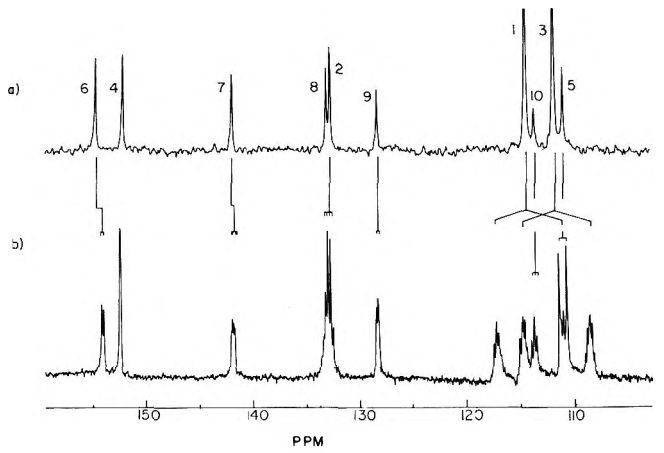


Figure 3. Carbon-13 spectra of the aryl region of hemigossypol (**2a**): (a) proton-decoupled spectrum before deuterium exchange; (b) proton-coupled spectrum after deuterium exchange. Upfield change in carbons 6 and 7 is due to deuterium isotope shift.

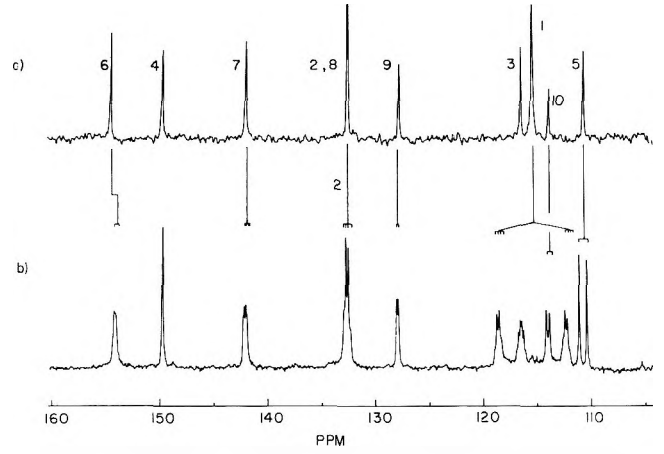


Figure 4. Carbon-13 spectra of the aryl region of gossypol (**2c**): (a) proton-decoupled spectrum before deuterium exchange; (b) proton-coupled spectrum after deuterium exchange. Upfield change in carbon 6 is due to deuterium isotope shift.

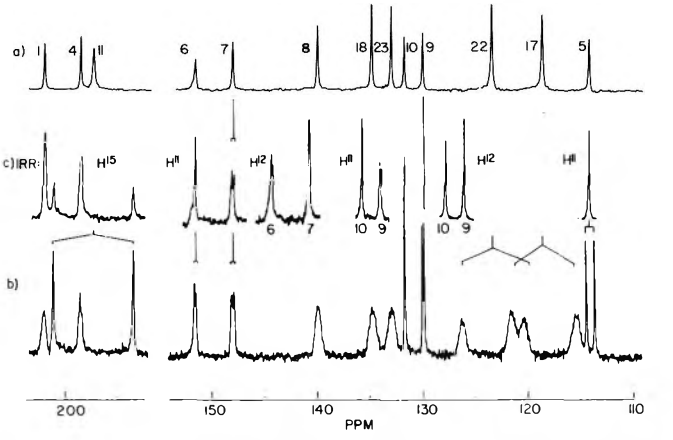


Figure 5. Carbon-13 spectra of the carbonyl, aryl, and alkenyl regions of heliocide H_1 (**3a**): (a) proton-decoupled spectrum after deuterium exchange; (b) proton-coupled spectrum after deuterium exchange; (c) proton-coupled spectra with single frequency irradiation of various hydrogens. Resonances numbered 17, 18, 22, and 23 are alkenyl carbons in the cyclohexenyl ring and in the R_2 side chain.

Table III. Deuterium Isotope Shifts[a]

Compd	C-6	C-7	C-5	C-8	Other
1a	−8.3	+4.3	+4.3	*b*	
b	−8.4	−1.5	*b*	*b*	
2a	−17.9	−5.6	*b*	*c*	+3.8 (C-4)
b	−19.6	−5.9	*b*	+2.4	+2.3 (C-4)
c	−17.9	−5.3	−4.0	−3.7	−7.5 (C-4)
3a	−12.6	−3.4	*b*	−2.3	
b	−8.9	−1.8	*b*	+1.9	
c	−10.7	−5.3	*b*	−4.1	
Salicyl-aldehyde[d]	−6.9	−3.9	*c*	−2.8	

[a] Shift changes are in Hz; negative values are upfield changes. [b] Shift change is within experimental error (±1.0 Hz). [c] Unobserved because of overlap with another resonance. [d] Salicylaldehyde was numbered to correspond to other compounds.

H-12, decoupled the larger three-bond coupling to carbon 7 and did not affect carbons 5 or 6.

The distinction between carbons 6 and 7 is confirmed by the isotope shifts that are observed upon deuterium exchange (Table III). The resonances assigned to carbon 6 consistently show a large shielding when deuterium replaces protium. Previously reported deuterium isotope shifts have been approximately 6 Hz for directly bonded deuterium and approximately 3 Hz for deuterium two bonds away.[16] Therefore, the shielding through two bonds at carbon 6 upon exchange is unusually large (8–20 Hz). These unusually large isotope shifts at carbon 6 are undoubtedly due to the exchange of a strongly hydrogen-bonded proton.[17] The resonances assigned to carbon 7 show smaller shieldings even in those cases where a proton on the C-7 hydroxy is being exchanged (**2a, 2c, 3a,** and **3c**). For **1a,** carbons 7 and 5 are deshielded upon exchange. The reason for this effect is unknown. At carbons further removed from the site(s) of exchange the effect is negligible.

It is important to note that carbon 7 in the methoxy compounds, **1b, 2b,** and **3b,** is consistently *upfield* from the C-6 hydroxy carbon (Table II). Simple additive shift relationships predict just the opposite, that the methoxy carbon should be *downfield* by approximately 6 ppm. However, this argument does not take into account the dominant effect which must account for the chemical shift relationship between these two oxygen-substituted vicinal carbons: the strong intramolecular hydrogen bonding between the C-6 hydroxy proton and the aldehyde oxygen (**4**). This influence is deshielding at carbon 6 if one compares phenol to salicylaldehyde.

The remaining downfield aryl resonance in the coupled spectrum of **1a** at δ 139.9 must be assigned to carbon 8 (Figure 2b). The shape of this resonance (a "broadened quartet") may be qualitatively analyzed as a doublet of septets where $^2J_{H12} > {}^3J_{H13}$. The resonance at δ 150.4 in the coupled spectrum of **1b** assigned to carbon 8 has this same broadened quartet shape (Figure 1b). Similarly shaped resonances in the coupled spectra of the other compounds allow the qualitative assignment of carbon 8.

Figures 3 and 4 present the decoupled and deuterium exchanged, coupled spectra for hemigossypol (**2a**) and gossypol (**2c**). These spectra are typical of the patterns observed for compounds containing two aromatic rings and an additional hydroxy substituent at carbon 4. This additional oxygen-substituted carbon appears as a sharp singlet after deuterium exchange and is not appreciably coupled to the hydrogens at carbon 1 and 3 or to the methyl group at carbon 2.

Chemical Shift Assignments for the Bridgehead Carbons 9 and 10. Carbons 9 and 10 are most easily distinguished in the compounds with two aromatic rings, **2a, 2b,** and **2c** (Figures 3 and 4, Table IV). In these compounds the principle chemical shift influence is the hydroxy group at carbon 4. This substituent is ortho and strongly shields carbon 10 compared to 9. Carbon 10 appears upfield as a triplet in the coupled

Table IV. Carbons 9 and 10: Chemical Shifts and Proton–Carbon Couplings[a]

Compd	C-9 Shift, δ	C-9 $^3J_{H12}$	C-10 Shift, δ	C-10 $^3J_{H3}$	C-10 $^3J_{H1}$
1a	126.4	4.1	125.9	4.9	
b	126.7	3.6	130.5	4.7	
2a	128.3	3.2	113.6	~6	~6
b	127.9	3.8	116.3	*b*	*b*
c	128.1	3.1	114.3		6.3
3a	130.0	4.2	131.8	<1	
b	129.0	4.5	135.9	<1	
c	131.5	4.5	129.1	<1	

[a] Chemical shifts are in ppm downfield from Me_4Si using central resonance of $CDCl_3$ as an internal reference; solvent for **1b, 3a, 3b,** and **3c** was deuteriochloroform and solvent for **1a, 2a, 2b,** and **2c** was acetone; coupling constants are in Hz (±0.5 Hz). [b] Overlap with C-3 resonance.

spectrum of hemigossypol (Figure 3b). This triplet is due to three-bond couplings to H-1 and H-3. In gossypol, this resonance becomes a doublet because of the absence of a hydrogen at carbon 3 (Figure 4b). It is important to note that carbon 10 is *not* coupled to the aldehydic hydrogen, H-11.

In the sesquiterpenoids **1a** and **1b** and in the C_{25} terpenoids **3a, 3b,** and **3c,** carbons 9 and 10 differ by 6 ppm or less and are more difficult to distinguish. For **1a,** irradiation of H-3 collapses the upfield doublet, and this resonance is therefore assigned to carbon 10 (Figure 2c). Irradiation of H-12 collapses the downfield doublet due to carbon 9. Similarly, carbon 10 is coupled to H-3 and carbon 9 to H-12 in **1b,** but their relative chemical shift positions are reversed, carbon 10 being downfield of carbon 9.

In the C_{25} terpenoids, carbon 10 is an uncoupled sharp singlet because the hydrogen at carbon 3 is now attached to an sp^3 rather than an sp^2 carbon. Carbon 9 is a doublet due to coupling to H-12 (Figure 5c). In all the compounds studied, irradiation of H-11 has no effect on the multiplicity of the resonances due to carbons 9 and 10. Thus, the aldehydic hydrogen is *not* appreciably coupled to either of these carbons.

It has been reported that three-bond carbon–proton couplings through sp^2 carbons are stereochemically dependent, with anti couplings consistently larger than syn couplings.[18] For example, in methyl salicylate the anti coupling of the hydroxy proton to carbon 3 is larger than the syn coupling to carbon 1 (**5,** 7.5 Hz vs. 4.4 Hz).[11] Similarly, the anti three-bond couplings of hydroxy protons in flavanoids and coumarins are 7–10 Hz while the corresponding syn couplings are 4–6 Hz.[12,14] In the present work, a similar stereochemical dependence has been found for the couplings of the aldehydic hydrogen to carbons 6 and 10. The anti couplings to carbon 6 range from 3.9 to 5.0 Hz (Table II, C-6), while no syn coupling is observed to carbon 10. This further confirms the syn stereochemistry of the aldehyde and the C-6 hydroxy function (**4**).[15]

Aryl Carbon Chemical Shift Changes. With the chemical shifts of all the aryl carbons firmly established through long-range couplings and deuterium exchange, it is worthwhile to compare the changes that occur in going from the 6,7-dihydroxy compounds (**1a, 2a,** and **3a**) to the corresponding 6-hydroxy-7-methoxy compounds (**1b, 2b,** and **3b**). Similar Δδ values are observed at all carbons for the three comparisons that may be made (Table V). The chemical shift changes observed at carbon 7 are close to the values predicted if one compares phenol to anisole. However, the carbons ortho and para to carbon 7 (carbons 6, 8, and 10) experience deshieldings upon change from hydroxy to methoxy. The reason for these deshieldings is not clear. They may be caused by steric interaction between the methoxy methyl and the isopropyl group in **1b, 2b,** and **3b.** This interaction may lead to a decrease in electron donation by the oxygen into the aryl ring and less shielding than expected, particularly at the para and ortho carbons, when compared to the shift changes observed in going from phenol to anisole. Whatever the exact explanation, it is important to be aware of these deshieldings because the change from hydroxy to methoxy is a frequent variation in structure in the terpenoids found in cotton.

Table V. Aryl Carbon Chemical Shift Changes: 7-Hydroxy → 7-Methoxy[a]

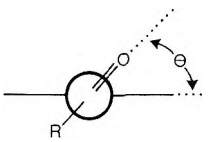
	C-5	C-6	C-7	C-8	C-9	C-10
Δδ, **1a → 1b**	+1.4	+6.4	+3.3	+8.9	−0.8	+3.4
Δδ, **2a → 2b**	+1.5	+4.8	+3.8	+10.6	−0.4	+2.7
Δδ, **3a → 3b**	+1.2	+6.6	+3.6	+9.4	−1.0	+4.1
Δδ, phenol → anisole[b]	−0.2	−1.3	+5.3	−1.3	−0.2	−0.3

[a] All chemical shift changes were determined from proton-decoupled spectra for compounds dissolved in deuteriochloroform; negative values are upfield changes. [b] Phenol and anisole were numbered to correspond to other compounds.

Chemical Shift Assignments for the Carbonyl Carbons 1, 4, and 11. Carbon 11 is easily assigned due to its large one-bond coupling to H-11 (Table VI). The quinoid carbonyls in **1a** and **1b** are distinguished by the three-bond couplings of carbon 1 to H-3 and H-15 (Figure 1b). Carbonyl carbon 4 is not appreciably coupled to either H-3 or H-15 and appears as a sharp singlet.

In **3a, 3b,** and **3c,** carbons 1 and 4 are no longer conjugated quinoid carbons and as a result are deshielded by approximately 20 ppm compared to the carbonyls of **1a** and **1b.** Further, since carbons 2 and 3 are now tetrahedral carbons, long-range coupling to H-3 and H-15 gives unresolved multiplets rather than well-defined coupling patterns (Figure 5b). The relative intensities of the resonances due to carbons 1 and 4 in the coupled spectrum allow qualitative chemical shift assignment. The downfield resonance at δ 202.3 is broader than the upfield resonance at δ 198.8 and may be tentatively assigned to carbon 1. It is expected that carbon 1 will be appreciably coupled through three bonds to the hydrogens on the angular methyl group and to H-3, resulting in a broader unresolved multiplet. This assignment is confirmed through the irradiation of the methyl hydrogens (Figure 5c). Although the resonance assigned to carbon 1 is not completely collapsed because it is still coupled to H-3, it is considerably narrower and grows in relative intensity compared to the resonance assigned to carbon 4.

The Stereochemistry of the Cyclohexadione Ring in 3a, 3b, and 3c. The angle of twist, θ, that the carbonyl group of a phenyl ketone makes with the aromatic ring (**9**) may be calculated from eq 1, where δ_c is the carbon-13 chemical shift



9

$$\cos^2\theta = 216.0 - \delta_c/20 \quad (1)$$

of the carbonyl carbon.[19,20] The angles calculated by this empirical method have been compared to those derived from ultraviolet and dipole moment studies of substituted phenyl ketones. The x-ray crystal structure of **3c** showed that the carbonyl groups lie above and below the plane of the aromatic ring. From these data it was found that carbons 1 and 4 make angles of 23.9 and 33.2° with respect to the aromatic ring.[5] Based on these angles, the calculated chemical shifts of car-

Table VI. Carbons 1, 4, and 11: Chemical Shifts and Proton–Carbon Couplings[a]

Compd	C-1 Shift, δ	$^1J_{H1}$	$^3J_{H3}$	$^3J_{H15}$	C-4 Shift, δ	C-11 Shift, δ	$^1J_{H11}$
1a	186.2		9.2	3.9	184.8	197.3	196.1
b	186.8		9.6	3.7	185.9	198.0	193.9
2a	114.4	156.1	u	u	152.3	198.4	189.9
b	115.5	157.1	u	u	152.2	198.5	191.3
c	115.8	157.3		5.5	150.2	198.4	189.5
3a	202.3		u	u	198.8	197.7	191.9
b	201.7		u	u	198.7	197.1	191.0
c	202.5		u	u	198.4	197.9	193.4

[a] Chemical shifts are in ppm downfield from Me_4Si using central resonance of $CDCl_3$ as an internal reference; solvent for **1b, 3a, 3b,** and **3c** was deuteriochloroform and solvent for **1a, 2a, 2b,** and **2c** was acetone; coupling constants are in Hz (±0.5 Hz); u, unresolved multiplet.

Table VII. Calculated Angles of Twist, θ, for Carbons 1 and 4

Compd	C-1, deg	C-4, deg
3a	34.1	22.0
b	31.9	21.6
c	34.8	20.3

bons 1 and 4 are δ 199.3 and 202.0, respectively. These are in good agreement with the observed values (δ 198.4 and 202.5) and confirm our earlier tentative chemical shift assignments. The calculated angles of twist for **3a, 3b,** and **3c** are shown in Table VII. It is seen that there is no significant change in these angles and that substituents on the cyclohexene ring do not appreciably change the conformation.

Experimental Section

Materials. All the compounds studied were isolated from 2–3-day-old cotton bolls and purified as described elsewhere: **1a,**[8] **1b,**[8] **2a,**[21] **2b,**[21] **2c,**[22] **3a,**[6] **3b,**[8] and **3c.**[7] Reagent grade deuteriochloroform (99.8 atom % D) and acetone were used for all NMR spectra. For proton-coupled carbon-13 spectra determined in acetone, approximately 15% by volume deuteriochloroform was added to provide a lock signal.

Carbon-13 Spectra. All carbon-13 spectra were obtained with a JEOL PFT-100 Nicolet 1080 Fourier transform spectrometer. Sample concentrations were in the range between 0.5 and 1.0 M. Proton-decoupled spectra required 1500–3000 average transients to obtain satisfactory signal to noise ratios. Proton-coupled and single frequency decoupled spectra required 6000–15000 average transients. Chemical shifts of the same compound at different concentrations in the same solvent were reproducible within ±1 Hz. Therefore, in the determination of the deuterium isotope shifts, chemical shift changes of less than ±1 Hz were considered negligible (Table III). The sweep width used for the coupled and single frequency decoupled spectra was selected to give the maximum resolution using 16K data points, to prevent "foldover" from either the alkyl or the carbonyl regions of the spectra, and ranged from 3500 to 4000 Hz. The precision of the coupling constant measurements was limited by the digital resolution, typically 4000 Hz/8000 data points = 0.05 Hz. For this reason, couplings of less than about 1.5 Hz were not resolved. Couplings in the range of 1.5 to 2.5 Hz occasionally appeared only as broadened resonances. For example, in the proton-coupled spectrum of **3a** the resonance at δ 148.3 is a doublet of doublets due to the four-bond coupling of H-11 to carbon 7. The downfield doublet is resolved ($^4J_{H11}$ = 2.4 Hz), but the upfield peak is a broadened singlet (Figure 5b).

The carbon-13 chemical shift assignments for the alkyl regions were based upon decoupled and off-resonance coupled spectra and are reported in ppm downfield from Me_4Si using the central resonance of $CDCl_3$ as an internal reference (δ 76.9). For the chemical shift changes presented in Table V, the aryl, carbonyl, C-2, and C-3 shifts for **1a, 2a,** and **2b** were determined from proton-decoupled spectra for these compounds dissolved in deuteriochloroform rather than acetone and these shifts are included below. Small chemical shift changes may be noted compared to the chemical shifts determined in acetone (Tables I, II, IV, and VI).

1a:[5] δ 187.3 (C-1), 148.9 (C-2), 133.8 (C-3), 187.3 (C-4), 115.6 (C-5), 152.0 (C-6), 149.1 (C-7), 141.5 (C-8), 127.5 (C-9), 127.1 (C-10), 198.7 (C-11), 28.4 (C-12), 19.6 (C-13, C-14), 16.3 (C-15).

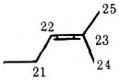
1b:[8] δ 28.7 (C-12), 20.8 (C-13, C-14), 16.3 (C-15).

2a: δ 116.7 (C-1), 133.9 (C-2), 113.1 (C-3), 151.7 (C-4), 111.6 (C-5), 155.6 (C-6), 142.7 (C-7), 134.3 (C-8), 129.4 (C-9), 114.3 (C-10), 199.4 (C-11), 27.8 (C-12), 20.1 (C-13, C-14), 21.4 (C-15).

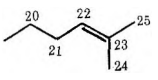
2b: δ 117.6 (C-1), 133.6 (C-2), 114.5 (C-3), 151.8 (C-4), 113.1 (C-5), 160.4 (C-6), 146.5 (C-7), 144.9 (C-8), 129.0 (C-9), 117.0 (C-10), 199.2 (C-11), 27.8 (C-12), 21.6 (C-13, C-14), 21.6 (C-15), 60.9 (C-16, OCH_3).

2c: δ 27.8 (C-12), 20.2 (C-13, C-14), 20.2 (C-15).

3a:[6] δ 28.8 (C-12), 19.8 and 19.6 (C-13, C-14), 23.6 (C-15), 32.3 (C-16), 118.6 (C-17), 135.0 (C-18), 39.5 (C-19), 21.4 (C-20, $R_3 = CH_3$), 27.6 (C-21, R_2 = chain A), 123.3 (C-22), 133.2 (C-23, R_2 = chain A), 25.6 (C-24, R_2 = chain A), 17.6 (C-25, R_2 = chain A).



Chain A



Chain B

3b:[8] δ 29.1 (C-12), 20.9 and 21.0 (C-13, C-14), 23.0 (C-15), 60.4 (C-26, OCH_3), 32.4 (C-16), 118.4 (C-17), 134.8 (C-18), 38.9 (C-19), 21.3 (C-20, $R_3 = CH_3$), 27.4 (C-21, R_2 = chain A), 123.3 (C-22, R_2 = chain A), 133.3 (C-23, R_2 = chain A), 25.6 (C-24, R_2 = chain A), 17.6 (C-25, R_2 = chain A).

3c:[5] δ 29.0 (C-12), 19.8 (C-13, C-14), 22.3 (C-15), 32.1 (C-16), 117.6 (C-17), 134.4 (C-18), 26.6 (C-19), 37.1 (C-20, R_3 = chain B), 26.0 (C-21, R_3 = chain B), 123.7 (C-22, R_3 = chain B), 131.4 (C-23, R_3 = chain B), 25.6 (C-24, R_3 = chain B), 17.6 (C-25, R_3 = chain B).

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Registry No.—Salicylaldehyde, 90-02-8; phenol, 108-95-2; anisole, 100-66-3.

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(15) The effect of strong intramolecular hydrogen bonding of the C-6 hydroxy proton to the aldehyde oxygen is also seen in the ^{1}H NMR shifts. In deuteriochloroform the C-6 hydroxy protons are far downfield (**1a**, δ 12.95; **1b**, δ 12.65; **2a**, δ 14.85; **2b**, δ 14.05; **2c**, δ 14.84; **3a**, δ 12.85; **3b**, δ 12.71; **3c**, δ 12.86). In contrast, the C-7 and C-4 hydroxy protons are observed between δ 5.80 and 6.60 (**1a**, δ 6.50; **2a**, δ 6.00 and 6.10; **2b**, δ 6.51; **2c**, δ 6.31 and 5.81; **3a**, δ 6.53; **3c**, δ 6.60).
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Optical Resolution Studies of Cyclophosphamide

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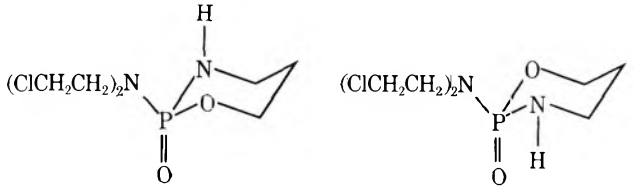
Cyclophosphamide (1) has been resolved by fluoride displacement (with c-$C_6H_{11}NH_3F$) of the optically active α-NpPhMeSi group of each chirality from the endocyclic nitrogen of the cyclophosphamide moiety in α-NpPhMeSi-c-$(NCH_2CH_2CH_2OP(O))N(CH_2CH_2Cl)_2$ ((−)-*S*(P)-*R*(Si)-**4**) and (+)-*R*(P)-*S*(Si)-**4**. The latter enantiomers were separated in high purity from their diastereomers ((+)-*R*(P)-*R*(Si)-**5** and (−)-*S*(P)-*S*(Si)-**5**, respectively) by recrystallization. The enantiomeric **5** derivatives could not be purified of **4** by a variety of techniques. Each diastereomeric mixture of **4** and **5** was synthesized by allowing the lithium salt of **1** (formed from **1** and *n*-BuLi) to react with (−)- and (+)-α-NpPhMeSiCl at low temperature. A simple method for the synthesis of anhydrous crystalline (±)-**1** is also described. The separation of the enantiomeric NH protons of anhydrous (±)-**1** in benzene-d_6 observed in the presence of the chiral shift reagent EuOpt offers a convenient method for estimating the optical purity of the enantiomers.

Introduction

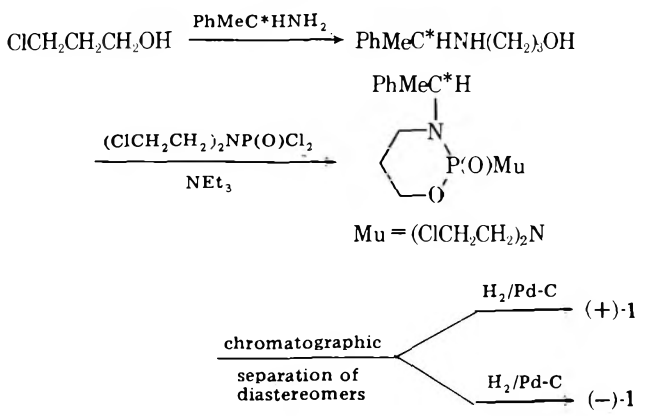
Racemic cyclophosphamide hydrate (Cytoxan, 2-[bis(2-chloroethyl)amino]-2-oxo-1,3,2-oxazaphosphorinane, (±)-**1**) is very effective in the clinical control of a variety of cancers.[1] After our efforts to resolve (±)-**1** were underway, Stec and



(+)-**1** (−)-**1**

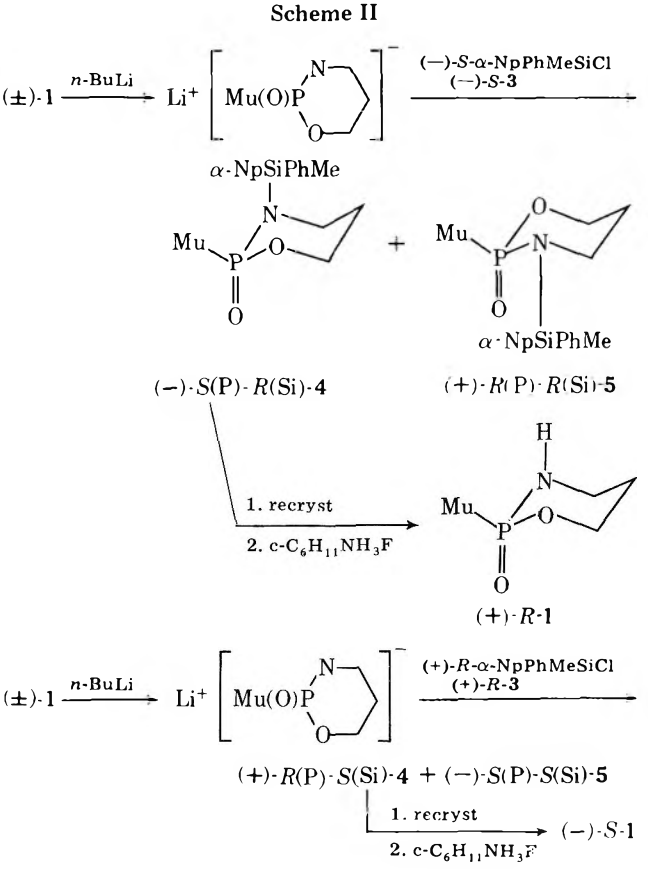
co-workers[2] published their approach to this problem which is outlined in Scheme I. In collaboration with Cox et al.[3] they showed that (−)-**1** is more efficacious against PC6 mouse tumors and the latter group demonstrated that (+)-**1** is preferentially metabolized in human patients.[3] Recently, the absolute configuration of (+)-**1** was shown to be *R* from the anomalous dispersion of x rays from the chlorine and phosphorus atoms.[4]

Scheme I



In view of the possibility that metabolic selectivity for a particular enantiomer may depend on the biological system under consideration, we decided to pursue the path outlined in Scheme II, since it would be of valuable aid in our current

Scheme II



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efforts to resolve two clinically used derivatives of cyclophosphamide, namely, isophosphamide and trophosphamide.

Experimental Section

(−)-(*S*)-2-[Bis(2-chloroethylamino)]-2-oxo-3(*R*)-α-naphthylphenylmethylsilyl-1,3,2-oxazaphosphorinane (−)-*S*(P)-*R*(Si)-4. (−)-(*S*)-α-Naphthylphenylmethylsilyl chloride [(−)-*S*-**3**] was prepared from (+)-(*R*)-α-naphthylmethylphenylsilane [(+)-*R*-**2**] ($[\alpha]^{25}_D$ +32.4°; c 2.51 in cyclohexane; optical purity is 95.4% based on $[\alpha]^{25}_D$ +33.7°; c 4.00 in cyclohexane) as previously described.[5] To a stirred solution of racemic cyclophosphamide, (±)-**1** (5.259 g, 20.14 mmol), in 30 mL of freshly dried ($LiAlH_4$) and distilled THF was added via syringe 10 mL of a 2 M *n*-hexane solution of *n*-butyllithium at −78 °C under a nitrogen atmosphere. After stirring for 10 min, a solution of (−)-*S*-**3** (5.430 g, 19.20 mmol) in 10 mL of dry ether was quickly syringed into the solution. Following continued stirring at −78 °C for 1 h, the solvent was removed under vacuum.

The tarry residue was chromatographed with chloroform on 80 g of silica gel (Baker, 60–200 mesh) to afford 9.541 g (97.9% yield) of a 1:1 mixture of (−)-*S*(P)-*R*(Si)-**4** and (+)-*R*(P)-*R*(Si)-**5** as a colorless paste which foamed on vacuum drying ($[\alpha]^{25}_D$ −4.1°; *c* 92.4 CH_2Cl_2). The ^1H NMR spectrum in $CDCl_3$ revealed the presence of the diastereomeric CH_3 protons [δ 1.06 (s, 1.5 H) and 1.09 (s, 1.5 H)]. Other assigned proton resonances are δ 1.55–1.90 (m, 2 H, CCH_2C), 3.04–3.65 (m, 10 H, $ClCH_2CH_2$, endocyclic CH_2N), 4.00–4.56 (m, 2 H, CH_2O), 7.20–8.08 (m, 11.5 H, C_6H_5, $C_{10}H_7$ of (−)-*S*(P)-*R*(Si)-**4** and C_6H_5, six protons of $C_{10}H_7$ of (+)-*R*(P)-*R*(Si)-**5**), and 8.39–8.50 (m, 0.5 H, one proton of $C_{10}H_7$ of (+)-*R*(P)-*R*(Si)-**5**, see Discussion). The ^{31}P chemical shifts of the diastereomers appeared at ($CDCl_3$) 11.7 and 11.3 ppm downfield of 85% H_3PO_4.

After recrystallizing three times from benzene–*n*-pentane (ca. 1:1) at 5 °C, further recrystallization gave no further increase in rotation of solutions of the colorless needles of (−)-*S*(P)-*R*(Si)-**4** ($[\alpha]^{25}_D$ −21.8°; *c* 1.53, CH_2Cl_2; mp 132.5–133.5 °C) which were obtained in 21% yield based on half the quantity of **2**: ^1H NMR ($CDCl_3$) δ 1.05 (s, 3 H, CH_3), 1.60–1.84 (m, 2 H, CCH_2C), 3.10–3.65 (m, 10 H, $ClCH_2CH_2$, endocyclic CH_2N), 4.10–4.50 (m, 2 H, CH_2O), 7.20–8.08 (m, 12 H, C_6H_5, $C_{10}H_7$). The ^{31}P chemical shift ($CDCl_3$) appeared at 11.8 ppm downfield of 85% H_3PO_4 and the P=O stretching frequency (KBr) at 1240 cm^{-1}. The mass spectrum (70 eV, 140 °C) revealed the parent ion at *m/e* 506.11138 (calcd 506.11131) and a base peak at *m/e* 267 corresponding to α-$NpPhSiCl^+$.

Because of its poor recrystallizing properties, diastereomer (+)-*R*(P)*R*(Si)-**5** could not be isolated in an optically pure state (see Discussion).

An effort was made to synthesize the above diastereomers by the reaction of (±)-**1** with (−)-*S*-**3** in the presence of Et_3N. Into a solution of **1** (3.338 g, 12.78 mmol) and Et_3N (1.80 mL, 12.9 mmol) in dry ether (50 mL) was added dropwise a solution of (−)-**3** (3.612 g, 12.77 mmol) in ether (30 mL) while stirring and cooling at 0 °C. After addition, the reaction mixture was allowed to stir at room temperature for 2 days and then cooled to −78 °C. The precipitate was collected and from it crude racemic **5** was obtained nearly quantitatively by extraction with THF and evaporation of the solvent. Recrystallization from MeOH gave crystals of (±)-**5** as plates [mp 145.0–146.0 °C (dec)] in 56.6% based on half the quantity of (−)-*S*(**3**). Its ^1H NMR spectrum in $CDCl_3$ showed δ 1.08 (s, 3 H, CH_3), 1.72 (m, 2 H, CCH_2C), 3.05–3.70 (m, 10 H, $ClCH_2CH_2$, $PNCH_2$), 4.00–4.55 (m, 2 H, PCH_2O), 7.35–7.94 (m, 5 H, C_6H_5; 6 H of $C_{10}H_7$), 8.35–8.50 (m, 1 H of $C_{10}H_7$). The high-resolution mass spectrum (70 eV, >200 °C) showed a parent *m/e* at 506.10992 (calcd for $C_{24}H_{29}Cl_2N_2O_2SiP$, 506.11131) and a base peak at *m/e* 267 corresponding to α-$NpPhSiCl^+$ ion. The IR spectrum (KBr) revealed ν_{PO} at 1250 cm^{-1}.

The filtrate of the reaction mixture was chromatographed on silica gel (50 g) with chloroform to afford 1.800 g of crude (±)-**4** in 55.6% yield as a colorless oil. The oil was recrystallized from benzene–hexane (1:1) to give 1.087 g (34.2% yield) of (±)-**4** as needles [mp 124.5–126.5 °C (dec)]. The ^1H NMR spectrum in $CDCl_3$ was identical to that of the separated enantiomers of **4** as was the position of the ν_{PO} frequency in the IR spectrum (KBr). The high-resolution mass spectrum (70 eV, 140 °C) showed a parent *m/e* peak at 506.10942 (calcd for $C_{24}H_{29}Cl_2N_2O_2SiP$: 506.11131) with a base peak at *m/e* 267. The relative heights of several peaks in the spectrum varied from (±)-**4** to (±)-**5** [e.g., (±)-**4** 429 < 491, whereas for (±)-**5** 491 < 429].

(+)-(*R*)-Cyclophosphamide, (+)-*R*-1. A solution of (−)-*S*(P)-*R*(Si)-**4** (0.865 g, 1.71 mmol) and cyclohexylammonium fluoride (0.276 g, 2.36 mmol) in 20 mL of CH_2Cl_2 was stirred at room temperature. By monitoring the reaction with TLC (ether eluant) it was shown that (−)-*S*(P)-*R*(Si)-**4** (R_f 0.6) was no longer detectable after about 2 h. The solvent was then evaporated from the reaction mixture to give a semisolid to which was added about 15 mL of benzene. The benzene filtrate was then chromatographed on 30 g of silica gel using a 195:5 chloroform–methanol mixture to give 0.390 g of (+)-*R*-**1** as a colorless oil (87.6% yield; $[\alpha]^{25}_D$ +2.1°; *c* 3.89 MeOH). Recrystallizing once from ether afforded optically pure product as prisms (0.311 g; 69.9% yield; mp 64.5–65.6 °C; $[\alpha]^{25}_D$ +2.3°; c 3.03 MeOH; ^{31}P NMR ($CDCl_3$) δ 12.5, (C_6D_6) δ 11.7; R_f 0.3 5% MeOH in $CHCl_3$) which compared well with the literature data[2] (mp 65–66 °C; $[\alpha]^{25}_D$ +2.3°; c 12.2 MeOH; ^{31}P NMR (MeOH–H_2O) δ 13.7).

An attempt was made to reduce the Si–N bond of (−)-*S*(P)-*R*(Si)-**4** by adding a benzene solution of this compound (0.585 g, 1.15 mmol in 20 mL of solvent) to an ether solution of $LiAlH_4$ (0.089 g, 9.4 mequiv in 10 mL of solvent) at room temperature. Distillation of the ether was followed by refluxing the reaction mixture at 90 °C overnight. Excess $LiAlH_4$ was decomposed with acetone and treated with crushed ice and 1 mL of concentrated HCl. Extraction with ether followed by drying the extract with Na_2SO_4, filtration, and evaporation of the solvent under vacuum gave a tarry residue which was chromatographed on silica gel with benzene. (+)-α-NpPhMeSiH was obtained in 13% yield and 82% optical purity ($[\alpha]^{25}_D$ +28°; c 0.36 c-C_6H_{12}). Subsequent elution gave (−)-α-NpPhMeSiOH in 31% yield and 17% optical purity ($[\alpha]^{25}_D$ −3.4°; *c* 0.88 *c*-C_6H_{12}). No evidence for **1** could be observed.

(+)-*R*(P)-*S*(Si)-4. This compound was prepared analogously to (−)-*S*(P)-*R*(Si)-**4** using (−)-(*S*)-α-naphthylphenylmethylsilane ($[\alpha]^{25}_D$ −32.5°; c 4.04 cyclohexane; optical purity 96.5%; mp 61.5–62.5 °C). The product was recrystallized three times from ca. 1:1 benzene–pentane at 5 °C in 21.4% yield ($[\alpha]^{25}_D$ +21.8°; c 1.41 CH_2Cl_2; mp 133.0–134 °C dec) and its ^1H NMR spectrum was identical with that of (−)-*S*(P)-*R*(Si)-**4**.

(−)-(*S*)-Cyclophosphamide, (−)-*S*-1. The same reaction which produced (+)-*R*-**1** was used to produce (−)-*S*-**1** from (+)-*R*(P)-*S*(Si)-**4**. The product was recrystallized once from ether in 65.8% yield and its properties ($[\alpha]^{25}_D$ −2.3°; *c* 3.17 MeOH; mp 64.5–65.5 °C) compared well with those found by Stec and co-workers.[2]

(−)-(*S*)-cyclophosphamide in lower optical purity was obtained from a sample of (+)-*R*(P)-*R*(Si)-**5** which was crude because of our failure to effect its purification (see Discussion). The 0.635-g sample ($[\alpha]^{25}_D$ +9.2°; c 6.35 CH_2Cl_2) consisted of (+)-*R*(P)-*R*(Si)-**5**, (−)-*S*(P)-*R*(Si)-**4**, and α-NpPhMeSiOH (apparently from partial hydrolysis experienced in workup) in ca. 11:4:1 ratio as determined by ^1H NMR spectroscopy. Its reaction with c-$C_6H_{11}NH_3F$ under the conditions described above afforded (−)-*S*-**1** in about 80% yield with an optical purity of 65% ($[\alpha]^{25}_D$ −1.5°; c 2.64 MeOH). The optical purity was verified to within 5% by the relative integrations of the somewhat broadened NH proton NMR singlets [(+)-**1**, δ 5.10, 1 H; (−)-**1**, δ 4.88, 5.7 H] observed in a C_6D_6 solution made up of 0.238 g of the product, 0.0592 g of EuOpt (13.8:1 mol ratio) in 0.7 mL of solvent.

Racemic cyclophosphamide, (±)-1. A solution of bis(2-chloroethyl)aminophosphoric dichloride (73.5 g, 28.4 mmol) in THF (150 mL) and a solution of 3-aminopropanol (21.3 g, 28.4 mmol) and triethylamine (79.0 mL, 56.8 mmol) in THF (150 mL) was added dropwise simultaneously into 300 mL of stirred dry THF over a period of 3 h at 0 °C and then the reaction mixture was stirred overnight at room temperature. Triethylammonium hydrochloride was filtered off and the filtrate evaporated under vacuum. The residue was chromatographed on silica gel (100 g) with chloroform–methanol (195:5) to give a colorless oil which was dried over P_4O_{10} under vacuum. The dried material was recrystallized from dry ether at −78 °C to afford 55.2 g (74% yield) of anhydrous (±)-**1** as prisms (mp 51.5–52.5 °C) which remained crystalline on storing under vacuum. A mass spectrum (70 eV) revealed the parent ion at *m/e* 261.6 (lit.[2] 260; calcd 261.1). Selected IR assignments are ν_{NH} (KBr) 3280, 3220 (sh), $\nu_{P=O}$ 1214 cm^{-1}, ν_{NH} (CCl_4 solution) 3380, 3200, $\nu_{P=O}$ 1235 cm^{-1}. The 100-MHz NMR spectrum exhibited the following features in $CDCl_3$: δ 1.84 (m, 2 H, $^3J_{HH}$ = 5.0 Hz, $CH_2CH_2CH_2$), 3.00–3.74 (m, 11 H, $ClCH_2CH_2$, $PNCH_2$, NH) and 4.04–4.60 (m, 2 H, $POCH_2$); and in C_6D_6: δ 1.25 (m, 2 H, $^3J_{HH}$ = 5.0 Hz, $CH_2CH_2CH_2$), 2.45–3.00 (m, 2 H, $PNHCH_2$), 3.00–3.50 (m, 8 H, $ClCH_2CH_2$), 3.50–4.20 (m, 2 H, $POCH_2$), and 4.55 (s, 1 H, NH). On adding tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) in a molar ratio of (±)-1:EuOPt of 26:1 in benzene, the signal for the NH protons separated completely (δ 4.55 and 4.75). By comparison, the remaining signals separated only slightly except for the $CH_2CH_2CH_2$ proton multiplet for which no separation could be observed.

Hydrated (±)-**1** can be dried over P_4O_{10} at room temperature to afford material suitable for optical resolution by the route described

here. Azeotropic distillation of the water with CH_2Cl_2 was not very satisfactory inasmuch as the last traces of CH_2Cl_2, which appeared to be difficult to remove, reacted with the *n*-butyllithium.

Discussion

Since fluoride cleavage of the Si–N bond in (−)-*S*(P)-*R*(Si)-**4** (Scheme II) is not expected to affect the phosphorus chiral center, (−)-*S*(P)-*R*(Si)-**4** must have the *S* configuration at phosphorus in order to produce (+)-*R*-**1**. That this compound has the *R* configuration at silicon is strongly indicated by the well-documented observation that α-NpPhMeSiCl undergoes inversion upon nucleophilic attack by pyrrole or its lithium salt and upon $LiAlH_4$ reduction.[6] Thus, (−)-*S*- or (+)-*R*-α-NpPhMeSiCl is expected to invert upon reaction with the nitrogen of the lithium salt of (±)-**1**, leading to the two pairs of diastereomers **4** and **5** shown in Scheme II. In the foregoing argument it is assumed that silylation of the anion of **1** occurs only on the ring nitrogen.[7] Although the ratio of fluoride to **4** in this reaction was originally 2:1, repetition with a 1:1 ratio produced very similar results. While the formation of α-NpPhMeSiF in the last step is expected to be stereospecific, this product was found to have racemized during chromatographic workup of the reaction mixture.

One of the aromatic protons in the enantiomers of **5** appears at rather low field in the $CDCl_3$ ^1H NMR spectrum (m, δ 8.39–8.50) in contrast to the absence of this multiplet in the spectrum of the enantiomers of **4**. It is conceivable that the conformation of the α-NpPhMeSi group in **5** is such that the proton at the C-8 position of the naphthyl substituent is experiencing deshielding from the periphery of the phenyl group, whereas such a conformation is not favored in diastereomeric **4**. Further evidence for the sensitivity of this proton to diamagnetic anisotropy effects is the movement of this resonance to lower field in C_6D_6. The diastereomers have slightly different ^{31}P chemical shifts (**4**, δ 11.8; **5**, δ 11.3). The conformation shown in Scheme II for the cyclophosphamide ring of **4**, **5**, and **1** is not unreasonable in view of the structural results obtained from x-ray diffraction studies of cyclophosphamide,[8] isophosphamide,[9] trophosphamide,[10ab] and several ring-substituted derivatives[10b] which exhibit an equatorial mustard group in the solid state. It should be noted, however, that stereoelectronic influences are capable of inverting this conformation in the solid state, since 4-hydroperoxyisophosphamide possesses an axial $ClCH_2CH_2NH$ group. Moreover, an equilibrium between both conformers in systems of this type is undoubtedly present in solution.[11,12]

According to the assignments deduced from the ^1H NMR spectra of anhydrous (±)-**1**, the NH proton which is apparently masked by the $ClCH_2CH_2$ and $PNCH_2$ protons in $CDCl_3$ is shifted downfield by C_6D_6 into a window in the spectrum at about 4.5 ppm. Addition of the EuOpt shift reagent to such a benzene solution causes one of the enantiomeric NH proton resonances to move downfield by ca. 0.2 ppm. This observation permits estimation of the optical purity of the resolved enantiomers of **1** and allows the assignment of the downfield NH resonance to (+)-*R*-**1** and the upfield one to (−)-*S*-**1**. The enhanced separation of the NH proton resonance in (±)-**1** in the presence of a lanthanide shift reagent is reasonable in view of its singlet nature and its close proximity to the complexing site which from the available evidence in similar systems appears to be the phosphoryl oxygen.[11] Recently, Zon et al.[13] showed that the separation of the α- and β-CH_2 proton NMR resonances of the mustard moiety of (±)-**1** in the presence of the chiral shift reagent tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) can also be used to determine the enantiomeric homogeneity of **1**. The heptafluoropropyl derivative of this shift reagent used in the present work offers the advantage that the ratio of **1** to reagent is considerably less (26:1) than with the trifluoromethyl derivative (1:1[13]). The ^{31}P chemical shifts in $CDCl_3$ of hydrated (±)-**1** (12.3 ppm) and anhydrous (±)-**1** (12.5 ppm) appear in the normal range, although they lie slightly to higher fields than the shift for **1** in a water–methanol solution.[2]

It was found that the lithiation of racemic cyclophosphamide must be carried out at low temperature to prevent its decomposition (possibly by intra or intermolecular nucleophilic attack of the anionic nitrogen on a CH_2Cl carbon[14]) prior to reaction with the enantiomers of **3**. In spite of the fact that THF is sufficiently basic to racemize optically active **3** slowly whereas Et_2O apparently is not, the former solvent was employed for the metallation reaction (using Et_2O to dissolve **3** for addition to metallated (±)-**1**). This was done because of the lower solubility of (±)-**1** and reduced product yields obtained when Et_2O alone was used. The use of Et_3N to facilitate the reaction of (±)-**1** with the enantiomers of **3** produced completely racemized **4** and **5** owing to more rapid racemization of optically active **3** in the presence of base. Substantially similar results were obtained with 1,5-diazabicyclo[5.4.0]-undec-5-ene (DBU).

All attempts to separate diastereomeric **4** and **5** by TLC, column chromatography (alumina and silica gel), and high-pressure liquid chromatography have so far failed. This result seems somewhat puzzling in view of the relative ease with which Stec and co-workers were able to separate the diastereomers in Scheme I by column chromatography.[2] Fortunately (−)-*S*(P)-*R*(Si)-**4** and (+)-*R*(P)-*S*(Si)-**4** are less soluble in benzene–pentane and form much more well-developed crystals than their diastereomers [(+)-*R*(P)-*R*(Si)-**5** and (−)-*S*(P)-*S*(Si)-**5**, respectively], and a separation of **4** could be accomplished in each case. Further recrystallizations aimed at purifying **5** were unsuccessful in eliminating diastereomeric **4** as a contaminant.

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Registry No.—(±)-**1**, 60007-95-6; (+)-*R*-**1**, 60030-72-0; (−)-*S*-**1**, 60007-96-7; (+)-*R*-**2**, 1025-08-7; (−)-*S*-**2**, 1025-09-8; (−)-*S*-**3**, 960-82-7; (+)-*R*-**3**, 13132-42-8; (±)-**4**, 64840-26-2; (−)-*S*(P)-*R*(Si)-**4**, 64870-01-5; (+)-*R*(P)-*S*(Si)-**4**, 64870-02-6; (±)-**5**, 64840-27-3; (−)-*S*(P)-*S*(Si)-**5**, 64911-63-3; (+)-*R*(P)-*R*(Si)-**5**, 64870-03-7; (−)-α-NpPhMeSiOH, 1028-62-2; bis(2-chloroethyl)aminophosphoric dichloride, 127-88-8.

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Photochemical Conversion of Methoxy-Substituted 6/6-Fused Cross-Conjugated Cyclohexadienones into Isomeric Tricyclodecenones[1]

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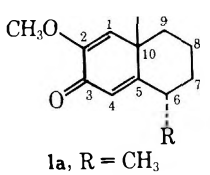
2-Methoxy 6/6-fused cross-conjugated cyclohexadienones of type **1** were irradiated in anhydrous dioxane. In addition to the expected lumiproducts, novel isomeric tricyclodecenone derivatives of type **5** were obtained as primary photoproducts. Phenolic compounds tentatively assigned structures of type **6** were also produced as primary photoproducts. The structure of the *p*-iodobenzoate **14**, a heavy-atom derivative of the tricyclodecenone **5b**, was established by x-ray crystallography. Possible modes of formation of enones of type **5** are discussed.

Recently, we reported the synthesis of the 2-methoxy 6/6-fused cross-conjugated cyclohexadienone **1a** and investigated its photochemical behavior on irradiation in protic solvents such as glacial and aqueous acetic aicd.[2] The expected spiro acetoxy- and spiro hydroxyenones **2a** and **2b**, respectively, were obtained and shown to be useful intermediates for the total synthesis of (±)-α-vetispirene.[2] We have now carried out irradiations of **1a** and the related normethyldienone **1b** in the aprotic solvent dioxane and wish to report these results.



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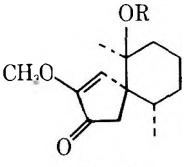
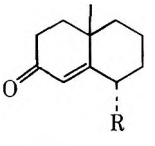
b, R = H

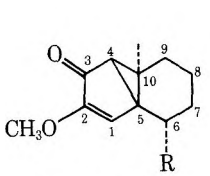


2a, R = Ac
b, R = H

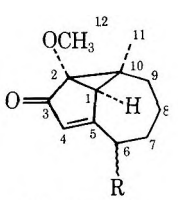


3a, R = CH_3
b, R = H

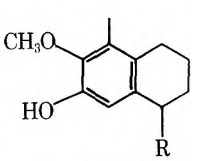
Dienone **1b** was prepared from the octalone **3b** by a route similar to that employed for the synthesis of **1a** from the corresponding octalone **3a**.[2] Dilute solutions (ca. 0.5%) of **1a** or **1b** in anhydrous dioxane were irradiated for 6.0 h at room temperature with a 7-W Hanau NK-20 low-pressure mercury lamp. Analysis of the photolysis mixtures by gas–liquid chromatography (GLC) using an internal standard showed that two tricyclic enones and a phenol were produced in ca. 25, 15, and 15% yields each from each of the dienones. In each case ca. 15% of the starting dienone remained at the end of the irradiation period. On the basis of the evidence presented below, the major enones were assigned the normal lumiproduct structures **4**, while the minor enones were assigned the tricyclic structures **5**. The phenolic products have been tentatively assigned structures **6**.



4a, R = CH_3
b, R = H



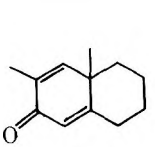
5a, R = CH_3
b, R = H



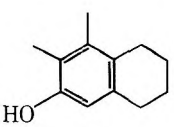
6a, R = CH_3
b, R = H

The phenolic products appeared to be primary photoproducts based on experiments in which a mixture of the isolated enones **4b** and **5b** were irradiated under similar conditions to the dienones **1**. In neither case were detectable amounts of the phenol **6b** formed. Enone **5b** was essentially unchanged under the irradiation conditions, whereas **4b** was almost completely destroyed, being largely converted into nonvolatile material. In one run the course of the photolysis of dienone **1b** was monitered carefully by GLC analysis. This revealed that after a short irradiation period, before **4b** was further rearranged, the kinetic ratio of primary photoproducts **4b** and **5b** was 4.4:1.

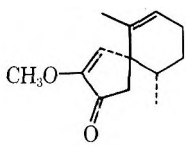
The tentative assignments of the structures of the phenols **6** were by analogy to the work of Kropp,[3] in which the 2-methyldienone **7** was shown to yield the phenol **8** as a primary photoproduct on irradiation in methanol or acetic acid. Phenol **8** was produced by a photochemically induced 1,2-methyl shift. This was a novel rearrangement pathway since cross-conjugated cyclohexadienones do not generally yield phenols as primary photoproducts. Phenolic products are often observed in dienone photolysis, but they normally arise by secondary processes in which initially formed lumiproducts are further rearranged.[4] Since phenols are formed as primary products from the irradiation of the 2-methoxydienones, it seems likely that they are also derived from a simple 1,2-methyl shift.



7



8



9

The spectral properties of the lumiproducts **4a** and **4b** were consistent with the assigned structures (see the Experimental Section). In addition, compound **4a** was converted into the known spiro dienone **9**[2] by cleavage of the external bond of the cyclopropane ring with sulfuric acid in acetic anhydride under the conditions described by Marshall and Johnson[5] for the conversion of the related normethoxy lumiproduct into the corresponding spiro dienone. This information seemed to provide excellent evidence for the structural assignments.

The spectral properties of the enones **5a** and **5b** as well as

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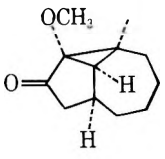
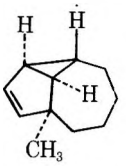
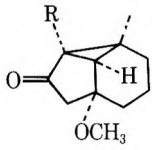
those of the dihydro derivative **10** of **5b** were also consistent with the assigned structures (see the Experimental Section), but they did not permit positive assignment of the relative stereochemistry at C-1 and C-10. Clearly, if the stereochemical assignment at C-10 were reversed, a much more highly strained system would result. However, strained systems such as the tricyclodecene derivative **11** which has trans-fused three- and seven-membered rings have been produced in photochemical reactions.[6] This raised the possibility that isomers of **5a** and **5b** with the 10-methyl groups β could have been produced in the irradiations of the corresponding dienones.



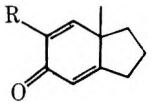
10



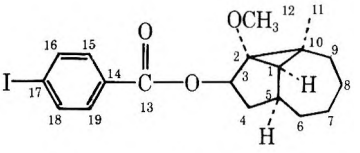
11



12a, R = H
b, R = CH_3



13a, R = H
b, R = CH_3



14

Irradiations of unsubstituted and methyl-substituted 6/6-fused dienones of type **1** and related compounds in dioxane normally yield lumiproducts of type **4** and derived secondary photolysis products,[4,7] but no isomeric primary photoproducts related to **5** have been observed in these systems.[8] Likewise, irradiations of α-halosantonin derivatives in nonprotic media have been reported to yield only lumisantonin derivatives related to **4**.[9] However, the tricyclononanones such as **12**, which we obtained upon irradiation of 6/5-fused dienones of the type **13** in methanolic acetic acid, were considered to arise via 1,4 addition of methanol to strained tricyclononenones related to **5**.[10]

Since the stereochemistry of compounds of the type **5** was of crucial importance with regard to their mechanism of formation, a derivative of **5b** was prepared for use in a single-crystal x-ray crystallographic analysis. Catalytic hydrogenation of **5b** gave the tricyclodecanone **10**. Reduction of the carbonyl group in **10** with lithium tri(*tert*-butoxy)aluminum hydride in tetrahydrofuran (THF) and reaction of the alcohol with *p*-iodobenzoyl chloride in pyridine gave the crystalline *p*-iodobenzoate derivative **14**. The details of the determination of the structure of **14** by x-ray analysis are given in the Experimental Section. The molecular structure of **14** (with the *p*-iodobenzoate group deleted) is shown in Figure 1. This provided unambiguous proof of the structural assignment of **5b** and the structure of **5a** except for the assignment of the configuration at C-6 (see below) followed by analogy.

The abnormal enones **5a** and **5b** may be considered to arise by a symmetry-allowed 1,4-sigmatropic rearrangement in a cyclopropyl intermediate of type **15** produced by electronic excitation and β,β bonding in the dienone system[4,11] or by a photo-induced [σ2a + π2a] cycloaddition process involving the 5,10-σ and the 1,2-π bond of the dienone.[11b] The former process would occur with retention of configuration at C-10, while the latter would involve inversion at C-10.[11b] Since either or both of these pathways may be involved, a prediction of the relative stereochemistry of the C-6 methyl group (α or β) in **5a** is not possible. Also, the spectral data for **5a** do not allow an unambiguous assignment of the C-6 configuration to be made. In addition, since C-6 is possibly an epimerizable

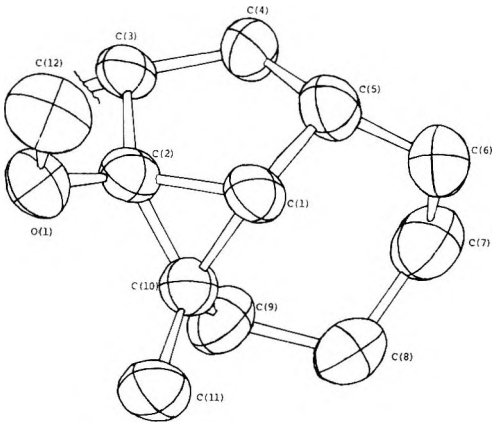
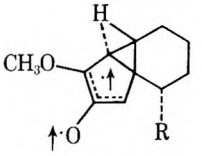


Figure 1.

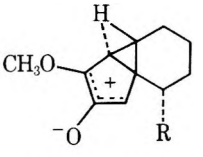
center, the product actually isolated may have arisen as a result of thermodynamic rather then kinetic control under the condition of the photolysis and isolation. For this reason it does not seem that unambiguous evidence for the mode of rearrangement of methoxydienones such as **1** would be obtained even if the structure of **5a** were fully established.

In the two methoxydienones studied, the abnormal rearrangement pathway competes only to a minor, although significant, extent with the normal mode of rearrangement involving either electron demotion in **15** to produce the ground-state dipolar species **16**, followed by a symmetry-allowed 1,4-sigmatropic shift, or a photo-induced [σ2a + π2a] cycloaddition involving the 1,10-σ and the 4,5-π bonds of the dienone.[11] Both of these pathways predict inversion of configuration at C-10 in the formation of the normal lumiproducts, and they are not distinguishable for that reason.[11b] In order to be allowed on orbital-symmetry grounds, cleavage of the 5,10 bond and formation of a 1,10 bond in the ground-state intermediate **16** would have to occur with inversion of configuration at C-10. This would necessarily lead to photoproducts with a trans fusion of the three- and seven-membered rings; such products were not observed.

The exact manner in which the methoxyl group influences these rearrangements is not clear. Its presence may increase the lifetime of triplet species such as **15** to allow time for re-



15a, R = CH_3
b, R = H



16a, R = CH_3
b, R = H

arrangement prior to election demotion, or it may cause selective excitation of the 1,2-π bond of the dienone. It is known that α-methoxy substituents and other polar groups may influence the energy of the lowest lying excited states of α,β-unsaturated ketones.[12]

Experimental Section[13]

Preparation of 2-Methoxy-3-keto-10-methyl-$\Delta^{1,4}$-hexahydronaphthalene (1b). To a solution of 41.0 g (0.093 mol) of lead tetraacetate in 200 mL of glacial acetic acid and 20 mL of acetic anhydride was added 10.0 g (0.061 mol) of 3-keto-10-methyl-$\Delta^{4,5}$-octahydronaphthalene (**3b**).[14] The reaction mixture was stirred under nitrogen at 70–80 °C for 24 h. The bulk of the solvent was removed under reduced pressure and the residue was partitioned between ether and water. The ether layer was extracted with saturated sodium bicarbonate and dried, and the solvent was removed in vacuo. Distillation of the residue yielded 5.22 g (39%) of a mixture of 2α- and 2β-acetoxy-3-keto-10-methyl-$\Delta^{4,5}$-octahydronaphthalene: bp 100–130

°C (0.005 mm); IR ($CHCl_3$) 1740, 1686, and 1619 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 1.25 (s, 0.6 H), 1.38 (s, 0.4 H), 2.07 (s, 3 H), 5.23 (br t, 1 H), 5.62 (br s, 0.4 H), and 5.67 (br s, 0.6 H). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.09; H, 8.16.

The mixture of acetoxyenones (2.26 g, 0.0102 mol) was dissolved in 150 mL of methanol, and a solution of 1.2 g (0.022 mol) of potassium hydroxide in 10 mL of water was added. While a slow stream of oxygen was being passed through the solution, it was stirred for 24 h at room temperature. The excess methanol was removed in vacuo and the residue partitioned between ether and water. The aqueous layer was extracted with two 50-mL portions of ether and the ether extracts were discarded. The aqueous layer was acidified with concentrated hydrochloric acid and extracted thoroughly with ether. The combined ether extracts were dried and the solvent was removed in vacuo. The viscous yellow residue was dissolved in 100 mL of dry *tert*-butyl alcohol and stirred under nitrogen, and a solution of potassium *tert*-butoxide [prepared from 0.45 g (0.115 g-atom) of potassium] in 50 mL of dry *tert*-butyl alcohol was added rapidly. After stirring for 0.5 h, 4.0 g (0.028 mol) of methyl iodide was added in one portion and the reaction mixture was then heated under reflux. After ca. 20 min the excess *tert*-butyl alcohol was removed by distillation and 50 mL of water added. Extraction with ether, drying, and removal of the solvent in vacuo gave 0.98 g (50%) of a yellow oil which crystallized on standing. Recrystallization from ether yielded pure **1b**: mp 106.5–107.0 °C; UV λ_{max} (95% EtOH) 250 nm (ϵ 10 000); IR ($CHCl_3$) 1658, 1635, and 1615 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 1.25 (s, 3 H, C_{10}-CH_3), 3.58 (s, 3 H, C_2-OCH_3), 5.58 (s, 1 H, C_4-H), and 5.93 (br s, 1 H, C_1-H). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 74.75; H, 8.23.

Irradiation of 1a. A solution of 1.00 g of 6α-methyl-2-methoxydienone **1a**[2] in 150 mL of dry dioxane was irradiated for 6.0 h. The solvent was removed in vacuo and the residue subjected to GLC analysis (column A)[13] using acetophenone as an internal standard. Response factors were calculated from GLC analysis of mixtures of the pure components [isolated by preparative GLC (column B)[13]] and acetophenone. In one run, the results of this analysis were compound **4a**, 28%; compound **5a**, 15%; phenolic compound **6a**, ~15%; starting compound **1a**, 14%.

The residue from three separate irradiations using a total of 2.8 g of dienone was combined and chromatographed on acetone-washed silica gel (60–200 mesh). Elution with 5% ether in hexane yielded an acidic compound tentatively assigned structure **6a** (0.07 g, 6%) which showed IR (CCl_4) 3550, 3410, 2925, 2860, and 1600 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 1.23 (d, J = 6 Hz, 3 H, C_6-CH_3), 2.08 (s, 3 H, C_1-CH_3), 3.68 (s, 3 H, C_2-OCH_3), 5.48 (br s, 1 H, C_3-OH), and 6.57 (s, 1 H, C_4-H). Further elution with 10% ether in hexane yielded 1.16 g (41%) of a mixture of enones **4a** and **5a** (fraction A). Continued elution with 15% ether in hexane yielded a crystalline solid which had identical spectral properties with that of the starting dienone **1a**.

Fraction A was readily separated into two components by preparative GLC (column B).[13] The first material eluted from the column was **5a** which showed the following properties: UV λ_{max} (95% EtOH) 240 nm (ϵ 5900); IR ($CHCl_3$) 2930, 1682, and 1585 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 1.18 (d, J = 6 Hz, 3 H, C_6-CH_3), 1.27 (s, 3 H, C_{10}-CH_3), 2.33 (s, 1 H, C_1-H), 3.47 (s, 3 H, C_2-OCH_3), and 5.47 (s, 1 H, C_4-H). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.41; H, 8.94.

The longer retention time component was assigned structure **4a**: UV λ_{max} (95% EtOH) 234 nm (ϵ 7800) and 285 (2200) shoulder); IR ($CHCl_3$) 2940, 1695, and 1618 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 1.15 (s, 3 H, C_{10}-CH_3), 1.22 (d, J = 6 Hz, 3 H, C_6-CH_3), 1.67 (s, 1 H, C_4-H), 3.65 (s, 3 H, C_2-OCH_3), and 6.15 (s, 1 H, C_1-H). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.41; H, 9.01.

Acid-Catalyzed Cleavage of 4a. To a solution of 220 mg (2.07 mmol) of lumiproduct **4a** in 3.7 mL of acetic acid and 0.073 mL of acetic anhydride was slowly added 0.073 mL of concentrated sulfuric acid. The reaction mixture was stirred for 24 h and then poured into cold 10% sodium hydroxide. Ether was added, the ether layer was separated, washed with saturated aqueous sodium chloride, and dried, and the solvent was evaporated in vacuo. This yielded 173 mg (79%) of a yellow oil which by GLC was mostly **9**. Preparative GLC (column B)[13] gave a pure sample of **9** which showed essentially identical spectral properties with those previously reported.[2]

Irradiation of 1b. A solution of 1.00 g of 2-methoxydienone **1b** in 250 mL of dry dioxane was photolyzed for 6.0 h. The solvent was removed in vacuo and the residue subjected to GLC (column A)[13] analysis using acetophenone as an internal standard. In one run, the results of this analysis were compound **4b**, 31%; compound **5b**, 18%; compound **6b**, 12%; compound **1b**, ~15%. In another run the photolysis mixture was analyzed after 15 min and showed that the ratio of **5b** to **4b** was 4.4 to 1.0 with about 96% of dienone **1b** remaining.

The products of five, separate photolysis runs were combined and chromatographed on silica gel. Elution with 15% ether in hexane gave a product (496 mg, 9.9%) tentatively identified as the phenol **6b**: IR (CCl_4) 3550, 3420, 2930, 2860, and 1597 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 1.70 (m, 4 H, C_7-H, C_8-H), 2.05 (s, 3 H, C_1-CH_3), 2.50 (m, 4 H, C_6-H, C_9-H), 3.65 (s, 3 H, C_2-OCH_3), 5.50 (br s, 1 H, C_3-OH), and 6.42 (s, 1 H, C_4-H). Further elution with 25% ether in hexane gave a 1.65-g (33%) mixture of **4b** and **5b** (fraction A). Continued elution with pure ether yielded a crystalline solid that had identical spectral properties with those of the starting dienone **1b**.

Fraction A was separated into two components by careful column chromatography on silica gel. Elution with 30% ether in hexane yielded 405 mg (8.1%) of pure **4b**: UV λ_{max} (95% EtOH) 237 nm (ϵ 8000) and 285 (2200) (shoulder); IR ($CHCl_3$) 2935, 1700, and 1620 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 1.17 (s, 3 H, C_{10}-CH_3), 1.61 (s, 1 H, C_4-H), 3.60 (s, 3 H, C_{10}-OCH_3), and 5.90 (s, 1 H, C_1-H); MS m/e (70 eV) 192.117 (EMC = 192.115). Further elution with 40% ether in hexane yielded 425 mg (8.5%) of pure **5b**: UV λ_{max} (95% EtOH) 241 nm (ϵ 5400); IR ($CHCl_3$) 2930, 1682, and 1590 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 1.26 (s, 3 H, C_{10}-CH_3), 2.32 (s, 1 H, C_1-H), 3.48 (s, 3 H, C_2-OCH_3), and 5.50 (s, 1 H, C_4-H); MS m/e (70 eV) 192.113 (EMC = 192.115). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 74.72; H, 8.45.

Irradiation of 4b and 5b. A mixture of 45 mg of **4b** and 5 mg of **5b** was dissolved in 100 mL of dry dioxane and photolyzed for 0.5 h. The solvent was removed in vacuo and the residue analyzed by GLC. This analysis showed that **4b** had completely disappeared, whereas the amount of **5b** remained essentially unchanged. Only trace amounts of other volatile components were produced. No volatile photoproduct with a retention time corresponding to phenol **6b** was obtained.

Hydrogenation of 5b. A solution of 425 mg of **5b** in 100 mL of 95% ethanol was mixed with 400 mg of 10% palladium on carbon in a pressure bottle and shaken on a Parr apparatus at 40 psi of hydrogen pressure for 4.0 h. The catalyst was removed by filtration and the solvent removed in vacuo. This yielded 362 mg (85%) of **10** (pure by GLC analysis) which showed mp 52–53 °C (from pentane); IR ($CHCl_3$) 2930 and 1718 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 1.18 (s, 3 H, C_{10}-CH_2), 1.73 (d, J = 6 Hz, 1 H, C_1-H), three peaks at 2.00, 2.03, and 2.17 (J = 8.8 and 10.0 Hz, 2 H, C_4-CH_2, geminal coupling not observable), 2.67 (m, 1 H, C_5-H), and 3.34 (s, 3 H, C_2-OCH_3); MS m/e (70 eV) 194.131 (EMC = 194.131).

Preparation of the *p*-Iodobenzoate 14. To a mixture of 107 mg (2.81 mmol) of lithium aluminium hydride and 50 mL of dry tetrahydrofuran (THF) was added 0.79 mL (625 mg, 8.43 mmol) of dry *tert*-butyl alcohol with stirring under nitrogen. A solution of 362 mg (1.87 mmol) of **10** in 4 mL of dry THF was added dropwise with stirring over a 10-min period, and stirring was continued at room temperature for 1.0 h. The reaction mixture was poured into excess hydrochloric acid and extracted with three 50-mL portions of ether. The combined ether extracts were back extracted with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride and then dried, and the solvent was removed in vacuo. This gave 370 mg (101%) of material which did not have significant infrared absorption at 1718 cm^{-1}. This material (370 mg, 1.89 mmol) was dissolved in 5 mL of dry pyridine and 755 mg (2.83 mmol) of *p*-iodobenzoyl chloride (Eastman 9541, mp 63–65 °C) was added with stirring over a 10-min period. This mixture was allowed to stand for 48 h at room temperature and then poured into a mixture of 50 g of ice and 10 mL of concentrated hydrochloric acid. After stirring for ca. 5 min, the mixture was extracted with three 50-mL portions of ether. The ether extracts were washed with water and dried, and the solvent was removed in vacuo. This yielded a yellow oil that was chromatographed on silica gel. Elution with 20% ether in hexane gave 415 mg (52%) of crystalline iodobenzoate **14** which showed mp 110–111 °C (from hexane); NMR δ_{Me_4Si} (CCl_4) 1.17 (s, 3 H, C_{10}-CH_3), 3.28 (s, 3 H, C_2-OCH_3), 5.90 (t, J = 8 Hz, 1 H, C_3-H), and 7.67 (s, 4 H, aromatic H). Anal. Calcd for $C_{19}H_{23}O_3I$: C, 53.53; H, 5.44. Found: C, 53.43; H, 5.47.

A single crystal suitable for x-ray analysis was prepared by dissolving 50 mg of **14** in 1.0 mL of hexane and 5 drops of toluene. The solid was brought into solution by heating to about 55 °C, and the solution was then allowed to cool overnight in a Dewar flask that contained water heated to 55 °C.

Crystallographic Data Collection. A needle-shaped crystal with approximate dimensions 0.2 × 0.2 × 0.4 mm was mounted on a glass fiber using epoxy cement such that the longest crystal dimension was approximately parallel to the fiber axis.

Unit cell parameters and the orientation matrix were determined on a Syntex $P2_1$ four-circle diffractometer equipped with a graphite monochromator (Bragg 2θ angle = 12.2°) using Mo$K\alpha$ radiation at a takeoff angle of 6.5°. Fifteen reflections whose 2θ values ranged from 6.0 to 24.0° were machine centered and used in least-squares refinement of the lattice parameters and orientation matrix. Unit cell pa-

rameters obtained were a = 7.073 (2) Å,[15] b = 23.354 (14) Å, c = 11.049 (7) Å, α = 90.0°, β = 91.05 (4)°, γ = 90.0°, and V = 1824 (2) Å^3. The calculated density of 1.55 g cm^{-3} for four formula units per unit cell agrees with the experimental density of 1.48 g cm^{-3} measured by the flotation method using aqueous zinc chloride. ω scans of several low 2θ angle reflections gave peak widths at half-height of less than 0.25°, indicating a satisfactory mosaic spread for the crystal.

Axial photographs indicated that the crystal belonged to the monoclinic system. Intensity data for zero and upper levels were collected at a rapid scan rate and the intensities examined carefully for systematic absences. The absence of $h0l$ with $h + l = 2n + 1$ and $0k0$ with $k = 2n + 1$ reflections is consistent with only space group $P2_1/n$.

Intensity data were collected using θ–2θ scans with x-ray source and monochromator settings identical with those used for determination of the unit cell parameters. A variable scan rate of from 4.5 to 29.3°/min was used and a scan width of 2° was sufficient to collect all of the peak intensity. Stationary background counts were measured at the beginning (bgd1) and at the end (bgd2) of each scan with a total background to scan time ratio, TR, of 1.0. No significant fluctuations were observed in the intensities of three standard reflections (0,0,10; 0,8,0; 2,0,0) monitored every 100 reflections. Intensities were calculated from the total scan count (CT) and background counts by the relationship

$$I = CT - (TR)(bdg1 + bgd2)$$

The intensities were assigned standard deviations according to the formula

$$\sigma(I) = [CT + (TR)^2(bgd1 + bgd2)]^{1/2}$$

from a total of 5223 reflections collected in a complete quadrant of data out to 2θ = 60°; 2454 were accepted as statistically above background on the basis that I was greater than $3\sigma(I)$. Lorentz and polarization corrections were made in the usual way.

Solution and Refinement of the Structure. Computations were performed using standard programs;[16] all computations were carried out on the CDC Cyber 74 system. For structure–factor calculations the scattering factors were taken from Cromer and Waber's tabulation[17] for all atoms. The scattering factor for iodine was corrected for the real and imaginary anomalous dispersion components, using the dispersion factors given by Cromer.[18] The agreement factors are defined in the usual way as

$$R = (\Sigma||F_o| - |F_c||)/(\Sigma|F_o|)$$

and

$$R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w(|F_o|)^2]^{1/2}$$

In all least-squares refinements, the quantity minimized was $w(|F_o| - |F_c|)^2$. A weighting scheme based on counting statistics [$w = 4I/\sigma^2(I)^2$] was employed for calculating R_w and in least-squares refinement.

Coordinates for the iodine atom were obtained from a three-dimensional Patterson synthesis; successive cycles of least-squares refinement and electron density calculation revealed the position of all carbon and oxygen atoms; hydrogen atoms were not located. All atoms were refined anisotropically. Least-squares refinement converged to give the residuals R = 0.056 and R_w = 0.050 (2454 observations, 208 variables). In the final refinement no parameter changed by more than one standard deviation from the previous value.

Registry No.—**1a,** 58355-87-6; **1b,** 64761-36-0; **3b,** 40573-28-2; **4a,** 64761-37-1; **4b,** 64761-38-2; **5a,** 64761-31-5; **5b,** 64761-32-6; **6a,** 64761-39-3; **6b,** 64761-40-6; **10,** 64761-33-7; **14,** 64761-34-8; 2-α-3-keto-10-methyl-$\Delta^{4,5}$-octahydronaphthalene, 64771-34-2; 2-β-3-keto-10-methyl-$\Delta^{4,5}$-octahydronaphthalene, 64761-35-9; methyl iodide, 74-88-4; p-iodobenzoyl chloride, 1711-02-0.

Supplementary Material Available: Table I listing final positional parameters (1 page). Ordering information is given on any current masthead page.

References and Notes

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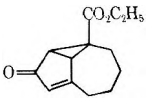

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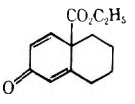

ii

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Comparative Study of *syn*- and *anti*-1,5-Bishomocycloheptatrien-2-yl Radicals and Carbocations

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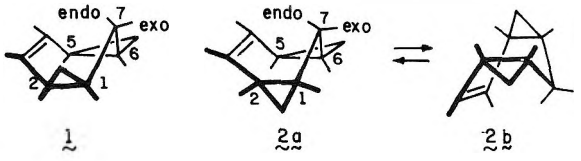
syn-1,5-Bishomocycloheptatriene (**1**) was found to undergo free-radical halogenation (*t*-BuOCl, *hν*) at one of its two equivalent allylic cyclopropyl positions to give unrearranged chloride **5**. Further treatment of **5** with this reagent led to symmetrical dichloride **6**. The conversion of *anti*-1,5-bishomocycloheptatriene (**2**) to **7** proceeded analogously, but **7** proved to be stable to the reaction conditions. Methanolysis of **5** and **7** in neat methanol at 100–150 °C or with silver trifluoroacetate catalysis at room temperature proceeded with opening of the functionalized three-membered ring to give ethers **10–12**. The regioselectivity of free radical hydrogen abstraction and the retention of structural integrity during the formation of **5** and **7** are contrasted with the chemical response obtained during conversion of these chlorides to their carbocations.

Hydrocarbons **1** and **2**, synthesized recently for the purpose of assessing long-range cyclopropyl interaction and σ homoaromaticity,[2-5] incorporate an interesting spectrum of unique structural features. For example, the conformationally rigid **1**, where both cyclopropyl groups adopt the thermodynamically favored extended "equatorial" arrangement, constrains H_2 and H_5 to lie in plane with the $p\pi$ orbitals located on C_3 and C_4 and projects $H_{7\text{-endo}}$ into a bisected ralationship with *both* three-membered rings. In anti isomer **2a**, H_5 remains well aligned with the C_3–C_4 π bond, but H_2 is now almost orthogonal to that plane. Also, while $H_{7\text{-endo}}$ bisects the 5,6-fused cyclopropane ring, $H_{7\text{-exo}}$ is oriented properly for maximum interaction with the "axial" three-membered ring positioned at C_1,C_2. However, since **2a** is in mobile degenerate equilibrium with **2b** at room temperature (E_a = 8.13 kcal/mol)[2] and these pairs of hydrogens experience rapid time averaging under such conditions, all four can presumably attain a chemical environment capable of substantially enhancing their chemical reactivity.

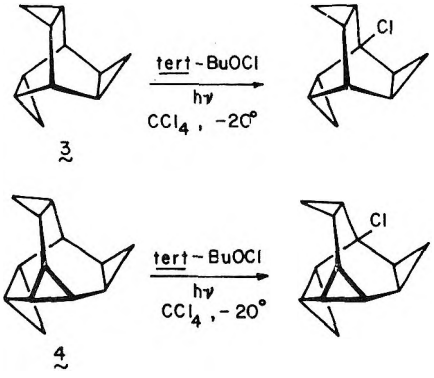


1 **2a** **2b**

Those forms of possible conjugative interaction available to **1** and **2** are therefore: (a) *allylic*, but with requisite abstraction of a cyclopropyl hydrogen (H_2 or H_5 in **1**, H_5 in **2a**, or H_2 in **2b**) to achieve delocalization; (b) *biscyclopropylcarbinyl* ($H_{7\text{-endo}}$ in **1** only); and (c) *cyclopropylcarbinyl* ($H_{7\text{-endo}}$ or $H_{7\text{-exo}}$ in **2**). In an effort to determine the extent to which these extrasymmetric factors affect the regioselectivity of free-radical attack, **1** and **2** have been subjected to chlorination with *tert*-butyl hypochlorite. Strikingly specific abstraction of H_2 or H_5 has been observed in both examples with formation of structurally unrearranged chlorides. This paper concerns an analysis of this unprecedented selectivity and contrasts the structural integrity of the intermediate bishomocycloheptatrienyl free radicals to the lability of their carbocationic counterparts.

Chlorination Experiments. Upon reaction of simple hydrocarbons with elemental chlorine in the gas phase, a reactivity order for hydrogen abstraction of tertiary > secondary > primary is generally seen, but the quite low selectivity (maximum range of 5–6)[6] usually leads to production of complex mixtures.[7] Low-level C–H bond elongation at the transition state has consequently been implicated,[8] although various degrees of looseness in the activated complex seemingly can become operational as hydrocarbon structure is altered.[9] The incorporation of cyclopropane rings into the molecular framework contributes to enhanced selectivity, especially favoring the cyclopropylcarbinyl site. Thus, while Walling and Fredricks established that cyclopropane itself has 1/20 the reactivity of a normal secondary hydrogen toward $Cl^\cdot$ at 0 °C,[10] Roberts and Mazur showed that methylcyclopropane undergoes photochlorination predominantly via methyl hydrogen abstraction to give chloromethylcyclopropane and 4-chloro-1-butene.[12]

With more highly strained molecules such as bicyclo[2.1.0]pentane[14] and nortricyclene,[15] chlorine prefers to enter into polar addition reactions. Olefinic substrates share this common problem. For abstraction of allylic hydrogens, the reagent of choice is *tert*-butyl hypochlorite, since *tert*-butoxy radical addition to double bonds does not prevail. Walling's extensive examination of the reactions of *t*-BuOCl with a variety of olefins has shown that an allylic hydrogen is activated with respect to a corresponding saturated hydrogen atom.[16] More recent work by de Meijere's group has established that the cyclopropylcarbinyl sites in trishomobarrelene (**3**) and trishomobullvalene (**4**) are specifically halogenated by this reagent.[17] Further, Schallner has demonstrated the utility of fluorotrichloromethane (Freon 11) as a low-temperature solvent for such photochlorinations.[18]



3 **4**

Irradiation of a cold (−63 °C) solution of **1** and *tert*-butyl hypochlorite in Freon 11 for 45 min provided a single monochloride (**5**) and a dichloride (**6**) as major products (85%), together with several more extensively halogenated materials which were not further investigated. Preparative VPC purification gave **5** and **6** in 46 and 6% isolated yields, respectively. When **5** was resubmitted to the conditions of chlorination, efficient conversion to **6** (71% isolated) was realized. Since the ^{13}C NMR spectrum of **5** consists of nine lines arising from one quaternary, five tertiary (including the two olefinic centers), and three secondary carbon atoms, substitution clearly had not occurred at a biscyclopropylcarbinyl site (C_7), a cyclopropyl methylene position, or the double bond (C_3, C_4).

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Comparable analysis of **6** revealed this dichloride to be a symmetrical molecule. Off-resonance decoupling established the five signals to arise from two quaternary, four tertiary, and three secondary sites. These data are uniquely consistent with radical substitution at C_1,C_6 or C_2,C_5 in the bishomotropilidene.

5 **6**

A clean distinction between these possibilities can be made by analysis of the ^{1}H NMR spectra. In $CDCl_3$, $H_{7\text{-exo}}$ and $H_{7\text{-endo}}$ of hydrocarbon **1** appear at δ 2.47 and 0.32 as a doublet of multiplets (J = 14 Hz) and a multiplet, respectively. This rather characteristic pattern is unaltered in **5** (δ 2.53 and 0.80) and somewhat more sharply structured in **6** [δ 2.60 (d of t, J = 14 and 5.5 Hz) and 0.07 (d of t, J = 14 and 11 Hz)]. Therefore, only long-range or virtual H–H coupling is affected upon chlorination. The protons adjacent to C_7 must consequently have remained intact. That chlorination had occurred at C_2 and C_5 is further revealed by the reduced level of spin–spin interaction operating on the cyclopropyl methylene protons relative to **1**.

With these assignments of structure, it is immediately obvious that the allylic cyclopropane hydrogens in **1** are most reactive. Furthermore, halogenative substitution has occurred without structural rearrangement, in line with the preestablished reluctance of cyclopropyl radicals to relieve strain through ring opening.[19]

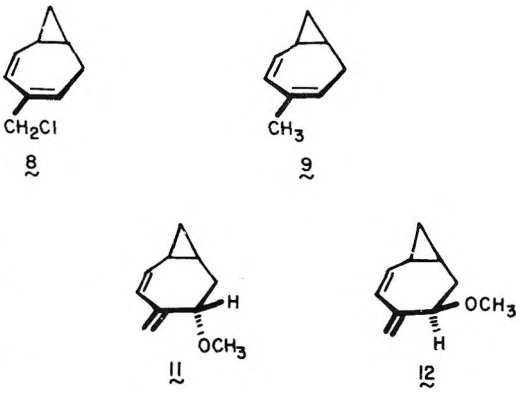
Submission of **2** to analogous reaction with *tert*-butyl hypochlorite gave 62% of a colorless oil composed predominantly (85%) of monochloride **7**. Although attempts to purify **7** by VPC and column chromatographic techniques usually led to rearrangement (see below), ^{13}C NMR analysis of a carefully purified sample (see Experimental Section) showed clearly that substitution had again taken place at a tertiary allylic cyclopropyl site (see Experimental Section). The ^{1}H NMR spectrum shows the protons bonded to C_7 to be widely separated (multiplets at δ 2.50 and 1.40), but does not provide indication whether the favored conformer is **7a** or **7b**. The ole-

7a **7b**

finic protons of the chloride appear as a multiplet centered at δ 5.70, at slightly lower field than in **2**. The two cyclopropyl methylene protons which are projected over the seven-membered ring have moved to higher field, with that presumed to be on the chlorinated ring appearing at δ 1.05 and the other at δ 0.70. The remaining hydrogens resonate in the region δ 1.50–1.10.

Molecule **7a** is so structured that the chlorine atom occupies a pseudoequatorial position, while in **7b** the halogen is projected in a pseudoaxial direction and normally should be less favored for the usual energetic reasons. For mechanistic reasons, **7b** must be the initial product of free-radical substitution. Since **7** is not subject to further chlorination as is **5**, this may mean that conformer **7a** (where H_2 is now properly stereoaligned with the π bond) is not present in reasonable quantities at low temperatures. The inference would be that **7b** is highly populated under these conditions. However, since the argument rests on negative evidence, this conclusion is obviously tenuous.

Rearrangement Reactions. To achieve purposeful rearrangement of **7** under purely thermal conditions, the neat chloride was sealed in a glass ampule and immersed in an oil bath heated at 150 °C for 4 h. ^{1}H NMR analysis of the product indicated that complete rearrangement to **8** had occurred. Similar results could be achieved upon passing **7** through VPC columns heated to 180 °C or more efficiently by elution through Florisil with hexane (100% yield). Structural assignment to **8** follows from mass spectral, combustion, ultraviolet, and NMR evidence. For example, its electronic spectrum (in cyclohexane) is characterized by a single maximum at 232 nm (ϵ 3100) as expected for such a homotropilidene.[20] In the NMR spectrum, the olefinic protons appear as a doublet of doublets (J = 5 and 11 Hz) at δ 6.22 (1 H) and a multiplet centered at δ 5.70 (2 H). Additionally, the $-CH_2Cl$ protons are seen as a broadened singlet at δ 3.87, downfield of the allylic cycloheptyl methylene multiplet at δ 2.43–1.97. This pattern, as well as that exhibited by the cyclopropyl hydrogens, is generally characteristic of this class of dienes and particularly **9**.[21]



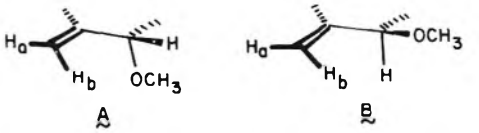
8 **9**

10 **11** **12**

The greater solvolytic reactivity of **7** as compared to **5** was made evident through experiments conducted in anhydrous methanol. Upon heating **7** in this solvent at 100 °C (sealed tube) for 4 h, conversion to a mixture of **10** (94%), **11** (4%), and **12** (2%) was observed; **5** remained unresponsive and could be recovered. However, at 150 °C **5** was transformed to **10** (95%), **11** (4%), and **12** (1%) after 4 h.

Treatment of either chloride with a slight excess of silver trifluoroacetate in methanol at room temperature for brief periods of time led to the same three methyl ethers, although in somewhat different ratios (for **5**, 73.5, 7, and 19.5%; for **7**, 67.5, 15, and 17.5%).

In the case of **10**, its structure follows directly from its ultraviolet and ^{1}H NMR spectra. With the exception of the methyl signal shown by **9** and the methoxylmethyl peaks exhibited by **10**, their spectra are otherwise essentially superimposable. The proton spectra of **11** and **12** clearly define their gross structural features. To distinguish between the epimers, recourse to molecular models was made. For **13**, the preferred conformation appears to be that which places the methoxyl substituent below the plane defined by the exo methylene group. In the geometry given by A, the magnetic environments



A **B**

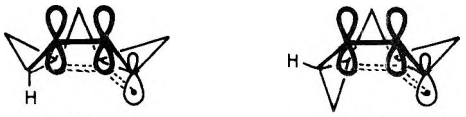
of the terminal olefinic protons become rather similar and could reasonably correspond to the broadened singlet absorption (2 H) shown by **11** a δ 5.03. For **12**, the same ring conformation appears again to be favored, thereby necessitating that the methoxyl group approach syn proton H_b rather closely (see B). Operation of a through-space shielding effect would be expected to cause H_b to appear at lower field than

H_a. In fact, ether **12** shows H_b and H_a to be widely divergent in their chemical shifts. These protons appear as multiplets centered at δ 5.27 and 4.97, respectively. Although this basis for stereochemical assignment is not totally unequivocal, it does appear entirely reasonable.

Independent treatment of **8** with silver trifluoroacetate in methanol afforded **10**, **11**, and **12** in the ratio 55:20.5:24.5. Since **10** proved to be stable to these reaction conditions, ethers **11** and **12** must be primary products in all the rearrangements examined in this study.

Discussion

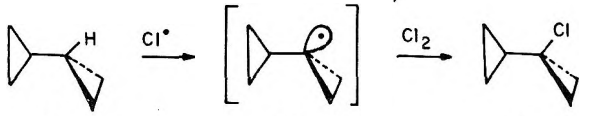
An interesting feature of the free-radical chlorination of bishomocycloheptatrienes **1** and **2** is the regioselectivity of abstraction favoring an allylic cyclopropyl hydrogen. The observed reactivity is viewed as the combined result of structurally enforced geometry which fixes H_2 or H_5 in plane with the pπ orbitals and the resonance stabilization available to free radicals **13** and **14**. The customary bond strength and



13 **14**

higher electronegativity of a cyclopropyl C–H bond is thereby effectively lowered to the point where other possible reactions are hardly competitive. This reasoning assumes that the transition states leading to **13** and **14** resemble products more than starting materials. In this way, the activated complexes can profit energetically from their proximity to the potential minima on the reaction profile.

The formation of tertiary chlorides **5** and **7** without structural rearrangement parallels earlier discoveries which have shown that cyclopropyl radicals normally fail to ring open. The closest analogy known to us is the vapor-phase chlorination of bicyclopropyl (**15**) which proceeds via cyclopropylcarbinyl-stabilized radical **16** to **17** with retained structural integrity.[22]



15 **16** **17**

In contrast to the stability of **13** and **14**, the cyclopropane ring comprising the seat of reaction during carbocation generation does not remain structurally intact. Since the product compositions obtained from direct methanolysis of these chlorides are identical, the intervention of a common intermediate satisfactorily represented by allyl cation **18** is implicated. The differences in the ratios of ethers **10**–**12** obtained in the Ag^+-assisted reactions are considered to arise because of somewhat earlier transition states where less structural reorganization has had time to occur. The isomeric differences between **13** and **14** consequently become more apparent.

Qualitatively speaking, the solvolytic behavior of **5** and **7** is somewhat enhanced relative to that of simpler cyclopropyl halides.[22-24] Chloride **7**, which necessarily must have one of its cyclopropane rings axially disposed, is the more reactive as a consequence of its higher ground-state energy. The products of methanolysis are consistent with electrocyclic ring opening concerted with ionization,[25] as found previously for 1-vinylcyclopropyl tosylate.[26] Significantly, disrotatory ring fission synchronous with departure of the leaving group would necessitate that only low-level positive change density actually develop on the originally functionalized carbon,[27] such charge distribution precluding the possibility of efficient vertical stabilization[28] by the adjoining vinyl group as in **19**. Evidently, any stabilization which might accrue to **19** is inadequate to impede the facile ring opening giving rise to **18** which releases inherent strain while likely occurring with little or no energy barrier.[27,29]

18 **19**

In summary, the preceding results reveal that the π bond of a vinylcyclopropane can activate an allylic cyclopropyl hydrogen to free-radical substitution but cannot reduce the barrier to (conrotatory?)[30] ring opening of the three-membered ring despite the possible release of ~30 kcal/mol of energy.[31] When cations are involved, essentially the reverse chemical response is seen. Cyclopropyl ring fission concurrent with ionization presumably obtains while delocalization of positive charge by comparable vertical stabilization is not of primary importance.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 467 spectrophotometer. The ^1H NMR spectra were determined with Varian A-60A and Bruker HX-90 instruments and apparent splittings are given in all cases. The ^{13}C spectra were also run on the Bruker spectrometer. Mass spectra were measured with an AEI-MS9 spectrometer at an ionization energy of 70 eV. Preparative scale VPC separations were performed on a Varian Aerograph Model A90-P3 instrument equipped with thermal conductivity detectors. Microanalytical determinations were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

2-Chloro-*syn*-1,5-bishomocycloheptatriene (5) and 2,5-Dichloro-syn-1,5-bishomocycloheptatriene (6). A solution of **1**[2] (300 mg, 2.5 mmol) and *tert*-butyl hypochlorite (400 mg, 36 mmol) in 3 mL of Freon 11 contained in a 10-mm Pyrex NMR tube was placed in a chloroform–liquid nitrogen slush bath (−63 °C) contained in a Pyrex Dewar flask. The reaction mixture was irradiated for 45 min with a Sylvania sunlamp, diluted with 15 mL of ether, washed with saturated sodium bicarbonate solution, and dried. Concentration and preparative VPC purification showed two products (ratio 85:15) to dominate the mixture (85%). The more rapidly eluted major component (176 mg, 46%) was a colorless oil identified as monochloride **5**: IR ν_{max} (neat) 3070, 3000, 2920, 2860, 1650, 1450, 1130, 825, and 725 cm^{-1}; ^1H NMR δ_{Me_4Si} (CCl_4) 5.62 (s, 2), 2.53 (d of t, J = 13 and 4 Hz, 1), 2.08–1.03 (br m, 4), 0.80 (d of t, J = 7 and 4 Hz, 1), 0.50 (t, J = 5.5 Hz, 1), and 0.00 (m, 2); ^{13}C NMR ($CDCl_3$) 131.4 (d), 128.9 (d), 41.2 (s), 34.3 (k), 28.7 (d), 25.1 (t), 15.0 (d), 14.2 (t), and 12.8 ppm (d); *m/e* calcd 154.0549, found 154.00554.

Anal. Calcd for $C_9H_{11}Cl$: C, 69.90; H, 7.17. Found: C, 69.74; H, 7.22.

The second component proved to be dichloride **6**: ^1H NMR δ_{Me_4Si} (CCl_4) 5.82 (s, 2), 2.60 (d of t, J = 14 and 5.5 Hz, 1), 1.92 (m, 2), 1.30 (d of d, J = 9 and 5 Hz, 2), 0.58 (t, J = 5 Hz, 2), and 0.07 (d of t, J = 14 and 11 Hz, 1); ^{13}C NMR ($CDCl_3$) 130.1 (d), 39.4 (s), 34.9 (t), 28.6 (d), and 25.1 ppm (t); *m/e* 188.

Chlorination of 5. A solution of **5** (20 mg, 0.13 mmol) and *tert*-butyl hypochlorite (17 mg, 0.16 mmol) in 0.4 mL of Freon 11 was irradiated as described above for 45 min. The reaction mixture was diluted with ether (10 mL), washed with saturated sodium bicarbonate solution, dried, and concentrated to give 17 mg (71%) of **6**, identical in all respects with the above sample.

2-Chloro-*anti*-1,5-bishomocycloheptatriene (7). A solution of **2**[2] (240 mg, 2.00 mmol) and *tert*-butyl hypochloride (220 mg, 2.04 mmol) in 2 mL of Freon 11 was allowed to react as described previously. Molecular distillation [65 °C (0.2 Torr)] afforded 119 mg (62%) of a colorless oil, VPC analysis of which showed it to be composed chiefly (86%) of one component. Preparative VPC purification under carefully controlled conditions (6 ft × 0.25 in. 5% SE-30 on Chromosorb G, 120 °C) gave pure **7**: IR ν_{max} (neat) 3020, 2920, 1645, 1450, 1123, 1037, 810, and 785 cm^{-1}; ^1H NMR δ_{Me_4Si} (CCl_4) 5.70 (m, 2), 2.50 (br m, 1), 1.40 (br m, 1), 1.50–1.10 (m, 5), 1.05 (m, 1), and 0.70 (m, 1); ^{13}C NMR ($CDCl_3$) 130.6 (d), 126.5 (d), 41.8 (s), 27.2 (t), 25.3

(d), 24.1 (t), 16.9 (d), 14.5 (d), and 12.8 ppm (t); *m/e* calcd 154.0549, found 154.0554.

Anal. Calcd for $C_{9}H_{11}Cl$: C, 69.90; H, 7.17. Found: C, 69.74; H, 7.33.

4-Chloromethylbicyclo[5.1.0]octa-2,4-diene (8). A. Thermal Rearrangement of 7. A small sample of chloride **7** was sealed neat in a small glass ampule which was immersed in an oil bath preheated to 150 °C. After 4 h, the ampule was opened and the residual liquid was examined by ^{1}H NMR. The spectrum was identical with that of **8** as prepared on a preparative scale below.

B. Florisil-Promoted Rearrangement of 7. Chloride **7** (50 mg, 0.32 mmol) was adsorbed onto 2 g of activated Florisil using hexane as solvent. After 15 min, the product was eluted with hexane to give 50 mg (100%) of **8**; ^{1}H NMR δ_{Me_4Si} (CCl_4) 6.22 (d of d, J = 11 and 5 Hz, 1), 6.00–5.40 (m, 2), 3.87 (br s, 2), 2.43–1.97 (m, 2), 1.80–0.70 (m, 3), and 0.43 (d of t, r = 9 and 3 Hz, 1); UV λ_{max} (cyclohexane) 232 nm (ϵ 3100); *m/e* calcd 154.0549, found 154.0552.

Anal. Calcd for $C_{9}H_{11}Cl$: C, 69.90; H, 7.17. Found: C, 69.48; H, 7.11.

Methanolysis Experiments. A. Silver(I)-Assisted Ionization. To a 0.1 M solution of **5** or **7** in anhydrous methanol (purified by distillation from magnesium methoxide) was added 1.1–1.2 equiv of silver trifluoroacetate (Aldrich). The resulting mixture was allowed to stir at room temperature for 1–4 h. After filtration and dilution with water, the products were extracted into petroleum ether and the combined organic layers were washed with brine, dried, and concentrated. Product analysis, accomplished by VPC methods on a 10 ft × 0.25 in. 15% XF-1150 column (Chromosorb P, 120 °C), revealed conversion to a mixture of ethers **10**, **11**, and **12**. The individual components were purified by preparative scale separation (for **5**, 73.5, 7, and 19.5%; for **7**, 67.5, 15, and 17.5%).

For **10**: IR ν_{max} (neat) 3000, 2920, 2880, 2830, 2810, 1610, 1440, and 1090 cm^{-1}; UV λ_{max} (cyclohexane) 251 nm (ϵ 2900); ^{1}H NMR δ_{Me_4Si} (CCl_4) 6.23 (d of d, J = 11.5 and 4.5 Hz, 1), 5.75 (m, 1), 5.60 (d, J = 11.5 Hz, 1), 3.82 (br s, 2), 3.29 (s, 3), 2.60–2.20 (m, 2), 1.63 (m, 1), 1.40–0.80 (m, 2), and 0.80–0.30 (m, 1); *m/e* calcd 150.1045, found 150.1048.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.83; H, 9.56.

For **11**: ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 5.80 (m, 2), 5.03 (s, 2), 3.80 (d, J = 8 Hz, 1), 3.34 (s, 3), 2.61 (m, 1), 1.70–0.80 (m, 4), and 0.15 (m, 1); *m/e* calcd 150.1045, found 150.1048.

For **12**: ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 5.83 (s, 1), 5.80 (br s, 1), 5.27 (m, 1), 4.98 (m, 1), 3.93 (m, 1), 3.43 (s, 3), 2.47 (m, 1), 1.70–0.70 (m, 4), and 0.20 (m, 1); *m/e* calcd 150.1045, found 150.1048.

Comparable treatment of **8** afforded 56% of **10**, 24% of **11**, and 20% of **12**.

B. Uncatalyzed Solvolyses. A solution of **7** (25 mg) in 2 mL of purified methanol was sealed in a glass ampule and heated in an oil bath at 100 °C for 4 h. The contents of the ampule were concentrated in vacuo and analyzed on the XF-1150 column: 94% of **10**, 4% of **11**, and 2% of **12**.

Comparable reaction of **5** but at 150 °C gave an identical distribution of the three ethers.

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Registry No.—**1**, 62211-22-7; **2**, 62163-62-6; **5**, 65027-53-4; **6**, 65027-54-5; **7**, 65058-85-7; **8**, 65027-55-6; **10**, 65027-56-7; **11**, 65027-57-8; **12**, 65058-86-8.

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Reaction Kinetics of Cinnamoyl, β-2-Furylacryloyl, and β-2-Thienylacryloyl Chlorides with Anilines in Benzene

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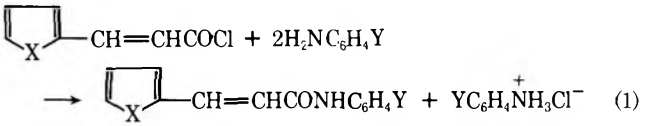
The reaction rates of cinnamoyl, β-2-furylacryloyl, and β-2-thienylacryloyl chlorides with substituted anilines have been measured in benzene at different temperatures. The reactions follow second-order kinetics. The activation parameters and the slopes of the Hammett and Brønsted plots are similar to those of the benzoylation reaction. The results show that the reaction mechanism of cinnamoyl, β-2-furylacryloyl, and β-2-thienylacryloyl chlorides with aniline is the same as for the benzoylation reaction. The cinnamoyl, β-2-furylacryloyl, and β-2-thienylacryloyl chloride reactivities are similar. The reaction rates of cinnamoyl and β-2-thienylacryloyl chlorides are faster than those of benzoyl and 2-thenoyl chlorides, whereas the reactivity of β-2-furylacryloyl chloride is similar to that of 2-furoyl chloride. The results show that, when a vinylene group is interposed between the reaction center and the heteroaromatic ring, the heteroaromatic nuclei behave as the benzene nucleus. The Hammett treatment of the data shows the variability of σ_{het} values. The data are well correlated by the Taft–Pavelich equation, indicating that the reactivity of the five-membered rings depends on steric and polar effects.

Several studies have been carried out with the purpose of comparing the side-chain reactivity in the furan and thiophene series with that of the benzene series.

Furyl and thienyl groups may be expected to exert two opposing electronic effects. There will be an electron-withdrawing inductive effect caused by the electronegatives of the heteroatoms; second, there will be an electron-donating mesomeric effect due to the ability of the heteroatoms to share their unshared electron pairs. It was pointed out that both the inductive and the resonance effects of the heterocyclic rings may contribute.[1]

In the past few years we have studied the kinetics of the reaction of 2-[2] and 3-thenoyl[3] and 2- and 3-furoyl chlorides[1,4] with anilines, 2- and 3-chloroacetylfuran, and 2- and 3-chloroacetylthiophenes with triethyl phosphite,[5] basic[6] and acid hydrolysis[7] of 2- and 3-furanilides, and 2- and 3-thenanilides. The data indicated that these heterocyclic rings, depending on the pattern of substitution and reaction considered, may act as electron donating or electron withdrawing.

Following this research work in this paper we report the reaction kinetics of cinnamoyl, β-2-furylacryloyl, and β-2-thienylacryloyl chlorides with anilines in benzene (eq 1) with the aim of studying the influence of the heteroaromatic rings on the reactivity of the acid chlorides where the heteroaromatic systems are separated from the reaction center by the insertion of a vinylene group.



$$\text{X-CH=CHCOCl} + 2\text{H}_2\text{NC}_6\text{H}_4\text{Y} \rightarrow \text{X-CH=CHCONHC}_6\text{H}_4\text{Y} + \text{YC}_6\text{H}_4\overset{+}{\text{N}}\text{H}_3\text{Cl}^- \quad (1)$$

X = CH=CH, O, S
Y = H, *m*-CH_3, *p*-CH_3, *m*-Cl, *p*-Cl, *m*-NO_2

Results and Discussion

The reactions of cinnamoyl, β-2-furylacryloyl, and β-2-thienylacryloyl chlorides with meta- and para-substituted anilines took place quantitatively according to eq 1. The reactions were followed kinetically as previously described[3,4] and in all cases the compounds gave excellent second-order kinetics.

The second-order rate constants, reported in Tables I, II,

Table I. Second-Order Rate Constants and Activation Parameters for the Reaction of Cinnamoyl Chloride with Meta- and Para-Substituted Anilines in Benzene

No.	Substituent	Registry no.	pK_a[a]	$k_2 \times 10^2$, L mol^{-1} s^{-1} 15 °C	25 °C	40 °C	E_A[b]	Log A	ΔS^*[c]
1	H	62-53-3	4.58	7.90	12.5	20.6	6.83	4.09	−41.8
2	*m*-CH_3	108-44-1	4.69	15.1	23.1	35.8	6.14	3.85	−42.9
3	*p*-CH_3	106-49-0	5.12	36.8	49.3	81.2	5.71	3.89	−42.7
4	*m*-Cl	108-42-9	3.34	0.491	0.778	1.53	8.16	3.88	−42.8
5	*p*-Cl	106-47-8	3.98	2.01	3.06	5.79	7.61	4.07	−41.9
6	*m*-NO_2	99-09-2	2.50	0.0496	0.0934	0.184	9.34	3.79	−43.2

[a] Reference 8. [b] In units of kcal/mol. [c] At 25 °C, in cal mol^{-1} K^{-1}.

Table II. Second-Order Rate Constants and Activation Parameters for the Reaction of β-2-Furylacryloyl Chloride with Meta- and Para-Substituted Anilines in Benzene

No.	Substituent	pK_a[a]	$k_2 \times 10^2$, L mol^{-1} s^{-1} 15 °C	25 °C	40 °C	E_A[b]	Log A	ΔS^*[c]
1	H	4.58	7.23	11.1	18.5	6.71	3.95	−42.4
2	*m*-CH_3	4.69	12.8	19.5	31.5	6.42	3.99	−42.2
3	*p*-CH_3	5.12	34.6	47.5	77.4	5.79	3.93	−42.5
4	*m*-Cl	3.34	0.454	0.690	1.34	7.78	3.55	−44.3
5	*p*-Cl	3.98	1.79	2.61	4.96	7.26	3.75	−43.3
6	*m*-NO_2	2.50	0.0431	0.0765	0.161	9.44	3.79	−43.2

[a] Reference 8. [b] In units of kcal/mol. [c] At 25 °C, in cal mol^{-1} K^{-1}.

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Table III. Second-Order Rate Constants and Activation Parameters for the Reaction of β-2-Thienylacryloyl Chloride with Meta- and Para-Substituted Anilines in Benzene

No.	Substituent	pK_a[a]	$k_2 \times 10^2$, L mol^{-1} s^{-1} 15 °C	25 °C	40 °C	E_A[b]	Log A	ΔS^*[c]
1	H	4.58	6.91	10.3	18.3	6.99	4.14	−41.6
2	m-CH_3	4.69	10.6	16.4	26.4	6.50	3.97	−42.3
3	p-CH_3	5.12	26.1	36.4	60.3	6.02	3.98	−42.3
4	m-Cl	3.34	0.394	0.621	1.22	8.12	3.75	−43.3
5	p-Cl	3.98	1.63	2.32	4.64	7.57	3.94	−42.5
6	m-NO_2	2.50	0.0385	0.0735	0.152	9.72	3.98	−42.3

[a] Reference 8. [b] In units of kcal/mol. [c] At 25 °C, in cal mol^{-1} K^{-1}.

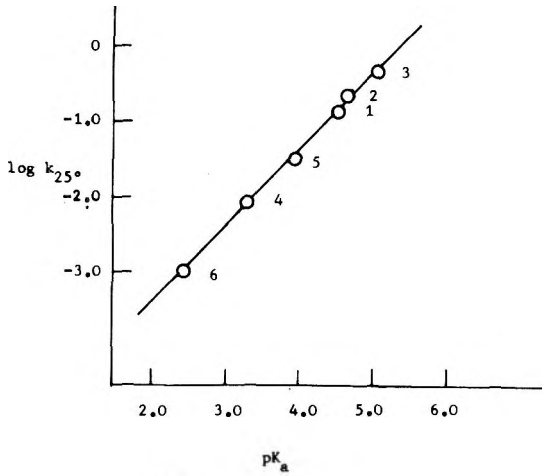


Figure 1. Plot of log k_{25} for the reaction of cinnamoyl chloride with anilines in benzene against the logarithm of their dissociation constants in water at 25 °C (Brønsted plot).

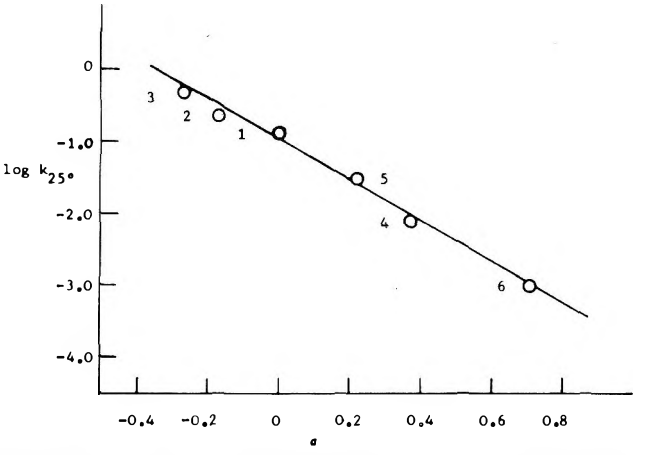


Figure 2. Hammett plot for the reaction of cinnamoyl chloride with anilines at 25 °C in benzene.

and III, show that electron-donating substituents accelerate and electron-withdrawing groups retard the reactions. The results indicate that the reactivity sequence is cinnamoyl chloride ≥ β-2-furylacryloyl chloride ≥ β-2-thienylacryloyl chloride. The difference of reactivity among them is small being the ratio $k/k' = 1.13 \pm 0.09$ and $k/k'' = 1.27 \pm 0.14$, where k are the reaction constants at 25 °C of cinnamoyl chloride, k' are the reaction constants at 25 °C of β-2-furylacryloyl chloride, and k'' are the reaction constants at 25 °C of β-2-thienylacryloyl chloride.

The activation parameters, listed in Tables I, II, and III, show a regular variation with the substituent in the aniline, as noted in the furoyl[1] and thenoyl chloride[3] reactions.

The large negative entropies of activation are as expected in reaction involving polar transition states and similar to those found previously in 2-[2] and 3-thenoyl[3] and 2- and 3-furoyl chloride[1] reactions.

As for the thenoyl[2,3] and furoyl chlorides[1] reactions, linear relationships were also found in the reactions of cinnamoyl, β-2-furylacryloyl, and β-2-thienylacryloyl chlorides with anilines between log k at 25 °C and the pK_a values at 25 °C in water of the corresponding protonated anilines[8] indicating that also the reaction rates of these acid chlorides with aniline depend on the electron density on the nitrogen atom. The slopes of the Brønsted plots, 1.04 (r = 0.998), 1.06 (r = 0.999), and 1.03 (r = 0.999), for cinnamoyl, β-2-furylacryloyl, and β-2-thienylacryloyl chlorides, respectively, are similar to those found for benzoylation and thenoyl[2,3] and furoyl chloride[1] reactions. The plot of log k at 25 °C of the reaction of cinnamoyl chloride with anilines against the pK_a values at 25 °C in water of the corresponding protonated anilines are reported in Figure 1.

The plot of log k at 25 °C for the reactions of cinnamoyl, β-2-furylacryloyl, and β-2-thienylacryloyl chlorides against Hammett's σ constants are linear with slopes of −2.77 (r = 0.995), −2.86 (r = 0.995), and −2.74 (r = 0.994), respectively. Figure 2 reports the plot of log k at 25 °C for the reaction of cinnamoyl chloride with anilines against Hammett's σ constants. The values of the slopes are similar to those found for benzoylation[9-11] and thenoyl[2,3] and furoyl chlorides[1] reactions.

From these results it is evident that cinnamoyl, β-2-furylacryloyl, and β-2-thienylacryloyl chlorides react with aniline in benzene with the same mechanism as the reaction of benzoylation involving the attack of the lone pair of the electrons of the amine group on the carbonyl carbon atom.[12]

The reaction rates of cinnamoyl and β-2-thienylacryloyl chlorides are faster than those of benzoyl[13] and 2-thenoyl chlorides,[2] whereas the reactivity of β-2-furylacryloyl chloride is similar to that of 2-furoyl chloride[1] being the ratio $k/k' = 1.18 \pm 0.16$, where k are the reaction rate constants at 25 °C of 2-furoyl chloride and k' are the reaction rate constants at 25 °C of β-2-furylacryloyl chloride.

In the reaction of 2- and 3-furoyl[1,4] and 2-[2,4] and 3-thenoyl[3,4] chlorides with aniline we have found the reactivity sequence 2-furoyl chloride > benzoyl chloride > 3-thenoyl chloride ≃ 3-furoyl chloride > 2-thenoyl chloride indicating that, in comparison with the benzene nucleus, the thienyl group behaves as electron donating, whereas the furyl group behaves as electron donating in the 3-furoyl chloride and as electron withdrawing in the 2-furoyl chloride. From the results here obtained it is clear that the reactivity of heterocyclic acid chlorides, when the heteroaromatic system is separated from the reaction center by the insertion of a vinylene group, is similar to that of benzene derivatives, indicating that the heteroaromatic nuclei behave as the benzene nucleus. The same trend was observed in the saponification of ethyl ester of cinnamic, β-2-furylacrylic, and β-2-thienylacrylic acids.[14]

The reactivity sequence (2-furyl > phenyl > 2-thienyl) of the reaction of acid chlorides with aniline[4] was observed in

Table IV. Application of the Taft–Pavelich Equation to the Reaction of Acid Chlorides (Ar–COCl) with Aniline in Benzene at 25 °C

No.	Ar	σ^*	E_s	Log k	Log $k - \delta E_s$
1	Phenyl	0.60[a]	−2.55[a]	−1.20[c]	1.42
2	2-Furyl	1.08[b]	−3.16[b]	−0.876[c]	2.38
3	3-Furyl	0.65[b]	−2.71[b]	−1.39[c]	1.40
4	2-Thienyl	0.93[b]	−3.39[b]	−1.59[c]	1.91
5	3-Thienyl	0.65[b]	−2.73[b]	−1.36[c]	1.45
6	5-Methyl-2-thienyl	0.84[b]	−3.58[b]	−1.99[d]	1.70
7	5-Chloro-2-thienyl	1.26[b]	−3.53[b]	−1.23[d]	2.40
8	5-Nitro-2-thienyl	1.65[b]	−3.19[b]	−0.374[d]	2.91

[a] J. Shorter, "Advances in Linear Free Energy Relationship", N. B. Chapman and J. Shorter, Ed., Plenum Press, London, 1972, p 76. [b] Reference 15. [c] Reference 1. [d] G. Alberghina, A. Arcoria, S. Fisichella, and G. Scarlata, *Gazz. Chim. Ital.*, **103**, 319 (1973).

Table V. Application of the Taft–Pavelich Equation to the Reaction of Acid Chlorides (R–COCl) with *m*-Nitroaniline in Benzene at 20 °C

No.	R	σ^*	E_s	Log k	Log $k - \delta E_s$
1	CH_3	0[a]	0[a]	−1.91[c]	−1.91
2	n-C_3H_7	−0.115[a]	−0.36[a]	−2.02[c]	−1.66
3	n-C_4H_9	−0.130[a]	−0.39[a]	−2.17[c]	−1.78
4	i-C_4H_9	−0.125[a]	−0.93[a]	−2.42[c]	−1.49
5	$C_6H_5CH_2$	0.215[a]	−0.38[a]	−1.68[c]	−1.30
6	$CH_3CH{=}CH$	0.36[a]	−1.63[a]	−2.32[c]	−0.693
7	$ClCH_2$	1.05[a]	−0.24[a]	−0.38[c]	−0.140
8	Cl_3C	2.65[a]	−2.06[a]	−0.558[c]	1.50
9	C_6H_5	0.60[a]	−2.55[a]	−3.49[c]	0.945
10	2-Furyl	1.08[b]	−3.16[b]	−3.24[d]	−0.0863
11	3-Furyl	0.65[b]	−2.71[b]	−3.80[d]	−1.10
12	3-Thienyl	0.65[b]	−2.73[b]	−3.69[d]	−0.965
13	$C_6H_5CH{=}CH$	0.41[a]	−1.89[a]	−3.18[e]	−1.29

[a] J. Shorter, "Advances in Linear Free Energy Relationship", N. B. Chapman and J. Shorter, Ed., Plenum Press, London, 1972, p 76. [b] Reference 15. [c] H. S. Venkataraman and C. N. Hinshelwood, *J. Chem. Soc.*, 4977 (1960). [d] Reference 1, interpolated at 20 °C from activation parameters. [e] This work, interpolated at 20 °C from activation parameters.

other nucleophilic substitution at the carbonyl group, as in the reaction of aryl chloromethyl ketones with triethyl phosphite,[5] in the alkaline hydrolysis of esters[15] and in the reduction of aryl methyl ketones by sodium borohydride.[16]

The Hammett equation was applied to 5-heteroaromatic rings[17,18] and, considering the heterocycle as a substituted benzene, σ_{het} constants for the replacement of a CH=CH group in the benzene ring by the heteroatoms were calculated by

$$\sigma_{het} = (\log k - \log k_0)/\rho \qquad (2)$$

where log k is the reaction rate at 25 °C of the heteroaromatic compounds, log k_0 is the reaction rate at 25 °C of the unsubstituted benzene derivative, and ρ is the reaction constant of benzene derivatives. The σ_{het} values for the reaction of furoyl and thenoyl chlorides with aniline in benzene[4] are $\sigma_{\alpha-0} = 0.31$, $\sigma_{\beta-0} = -0.05$, $\sigma_{\alpha-S} = -0.20$, and $\sigma_{\beta-S} = -0.04$ using the $\rho = 1.42$ and log $k_0 = -1.31$ values.[19] The Hammett treatment was also applied to other nucleophilic substitutions at the carbonyl group and the results show the variability of σ_{het} values.[20]

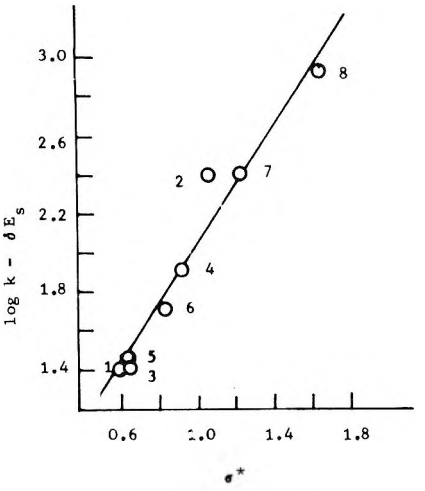


Figure 3. Plot of (log $k - \delta E_s$) for the reaction of acid chlorides with aniline in benzene at 25 °C against σ^* constants.

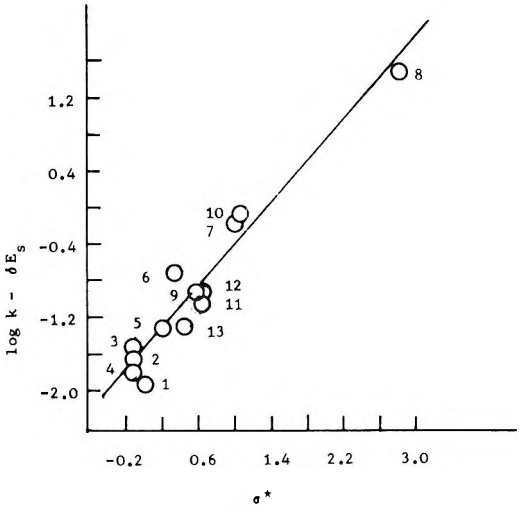


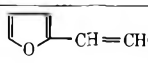
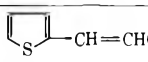
Figure 4. Plot of (log $k - \delta E_s$) for the reaction of acid chlorides with *m*-nitroaniline in benzene at 20 °C against σ^* constants.

The Taft–Pavelich[21] (eq 3) equation that takes into account both polar (σ^*) and steric effects (E_s) was recently used to correlate the kinetic data of reactions of heteroaromatic compounds to the carbonyl group.[20]

$$\log k/k_0 = \rho^*\sigma^* + \delta E_s \qquad (3)$$

We applied eq 3 in the reactions of acid chlorides with aniline at 25 °C (Table IV) and with *m*-nitroaniline at 20 °C in benzene (Table V). Table V contains only the value of cinnamoyl chloride, because the σ^* and E_s values for β-2-furylvinyl and β-2-thienylvinyl groups are not known. The data are well correlated by eq 3, obtaining $\rho = 1.52$ (standard deviation, $s = 0.12$), $\delta = 1.03$ ($s = 0.11$), log $k_0 = 0.489$ for the reaction of acid chlorides with aniline and $\rho = 1.19$ ($s = 0.09$), $\delta = 1.01$ ($s = 0.06$), and log $k_0 = -1.68$ for the reaction of acid chlorides with *m*-nitroaniline. The plots of log k at 25 °C and at 20 °C for the reactions of acid chlorides with aniline and *m*-nitroaniline, respectively, cleaned from the contribution of the steric effect (log $k - \delta E_s$) against σ^* constants give linear relationships with $r = 0.98$ (Figure 3) for the reaction of acid chlorides with aniline and $r = 0.97$ (Figure 4) for the reaction of acid chlorides with *m*-nitroaniline, indicating that the reactivity of five-membered rings depends on steric and polar effects. Conjugative effects cannot be excluded because E_s values for aromatic and unsaturated groups include conjugative contributions.[22]

Table VI. Physical Constants of Anilides[a,b]

No.	X	Ph—CH=CHCONHC$_6$H$_4$X					
		Mp, °C	Registry no.	Mp, °C	Registry no.	Mp, °C	Registry no.
1	H	151[c]	3056-73-3	128[g]	15341-86-3	143[f]	28424-57-9
2	*m*-CH_3	114[d]	57830-64-5	111[g]	15341-96-5	136[f]	64741-17-9
3	*p*-CH_3	162[d]	6876-68-2	156[g]	15341-94-3	143[h]	28424-60-4
4	*m*-Cl	120[e]	64741-15-7	104[g]	15341-89-6	101[h]	64741-16-8
5	*p*-Cl	185[e]	53691-91-1	173[g]	15341-87-4	173[f]	64741-20-4
6	*m*-NO_2	177[f]	55000-38-9	165[f]	64741-18-0	154[f]	64741-19-1

[a] All the compounds were crystallized from aqueous ethanol. [b] Satisfactory data for N (±0.2%) were reported. [c] A. P. De Jonge, A. Verhge, and B. Van der Ven, *Recl. Trav. Chim. Pays-Bas*, 83, 949 (1964). [d] P. I. Ittyerah and K. C. Pandya, *J. Indian Chem. Soc.*, 30, 717 (1953). [e] M. V. George and P. I. Jttyerah, *Agra Univ. J. Res. Sci.*, 4, 551 (1955). [f] This work. [g] L. F. Golovyashkina, *Uzh. Khim. Zh.*, 11, 24 (1967). [h] T. Yabuuchi, *Chem. Pharm. Bull.*, 8, 169 (1960).

Experimental Section

Materials. Cinnamoyl chloride (Aldrich commercial product), bp 256–8 °C, was purified twice by distillation.

The β-2-furylacryloyl and β-2-thienylacryloyl chlorides were prepared by refluxing 2 g of the corresponding acids (Aldrich commercial products) with 10 mL of thionyl chloride for several hours. The excess of thionyl chloride was removed by water bath distillation, and the acid chlorides were purified under reduced pressure: β-2-furylacryloyl chloride, bp 128–30 °C (6 mmHg);[23] β-2-thienylacryloyl chloride, bp 126 °C (30 mmHg).[24]

The anilines (Carlo Erba commercial products) were purified to constant melting point on boiling point by recrystallization or fractionation.

The solvent was benzene (R. P. Carlo Erba); no special purification was undertaken.[2]

Kinetic Procedure. The reactions were followed kinetically, as previously,[3,4] by filtering the completely insoluble aniline hydrochloride, dissolving it in water, and estimating the chloride with 0.01 N mercury(II) nitrate, using diphenylcarbazone as indicator, in the presence of bromophenol blue.

The second-order rate constants were calculated with constant molar ratios of the reactants (1:2): 1 mol of acid chloride with 2 mol of aniline. For the *m*- and *p*-toluidine reactions the initial concentrations of the reactants after mixing were acid chloride 0.0025 M and aniline 0.005 M.

All compounds gave excellent second-order kinetics.

All rates were run in duplicate to the least 75–80% completion with less than 3% deviation between the two rate constants.

All rate constants were calculated by a least-squares computer program with a Hewlett-Packard 9100 B.

The activation parameters were calculated from a least-squares treatment of log k against T^{-1}. The estimated precision is ca. ±0.7 kcal mol^{-1} in E_A and ±2.5 cal mol^{-1} in ΔS^*.

Product Analysis. Standard solutions of the appropriate aniline and acid chloride in benzene were placed in a glass-stoppered bottle and maintained at the kinetic temperature until completion. After concentration of the benzenic solution to small volume, the anilides were filtered, washed free from aniline hydrochloride with water, dried, and recrystallized from aqueous ethanol. In all cases the amount of the anilide was ≥95% of that expected from the formation of 1 mol of anilide per mol of acid chloride consumed. Physical constants and analytical data of the anilides are reported in Table VI.

Acknowledgments. The authors are grateful to the Consiglio Nazionale delle Ricerche for financial support.

Registry No.—Cinnamoyl chloride, 102-92-1; β-2-furylacryloyl chloride, 20689-54-7; β-2-thienylacryloyl chloride, 28424-61-5; benzene, 71-43-2.

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Kinetics and Mechanism of Lithium Aluminum Hydride and Lithium Alkoxyaluminohydride Reductions of Ketones in Tetrahydrofuran

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The kinetics of reaction of camphor with excess lithium and sodium aluminum hydride were studied by stopped-flow UV spectroscopy in tetrahydrofuran solution at 25.0 °C. The reductions are first order in camphor and first order in $LiAlH_4$. Reduction by $NaAlH_4$ is ca. ten times slower than reduction by $LiAlH_4$, and the pseudo-first-order rate constants are nonlinearly dependent upon $NaAlH_4$ concentration. The kinetics and products of reaction of camphor and the products of reaction of 3,3,5-trimethylcyclohexanone with lithium *tert*-butoxyaluminohydrides and lithium methoxyaluminohydrides are consistent with disproportionation of the alkoxide species, with reduction taking place predominantly through $LiAlH_4$ itself. The rate of reduction of camphor by $LiAlH_4$ is depressed by the addition of either lithium bromide or crown ether **4**. The rate decreases linearly with increasing [crown ether]/[$LiAlH_4$] ratio but is nonzero at a ratio of 1.0. A complex of the crown ether and $LiAlH_4$ was isolated, and the rate of reaction of the complex with camphor was measured.

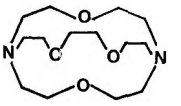
The mechanism and stereochemistry of reduction of ketones by lithium aluminum hydride and its alkoxide derivatives have been the subject of much investigation. Most mechanistic proposals have been based on the relative yields of epimeric alcohols formed upon reduction of model ketones by various hydride reagents.[2-12] In addition, some kinetic studies have been conducted.[13-16]

Mechanistic studies have been limited by a lack of information regarding the composition of complex metal hydrides in solution. Ashby, Dobbs, and Hopkins recently reported the results of association measurements on several complex metal hydrides in diethyl ether and tetrahydrofuran (THF) solutions.[17] Both lithium and sodium aluminum hydride are reported to exist as ion pairs or triple ions in THF,[17a] with the association i values for both hydrides ranging from about 1.0 at 0.04 m to 1.7 at 0.4 m. In contrast, $LiAlH_4$ in ether is more highly associated, with i varying from 1.75 to 2.2 between 0.1 and 0.45 m.[17b] Association curves for some lithium methoxy- and *tert*-butoxyaluminohydrides in THF were also reported.[17b]

Recently we reported on the kinetics of reduction of several alkyl-substituted benzophenones by $LiAlH_4$ and lithium *tert*-butoxyaluminohydrides in ether.[16] With $LiAlH_4$ in ether we found that the principal reducing agent in solution is monomeric lithium aluminum hydride, although the dimer may exhibit a small reactivity with less hindered ketones. The lithium *tert*-butoxyaluminohydride system is characterized by partial disproportionation[3,18] of the alkoxides, and the available data indicate that $LiAlH_4$ is the dominant reducing agent, although lithium mono-*tert*-butoxyaluminohydride may also serve as a hydride donor.

In contrast to these kinetic results obtained in ether, the reduction of 2,4,6-trimethylbenzophenone by $LiAlH_4$ and $NaAlH_4$ in THF was reported to be first order in ketone and first order in hydride,[15] as were the reactions of some substituted benzophenones[14] and cyclohexanones[13] with $LiAl(O\text{-}t\text{-}Bu)_3H$ in THF.

The role of the cation in ketone reductions with aluminohydrides has received much attention. The requirement of electrophilic catalysis, either by a cation or by protic solvent, in reductions with the related borohydrides is well-documented,[19] and House[20] has suggested that the mechanism of reduction of ketones by $LiAlH_4$ involves prior or concurrent association of the lithium ion with the carbonyl oxygen atom. It has been suggested that the reduction of 2,4,6-trimethylbenzophenone in THF involves the solvent-separated $LiAlH_4$ ion pair as the reactive species, with the lithium ion coordinated to the carbonyl oxygen in a six-centered transition state.[15] Pierre and Handel[21] concluded that the lithium ion is an essential catalyst in the aluminohydride reduction of many functional groups, based on the observation of no reaction in the presence of the lithium ion complexing agent [2.1.1]cryptand (**1**). Variations in the stereochemistry of reduction of ketones with the nature or concentration of cation have been interpreted in terms of complexation of the carbonyl oxygen by the cation prior to or synchronous with hydride transfer.[10,21c,d]



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The purpose of the present research was to determine the kinetics and mechanism of reduction of ketones by lithium aluminum hydride and the lithium methoxy- and *tert*-butoxyaluminohydrides in THF solution. Camphor (**2**) was selected as a substrate because of its convenient rate level and because of its previous use in studies of stereoselectivity of complex metal hydrides.[4,10b] The quantitative dependence of the rate of reduction upon lithium ion concentration was also investigated. Studies of lithium ion dependence and of reduction by the lithium methoxyaluminohydrides were hindered in diethyl ether by solubility limitations.

Results and Discussion

Reduction of Camphor by $LiAlH_4$. The rate of disappearance of camphor was measured at 290 nm by stopped-flow ultraviolet spectroscopy at 25.0 °C in THF solution at ketone concentrations of 0.003–0.0102 M and $LiAlH_4$ concentrations of 0.0208–0.177 M. In all cases excellent adherence to a first-order rate law was observed throughout a kinetic run. The measured first-order rate constants were independent of initial ketone concentration, indicating the reaction to be first order in camphor.

The dependence of the observed first-order rate constants upon the concentration of $LiAlH_4$ is linear with zero intercept (Figure 1), indicating the reduction of camphor to be first order in $LiAlH_4$ in tetrahydrofuran solvent (eq 1). Unweighted linear least-squares analysis of the kinetic data in Figure 1 yields a second-order rate constant k_1 of 181 ± 5 M^{-1} s^{-1} (r = 0.994).

$$-d[\text{camphor}]/dt = k_1[LiAlH_4][\text{camphor}] \quad (1)$$

These kinetic orders are in agreement with the report[15] that the reduction of 2,4,6-trimethylbenzophenone in THF is first

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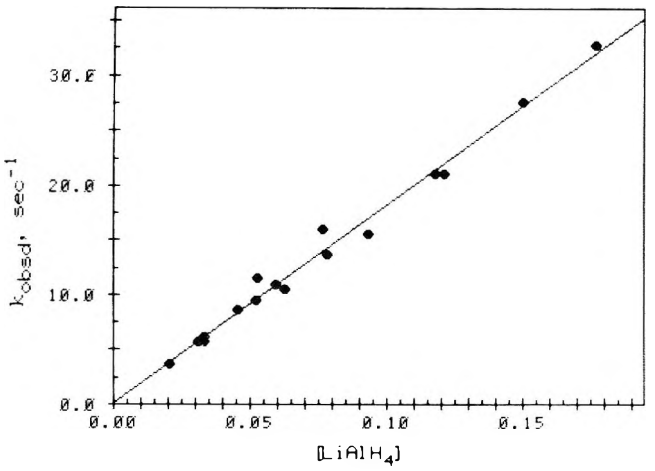


Figure 1. Plot of k_{obsd} vs. $[LiAlH_4]$ for reduction of camphor in THF at 25.0 °C.

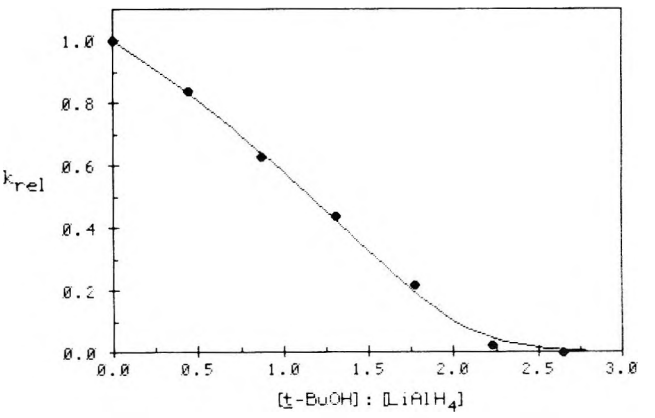


Figure 2. Plot of k_{rel} vs. $[t\text{-BuOH}]/[LiAlH_4]$ for reduction of camphor (0.01 M). Initial $LiAlH_4$ concentration 0.118 M. The line was calculated from eq 2.

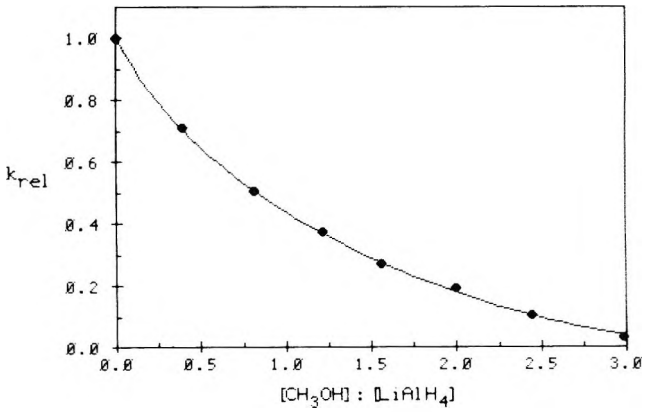


Figure 3. Plot of k_{rel} vs. $[CH_3OH]/[LiAlH_4]$ for reduction of camphor (7.5×10^{-3} M). Initial $LiAlH_4$ concentration 0.0768 M. The line was calculated from eq 3.

order in ketone and in $LiAlH_4$. However, these results are in marked contrast to the observed one-half order in $LiAlH_4$ for reduction of 2,4,6-trimethylbenzophenone in diethyl ether.[16] The one-half order dependence was ascribed to reaction taking place primarily through monomeric lithium aluminum hydride in equilibrium with the dimer, which predominates in solution. That reduction of camphor in THF is first order in $LiAlH_4$ is consistent with the known[17] lesser degree of molecular association of $LiAlH_4$ in THF than in ether.

Reduction of Camphor by Lithium Alkoxyaluminohydrides. The kinetics of reaction of camphor with a series of reagents prepared by adding various quantities of dry *tert*-butyl alcohol or methanol to standard stock solutions of $LiAlH_4$ in THF also were measured. The observed pseudo-first-order rate constants decrease markedly as the molar ratio of alcohol to $LiAlH_4$ increases from 0 to 3. The variation in rate constants with the $[t\text{-BuOH}]/[LiAlH_4]$ ratio is seen in Figure 2 and the variation with the $[CH_3OH]/[LiAlH_4]$ ratio in Figure 3. The measured values of k_{obsd} are divided by k_{obsd} for $LiAlH_4$ alone at the concentration of total aluminum used in order to obtain the relative rate constant, k_{rel}. Each reaction displayed good first-order kinetics within a run.

The dependence of k_{rel} upon the $[t\text{-BuOH}]/[LiAlH_4]$ ratio for reduction of camphor (Figure 2) is very similar in shape to the corresponding curves obtained for reductions of several benzophenones in ether.[16] The effect of t-BuOH on k_{rel} thus may be interpreted in terms of disproportionation of the alkoxyaluminohydrides to regenerate $LiAlH_4$, as in the following equations. In the absence of adequate data, all hydride species are assumed to be monomeric in this scheme.

$$2LiAl(O\text{-}t\text{-}Bu)H_3 \overset{K_1}{\rightleftharpoons} LiAlH_4 + LiAl(O\text{-}t\text{-}Bu)_2H_2$$

$$2LiAl(O\text{-}t\text{-}Bu)_2H_2 \overset{K_2}{\rightleftharpoons} LiAl(O\text{-}t\text{-}Bu)H_3 + LiAl(O\text{-}t\text{-}Bu)_3H$$

$$k_{calcd} = k_1[LiAlH_4] + k_2[LiAl(O\text{-}t\text{-}Bu)H_3] \quad (2)$$

It was not necessary to consider the third stage of disproportionation, since $LiAl(O\text{-}t\text{-}Bu)_4$ cannot be formed in THF under these conditions.[22]

Computer simulation of the kinetic data using this model was carried out using the interactive graphics of the PLATO IV computer-based education system.[23] The equilibrium concentrations of all hydride species at a given ratio of alcohol to $LiAlH_4$ were calculated to satisfy the specified values of the disproportionation equilibrium constants. A theoretical curve of k_{rel} vs. $[t\text{-BuOH}]/[LiAlH_4]$ was then calculated using the known value of the rate constant for reaction of $LiAlH_4$ with camphor. A very good fit to the data is obtained when a term representing the contribution from the mono-*tert*-butoxyaluminohydride species is included in the rate law (eq 2). The curve shown in Figure 2 was calculated from eq 2 using values of 0.3 for K_1, 0.05 for K_2, 181 for k_1, and 120 for k_2. While there is some uncertainty in the numerical values of these parameters, it is clear that the mechanism of reaction of camphor with the lithium *tert*-butoxyaluminohydrides in THF is very similar to that of analogous reactions in diethyl ether.

The dependence of k_{rel} upon the $[CH_3OH]/[LiAlH_4]$ ratio (Figure 3) is markedly different from that seen with the *tert*-butoxyaluminohydrides. Not only are the shapes of the curves different, but the relative reactivity at a molar ratio of 3.0 is much greater in the methoxyaluminohydride system. The work of Brown and Shoaf[24] indicates that all four hydrides on $LiAlH_4$ may react with methanol in THF, and thus a more extensive disproportionation scheme is indicated than used for the *tert*-butoxyaluminohydrides.[17b] All methoxides were regarded as monomeric in the absence of definitive association data.

$$2LiAl(OCH_3)H_3 \overset{K_1}{\rightleftharpoons} LiAlH_4 + LiAl(OCH_3)_2H_2$$

$$2LiAl(OCH_3)_2H_2 \overset{K_2}{\rightleftharpoons} LiAl(OCH_3)H_3 + LiAl(OCH_3)_3H$$

$$2LiAl(OCH_3)_3H \overset{K_3}{\rightleftharpoons} LiAl(OCH_3)_2H_2 + LiAl(OCH_3)_4$$

$$k_{calcd} = k_1[LiAlH_4] \quad (3)$$

Table I. Products from Reaction of Lithium *tert*-Butoxyaluminohydrides with Camphor in THF at 25.0 °C[a]

[*t*-BuOH]/[$LiAlH_4$]	% exo alcohol[b]
0.0	92
0.446	92
0.874	90
1.31	91
1.77	90
2.23	91
2.65	91
3.00	96

[a] Total Al concentration = 0.118 M. Camphor = ca. 0.01 M. [b] Average of 3–5 quantitative gas chromatographic analyses. All values have an uncertainty of ca. ±1.5%.

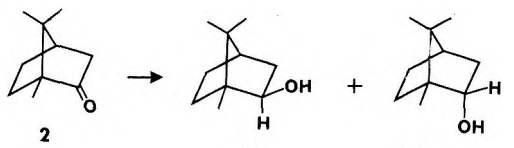
Table II. Products from Reaction of Lithium Methoxyaluminohydrides with Camphor in THF at 25.0 °C[a]

[CH_3OH]/[$LiAlH_4$]	% exo alcohol[b]
0.0	93
0.391	92
0.813	93
1.22	93
1.56	92
2.00	93
2.44	92
3.14	92

[a] Total Al concentration = 0.0768 M. Camphor = ca. 0.0075 M. [b] Average of 3–5 quantitative gas chromatographic analyses. All values have an uncertainty of ca. ±1%.

Computer modeling of the data in Figure 3 according to this scheme leads to an excellent fit using values of $K_1 = K_2 = K_3 = 0.9$, with only $LiAlH_4$ regarded as an active reducing agent ($k_1 = 181$ in eq 3). While the simple assumptions of monomeric hydrides and equality of the equilibrium constants are not necessarily accurate, the data do not require postulation of a more complicated reaction scheme.

The available evidence which indicates that disproportionation takes place in both the lithium methoxyaluminohydride and *tert*-butoxyaluminohydride systems in THF[18,24] suggests that discrete species containing one or two alkoxide ligands are *not* formed when 1 or 2 equiv of alcohol react with $LiAlH_4$. Reported association data[17b] on such alkoxyaluminohydrides probably represent a weighted average degree of association of all species present in solution. Associated species may be involved in the alkoxyaluminohydride reactions but are not required to describe these kinetic data.



2 exo endo

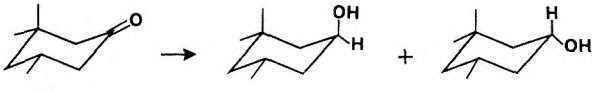
Products of Reaction of Ketones with Lithium Alkoxyaluminohydrides. The products of reduction of camphor (2) by the various alkoxyaluminohydrides were determined by gas chromatographic analysis of the quenched effluent from the stopped-flow instrument. Within experimental error, reduction with all of the lithium *tert*-butoxyaluminohydride solutions yielded the same mixture of products as obtained from reduction by $LiAlH_4$ itself, containing an average of 91% of the exo alcohol (Table I). ($LiAlH_4$ reduction of camphor in THF is reported to yield 91–92% of the exo alcohol.[4,10b]) However, reduction by $LiAl(O\text{-}t\text{-}Bu)_3H$ formed 96% of the exo alcohol (lit.[4] 97%). These data suggest that $LiAlH_4$ is responsible for most of the reduction of camphor, regardless of the [*t*-BuOH]/[$LiAlH_4$] ratio, in agreement with the kinetic data. Similarly, reduction of camphor with all of the methoxyaluminohydride solutions gave an essentially constant 92% exo alcohol (Table II), as did reaction with stoichiometric $LiAl(OCH_3)_3H$ (lit.[4] 99%). The kinetic evidence for three stages of disproportionation does indicate that the trimethoxide species should exhibit a selectivity comparable to that of pure $LiAlH_4$, as observed. The discrepancy between the present and the reported values for reduction by $LiAl(OCH_3)_3H$ may be due to the fact that reactions were carried out at different temperatures.

Table III. Products from Reaction of Lithium *tert*-Butoxyaluminohydrides with 3,3,5-Trimethylcyclohexanone in THF at 25.0 °C[a]

[*t*-BuOH]/[$LiAlH_4$]	% trans alcohol[b]
0.0	83
0.413	83
0.773	82
1.17	82
1.58	82
1.97	82
2.57	77
3.00	91

[a] Total Al concentration = 0.0635 M. Ketone = ca. 0.006 M. [b] Average of 3–5 quantitative gas chromatographic analyses. All values have an uncertainty of ca. ±1%.

Camphor may not be a very sensitive probe for changes in stereochemistry of reduction, since it is a highly hindered ketone which exhibits a substantial bias for formation of a single product even upon reaction with $LiAlH_4$. Therefore, the products of reduction of 3,3,5-trimethylcyclohexanone (3) by



3 trans cis

the lithium methoxy- and *tert*-butoxyaluminohydrides were also determined, using the efficient mixing chamber in the stopped-flow instrument. (The rate of reaction of ketone 3 with $LiAlH_4$ is too rapid to measure with our current stopped-flow equipment.) Reduction by $LiAlH_4$ yields 83% *trans*-3,3,5-trimethylcyclohexanol (lit.[3,10b] 74–89% in tetrahydrofuran), and reduction with a series of lithium *tert*-butoxyaluminohydrides yields nearly the same product distribution (Table III). However, reduction with $LiAl(O\text{-}t\text{-}Bu)_3H$ forms 91% of the trans alcohol, whereas 85% is formed using stoichiometric $LiAl(OCH_3)_3H$. These results further support the concept of disproportionation and predominant reaction through $LiAlH_4$, although $LiAl(O\text{-}t\text{-}Bu)_3H$ itself does exhibit a greater stereoselectivity than do the other *tert*-butoxyaluminohydride solutions, suggesting that it does not undergo disproportionation.

Reduction of Camphor by $NaAlH_4$. The rate of reduction with $NaAlH_4$ was measured at hydride concentrations of 0.0222–0.185 M in THF. As seen in Figure 4, the pseudo-first-order rate constants exhibit a nonlinear dependence upon the $NaAlH_4$ concentration, with an apparent order of 0.73. Ashby and Boone[15] reported that reduction of 2,4,6-trimethylbenzophenone with dilute solutions of $NaAlH_4$ in THF is first order in hydride. Our attempts to examine the carbonyl region of the infrared spectrum of a reacting solution of camphor and sodium aluminum hydride were unsuccessful due to interfering absorbances by solvent and hydride. The

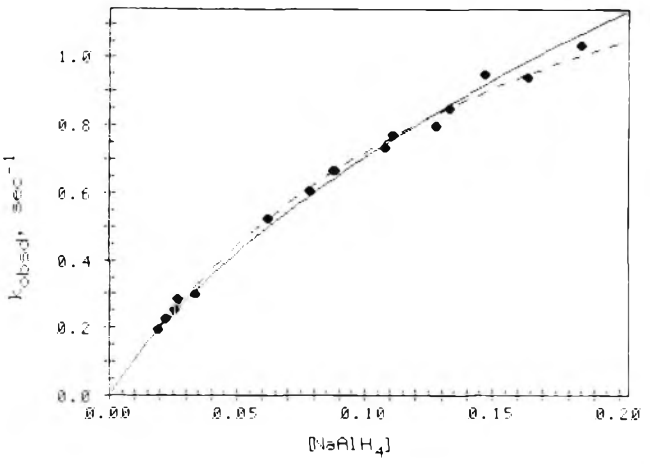


Figure 4. Plot of k_{obsd} vs. $[NaAlH_4]$ for reduction of camphor in THF at 25.0 °C. The solid line was calculated from eq 4. The dashed line was calculated assuming the formation of an intermediate.

Table IV. Products from Reaction of Lithium Methoxyaluminohydrides with 3,3,5-Trimethylcyclohexanone in THF at 25.0 °C[a]

$[CH_3OH]/[LiAlH_4]$	% trans alcohol[b]
0.0	82
0.427	82
0.868	80
1.24	80
1.70	81
2.03	80
2.52	80
3.03	85

[a] Total Al concentration = 0.0445 M. Ketone = ca. 0.005 M. [b] Average of 3–5 quantitative gas chromatographic analyses. All values have an uncertainty of ca. ±1%.

reduction of camphor by $NaAlH_4$ formed 90% of the exo alcohol.

Several mechanistic possibilities could give rise to curvature in the plot of k_{obsd} vs. $[NaAlH_4]$. The curvature may be due to molecular association of the hydride, with reaction taking place via a monomeric species (as seen in reactions of organolithium reagents[25] and lithium aluminum hydride[16] with ketones in ether); or it could reflect the presence of an intermediate along the reaction pathway (as seen in reactions of Grignard reagents with ketones[26]).

Ashby's data suggest that $NaAlH_4$ is moderately associated in THF solution,[17b] and if monomeric $NaAlH_4$ is the reactive species, then an apparent order in stoichiometric $NaAlH_4$ less than 1.0 would be observed. Thus, the mechanism below may be used to describe the data in Figure 4. A good fit to the data is obtained using values of 6 M^{-1} for K and 12 $M^{-1}\,s^{-1}$ for k_3; the theoretical plot of k_{obsd} vs. stoichiometric $[NaAlH_4]$ is the solid line in Figure 4.

$$2NaAlH_4 \overset{K}{\rightleftharpoons} (NaAlH_4)_2$$

$$NaAlH_4 + \text{camphor} \xrightarrow{k_3} \text{products}$$

$$k_{obsd} = k_3[NaAlH_4] \qquad (4)$$

The expected association i values calculated for $NaAlH_4$ using the value of 6 M^{-1} for the monomer–dimer equilibrium constant give qualitative agreement with Ashby's experimental data. However, it is not entirely satisfying to explain the different kinetic behavior of reactions of $LiAlH_4$ and $NaAlH_4$ on the basis of association, as the states of aggregation for both

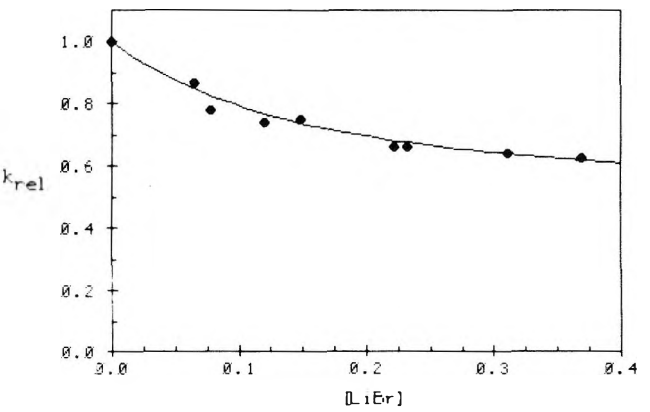


Figure 5. Plot of k_{rel} vs. [LiBr] for the reduction of camphor (4.92×10^{-3} M) with 0.053 M $LiAlH_4$ in THF at 25.0 °C.

hydrides are reported to be very similar.[17b] Differences in the relative reactivities of monomer and dimer in the two cases could account for the different shapes of the curves in Figures 1 and 4.

The data in Figure 4 were also analyzed in terms of formation of an intermediate. The theoretical curve calculated on this basis is the dashed line in Figure 4, and clearly describes the data quite well. However, the results of UV spectral studies of ketones in the presence of $LiClO_4$ and $NaClO_4$ (see Experimental Section) suggest that complexation of the carbonyl group in camphor takes place less readily with a sodium ion than with a lithium ion. The formation of an intermediate of this type between camphor and $NaAlH_4$ is thus regarded as unlikely.

Both the association model and the intermediate model can yield comparable fits to the experimental kinetic data. We conclude that it is not possible to distinguish between these mechanistic possibilities using the available data. It is of interest to note that, below about 0.05 M, the association model, the presence of an intermediate, and a simple second-order reaction all will approach a linear dependence of k_{obsd} upon the $NaAlH_4$ concentration. It is thus likely that the apparent discrepancy between our results on the $NaAlH_4$ reduction of camphor and those of Ashby[15] for the reduction of 2,4,6-trimethylbenzophenone simply reflects the fact that Ashby's experiments were conducted using quite dilute (<0.05 M) solutions of $NaAlH_4$, in which any curvature may be so slight as to go undetected.

Effect of Lithium Ion Concentration on Reduction of Camphor by $LiAlH_4$. The rate of reduction of acetone by sodium or lithium borohydride in isopropyl alcohol is enhanced by the addition of lithium salts.[19b] In contrast, Figure 5 shows that the addition of lithium bromide (0.06–0.37 M) depresses the rate of reaction of camphor with lithium aluminum hydride in THF. The shape of the curve in Figure 5 is suggestive of an equilibrium process and could result from formation of a less reactive LiBr–ketone complex (reducing the concentration of free ketone), or from association of LiBr with $LiAlH_4$ (reducing the concentration of monomeric $LiAlH_4$). In addition, the relatively polar character of the lithium bromide in these solutions may be exerting a medium effect upon the reaction.

The rate of reaction of camphor with $LiAlH_4$ was also measured as a function of the ratio of the crown ether **4** to $LiAlH_4$. This macrocyclic ligand was selected because of its strong complexation behavior toward lithium ion,[27] its ready accessibility from inexpensive starting materials,[28] the solubility of the resulting crown ether–$LiAlH_4$ complex in THF,[29] and the presence of the tetrahydrofuran moiety in the ligand itself. Figure 6 shows that the rate of reaction of camphor with $LiAlH_4$ decreases linearly with increasing [crown ether]/

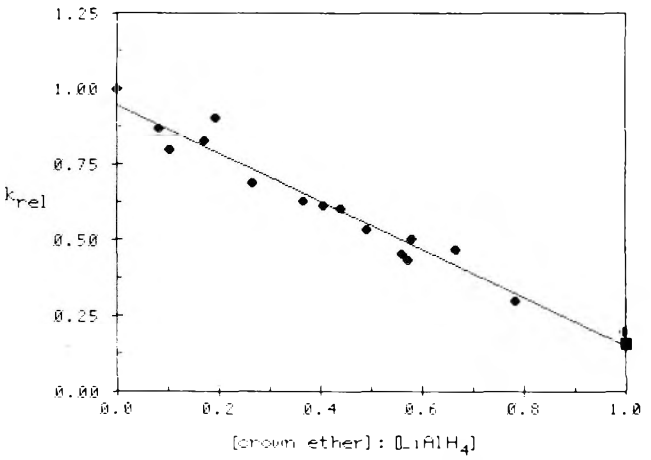
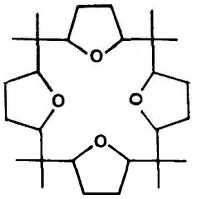


Figure 6. Plot of k_{rel} vs. [crown ether]/[$LiAlH_4$] for reduction of camphor (ca. 4×10^{-3} M) with 0.0314 M $LiAlH_4$ in THF at 25.0 °C. The least-squares line through the data is shown. The square point was obtained from a solution of the 1:1 crown ether–$LiAlH_4$ complex.

[$LiAlH_4$] ratio. The least-squares line through the data has a slope of -0.80 ± 0.05 ($r = 0.976$). However, reaction is still observed when 1 equiv of crown ether has been added. This suggests that either the complexed $LiAlH_4$ is an active reducing agent or the equilibrium constant for complex formation is small and incomplete complexation takes place. The lack of curvature in the data and the estimated value of 10^6 for the equilibrium constant for formation of the 1:1 crown ether–lithium picrate complex[27] argue against only weak complex formation between $LiAlH_4$ and crown ether.



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The 1:1 complex formed between $LiAlH_4$ and the crown ether can be isolated by crystallization from THF. This complex is moderately soluble in THF and reduces camphor with a second-order rate constant of 30 M^{-1} s^{-1}, assuming that the reaction is first order in complex. This rate constant corresponds to a relative rate constant of 0.17 compared to $LiAlH_4$ alone, in excellent agreement with the data shown in Figure 6. The products from this reaction contained 95% of the exo alcohol.

Thus, it appears that reaction may take place either through free $LiAlH_4$ or through the complexed hydride, which probably resembles the solvent-separated ion pair of $LiAlH_4$ in THF. Both the kinetic results and reported association data[17] suggest that the free AlH_4^- ion is not an active reducing agent. By comparison, addition of 2 equiv of a polyamine chelating ligand to $LiAlH_4$ in THF reduced its reactivity toward 2,4,6-trimethylbenzophenone by about a factor of 2,[15] whereas reduction of ketones in ethereal solvents has been variously reported to be partially[30] or completely[21] inhibited in the presence of the [2.1.1]cryptand 1.[29] It has also been observed that, besides $LiAlH_4$ and $NaAlH_4$, both $KAlH_4$ and even NR_4AlH_4 (tri-*n*-octyl-*n*-propylammonium aluminum hydride) can reduce ketone **3** in THF, albeit with differing stereochemistry.[10b] It is thus likely that, while the cation is probably involved in the transition state for aluminohydride reductions of ketones, the lithium ion does not seem to be an indispensible catalyst[21] required for reduction to take place.

Experimental Section

General. Ultraviolet spectra were recorded with a Perkin-Elmer Model 202 spectrophotometer using matched 1-cm quartz cells. Nuclear magnetic resonance spectra were obtained on Varian T-60 and EM-390 spectrometers. Analytical data were obtained by Mr. J. Nemeth and associates at the University of Illinois. Capillary melting points were taken on a Büchi melting point apparatus and are uncorrected. All kinetic measurements were performed under pseudo-first-order conditions of excess hydride on a stopped-flow ultraviolet spectrophotometer which has been described previously.[25] Data collection and analysis were as described previously.[16] Absorbance changes of 0.1 were typically monitored at 290 nm.

Materials. D-Camphor and lithium tri-*tert*-butoxyaluminohydride were obtained from the Aldrich Chemical Co. and were used as received. 3,3,5-Trimethylcyclohexanone (**3**) was prepared by catalytic hydrogenation of 3,5,5-trimethylcyclohex-2-enone. $LiClO_4$ and $NaClO_4$ (G. Frederick Smith Chemical Co.) and LiBr (Mallinckrodt N. F.) were dried to constant weight over P_2O_5 at 0.1 Torr and 110 °C. $LiAlH_4$ (Ventron) and $NaAlH_4$ (Ventron) were recrystallized from ether–benzene or THF–benzene as previously described.[16] *tert*-Butyl alcohol was dried by passage through a 40-cm column packed with activated 4 Å molecular sieves, followed by distillation under N_2. Methanol was dried by passage through molecular sieves, followed by distillation from magnesium methoxide under N_2. Solutions of $NaAlH_4$ and $LiAlH_4$ were prepared under argon using Mallinckrodt reagent THF distilled from $LiAlH_4$ in an all glass apparatus. Solutions of $LiAlH_4$ and $NaAlH_4$ were analyzed by Felkin's iodine titration method.[31] Alkoxyaluminohydride solutions were prepared as described previously[16] and were clear, colorless, and stable.

Product Analyses. The effluent from the stopped-flow instrument was quenched on ether-drenched crushed ice, which was then acidified with dilute H_2SO_4 to dissolve the salts formed. The layers were separated, and the aqueous layer was extracted with ether. The combined ethereal extracts were washed with 10% aqueous $NaHCO_3$ and with water, dried over $MgSO_4$, and filtered, and the solvents were removed by careful fractional distillation. The pot residue was subjected to repetitive quantitative gas chromatographic analysis on an F & M Model 700 chromatograph equipped with a thermal conductivity detector.

Borneol and isoborneol were separated on a 12 ft × 0.125 in. Carbowax 20M on 60/80 Chromosorb W (DMCS) column, using a column temperature of 135 °C and an He flow rate of 25 mL/min. *cis*- and *trans*-3,3,5-trimethylcyclohexanol were separated on the same column, at 125 °C and 25 mL/min of He. Peak areas were measured by disk integration and were corrected for thermal conductivity responses. Identification of the reduction products from camphor was achieved by comparison with authentic samples (Aldrich). The order of elution was camphor, exo alcohol, endo alcohol. The reduction products from 3,3,5-trimethylcyclohexanone were separated by preparative gas chromatography on a 12 ft × 0.25 in. 10% Carbowax 20M on 60/80 Chromosorb W (DMCS) column at 125 °C. The first eluted alcohol had a melting point of 58.5–59.5 °C and was determined to be *trans*-3,3,5-trimethylcyclohexanol (lit.[32] 58.5 °C). The second compound had a melting point of 36.0–36.5 °C and was identified as the cis alcohol (lit.[32] 36–38 °C). No unreacted ketone nor extraneous peaks were ever observed.

Reductions carried out in flasks in the usual preparative fashion had internal standards added. Mesitylene was used as standard for reductions of ketone **3**, and ketone **3** was used in reductions of camphor. Yields measured in this way were normally 100 ± 10%. The reductions of ketones **2** and **3** by $LiAl(O\text{-}t\text{-}Bu)_3H$ and $LiAl(OCH_3)_3H$ were conducted in flasks.

2,2,7,7,12,12,17,17-Octamethyl-21,22,23,24-tetraoxaperhydroquaterene (4).[28] Anhydrous $LiClO_4$ (2.12 g, 0.2 mol) was placed in a 300-mL flask fitted with a mechanical stirrer and reflux condenser. Absolute ethanol (60 mL) was added, and the mixture was stirred until homogeneous. Concentrated HCl (32 mL) and 46.4 g (0.8 mol) of acetone were added, then 27.2 g (0.4 mol) of furan was added in one portion. After stirring at room temperature 1.5 h, 20 mL of H_2O was added. The mixture was extracted with 3 × 80 mL of benzene, and the organic layer was washed with water. Benzene was removed under vacuum, ethanol was added, and the white solid was washed with several portions of cold ethanol. The product was recrystallized from ethanol to yield 12.6 g (29%) of the unsaturated macrocycle, mp 232–235 °C (lit.[28] 238–240 °C). This product was hydrogenated over 1 g of 5% Pd/C in absolute ethanol at 105 °C and 1600 psi of H_2 for 4.5

h. The reaction mixture was filtered, and the filtrate was concentrated to dryness under reduced pressure. The filter cake was dissolved in hot chloroform and filtered, and the chloroform was removed under vacuum to yield another portion of product. The combined products were recrystallized from $CHCl_3$–EtOH to yield the crown ether **4** in 57% yield as a mixture of isomers (by NMR), mp 206–209 °C (lit.[28] 208–211 °C). Anal. C, H.

Complex of $LiAlH_4$ and Crown Ether 4. $LiAlH_4$ (34 mL, 0.0627 M) in THF was added to 1.24 g (2.77 mmol) of crown ether. The crown ether dissolved completely with shaking, and a precipitate gradually appeared upon standing. The solution was filtered in an argon-filled dry box, and the filtrate was concentrated by distillation to afford a second crop of crystals. The combined dried products had a weight of about 0.5 g. The white crystals melted with hydrogen evolution at ca. 235 °C. The NMR spectrum (CD_2Cl_2) resembled the spectrum of the crown ether but had substantial shifts in some peak positions. Elemental analysis: C, 68.56; H, 10.65; Al, 4.90 (which is close to that expected for a 1:1 complex between $LiAlH_4$ and the crown ether: Calcd for $C_{28}H_{52}O_4LiAl$: C, 69.09; H, 10.80; Al, 5.53. The incorporation of one molecule of THF into the $LiAlH_4$–crown ether crystals provides an elemental composition which is in very close agreement with that found (Calcd for $C_{32}H_{60}O_5LiAl$: C, 68.77; H, 10.84; Al, 4.83).

UV Spectra of Ketones in the Presence of $LiClO_4$ and $NaClO_4$. The UV spectrum of benzophenone (6.91×10^{-5} M) in diethyl ether was measured in the presence of anhydrous $LiClO_4$ (0–2.03 M), with an equivalent concentration of $LiClO_4$ in the reference beam. The $\pi\pi^*$ band gradually shifted from λ_{max} at 247.5 nm (ϵ 18 820) to λ_{max} at 258 nm ($\epsilon_{apparent}$ 14 070), with an isosbestic point at 253.5 nm, indicating the formation of a complex between $LiClO_4$ and the carbonyl group. An equilibrium constant of ca. 2 was estimated for complex formation.

The UV spectrum of camphor (0.0416 M) was measured in THF in the presence of $LiClO_4$ (0–1.51 M). In contrast to the red shift observed with benzophenone and $LiClO_4$ in ether, λ_{max} of the $n\pi^*$ band of camphor shifted from 290 nm (ϵ 26.6) to 286.5 nm ($\epsilon_{apparent}$ 31.3), a blue shift. An isosbestic point was observed at 297 nm.

The UV spectrum of camphor in THF in the presence of anhydrous $NaClO_4$ (0–1.3 M) showed no change in curve shape of λ_{max}.

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Registry No.—**4**, 50451-63-3; **4** ($LiAlH_4$ complex), 64475-64-5; **4** ($LiAlH_4$/THF complex), 64475-63-4; acetone, 67-64-1; furan, 110-00-9; $LiAlH_4$, 16853-85-3; benzophenone, 119-61-9; camphor, 464-49-3; $NaAlH_4$, 13770-96-2; LiBr, 7550-35-8; 3,3,5-trimethylcyclohexanone, 873-94-9; THF, 109-99-9.

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Kinetics and Mechanism of the Oxidation of Heteroaromatic Cations by Ferricyanide Ion[1]

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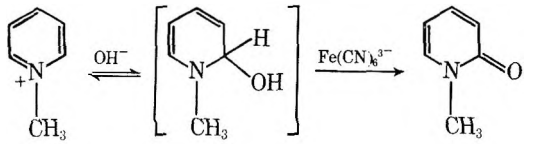
The rates of oxidation of a series of *N*-(X-benzyl)-5-nitroisoquinolinium cations (8) to the corresponding 1-isoquinolinones have been investigated in 20% acetonitrile–water at 25 °C, ionic strength 1.0 over the range 0.02–1.0 M KOH. These reactions are strictly first order in both heterocycle and ferricyanide and are not inhibited by up to 12-fold excess of ferrocyanide ion over ferricyanide ion. The dependence of the rate of oxidation on [OH^-] indicates that the rate-determining step involves ferricyanide attack on the alkoxide ion of the pseudobase derived from 8. The pH-independent second-order rate constant, k_2^H is correlated with the Hammett σ constants for the substituents X in the benzyl ring of 8: $\log k_2^H = -1.29\sigma + 2.29$. For the corresponding 1-deuterio cations the correlation line is $\log k_2^D = -0.96\sigma + 1.93$. The different ρ values for k_2^H and k_2^D indicate a kinetic isotope effect (k_2^H/k_2^D) which is dependent on the substituent X; this isotope effect varies from 1.41 for X = 4-CN to 3.25 for X = 4-CH_3O. The sign and magnitude of the ρ values require close to a full unit positive charge on the ring nitrogen atom in the transition state, while the magnitude of the kinetic isotope effect is only consistent with C(1)–H bond breaking in this transition state. The only mechanism consistent with both of these requirements is rate-determining abstraction of hydride by ferricyanide ion to give the isoquinolinone and a species "$HFe(CN)_6^{4-}$", which rapidly reacts with a second ferricyanide ion to give two ferrocyanide ions. The substituent-dependent isotope effect is readily rationalized in terms of a "product-like" transition state for hydride transfer. Possible structures for $HFe(CN)_6^{4-}$ are considered, and other reactions which probably also involve hydride transfer to ferricyanide are suggested.

The use of aqueous alkaline solutions of potassium ferricyanide to oxidize pyridinium ions (e.g., 1) to the corresponding pyridinones (e.g., 3) is long established as a useful



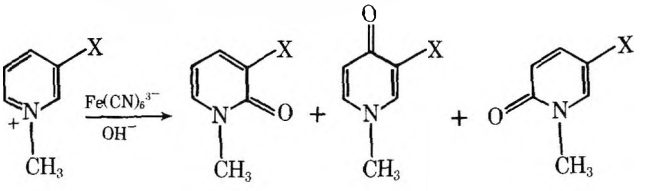
1 2 3

synthetic procedure.[3-11] A particularly impressive example of the use of this reaction is found in the establishment of C-4 as the site of hydride addition in the reduced form of the nicotinamide adenine dinucleotide coenzyme.[9,12] This oxidation reaction is common to all nitrogen heteroaromatic cations and has been often used for the assignment of the quaternization site in heteroaromatic molecules containing nonequivalent nitrogen atoms.[13-19]

Despite the usefulness of this reaction in synthetic and structural organic chemistry, there does not appear to have been a detailed quantitative study of the kinetics and mechanism of such ferricyanide oxidations. The reaction is generally assumed to proceed by the attack of ferricyanide ion on the pseudobase (e.g., 2) rather than by direct attack on the cation.[6,20-22] While this interpretation would appear to be quite reasonable, the first report of the influence of pH on the rate of this reaction only appeared[23] during the preparation of the current manuscript. Such a study is a minimum requirement for establishing that the pseudobase is indeed involved since the pseudobase (QOH) is involved in an acid–base equilibrium with the heteroaromatic cation (Q^+) as described in eq 1. For simple pyridinium ions such as 1, this equilibrium favors the cation even in very basic aqueous solutions, and no spectroscopic evidence for the presence of pseudobases in such solutions is obtainable.[24-26] However, for benzylogous pyridinium ions, or for pyridinium ions bearing strongly electron-withdrawing substituents, the presence of pseudobase species in equilibrium with the heteroaromatic cations is readily demonstrable spectroscopically, and equilibrium constants (pK_{R+}) for eq 1 can be measured.[19,27-29]

$$Q^+ + H_2O \rightleftharpoons QOH + H^+ \qquad (1)$$

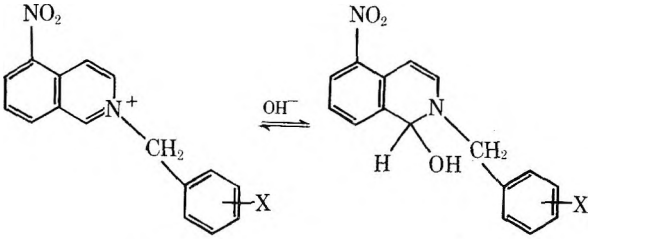
Abramovitch and Vinutha[22] have reported a semiquantitative study of substituent effects on the rates of ferricyanide oxidation of 3-substituted 1-methylpyridinium ions (4 X = H, CH_3, CN, CO_2CH_3). However, these substituent effects are not readily interpretable so as to provide mechanistic information on this reaction and are complicated by the presence in 4 of three nonequivalent sites that are susceptible to oxi-



4 5 6 7

dation. On the basis of the product ratio 5/7 being the same for the oxidation of the 2-deuterio and 6-deuterio isomers of 4 (X = CH_3), these workers concluded that cleavage of the C–H bond is not rate determining in these reactions.

We have recently reported pK_{R+} values for the 5-nitroisoquinolinium cations (8) bearing various substituents on the benzyl ring of the N-substituent.[30] Isoquinolinium cations are



8 9

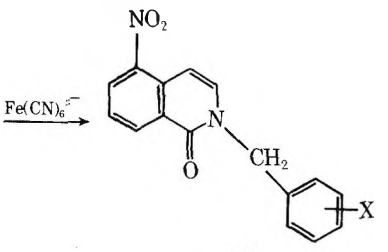


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Table I. Spectral and Equilibrium Data[a] for Formation of 11

X	Registry no.	λ_{max} (0.02 M KOH), nm	λ_{max} (1 M KOH), nm	K_d, M^{-1}	K_d,[b] M^{-1}
4-CN	64840-35-3	450	493	11.9 ± 0.5	13.2 ± 1.0
3-CN	64840-36-4	452	495	9.7 ± 0.7	
4-Br	64840-37-5	456	501	11.2 ± 0.4	
3-F	64840-38-6	456	500	11.5 ± 0.6	11.3 ± 0.5
H	64840-39-7	456	504	10.2 ± 0.5	
4-CH_3	64840-40-0	458	506	10.1 ± 0.9	
4-CH_3O	64840-41-1	458	507		10.3 ± 0.9

[a] All data in 20% acetonitrile–water at 25 °C, ionic strength 1.0 (KCl + KOH). [b] Data for 1-deuterio derivative.

well established[3b,31] as undergoing oxidation uniquely at C-1 of the isoquinoline moiety (e.g., 8 → **10**). We felt that a detailed kinetic study of the pH dependence and substituent effects of X on the ferricyanide oxidation of the isoquinolinium cations 8 would be useful in definitively establishing whether pseudobase species **9** are intermediates in this type of reaction. Furthermore, the substituent effect of X on the rate of oxidation has the potential for allowing a choice to be made between several alternative mechanistic pathways for these ferricyanide oxidations. Our data firmly establish that the rate-determining step in these reactions involves hydride transfer to ferricyanide ion from the alkoxide ion derived from the pseudobase. To the best of our knowledge, this study represents the first unambiguously established case of hydride ion transfer to the one-electron oxidant ferricyanide ion during the oxidation of an organic molecule.

Results

All kinetic data, spectral data, and equilibrium constants reported in this study were obtained in 20% v/v acetonitrile–water, ionic strength 1.0 (KOH + KCl) at 25 °C. In the case of 8 (X = 4-CN) additional data at 35, 45, and 55 °C were also obtained. The presence of acetonitrile in the reaction solvent was required to prevent the precipitation of the products **10** since strictly aqueous solutions tended to become cloudy during the course of the oxidation reaction even at the low concentration (7.5×10^{-5} M) used in this spectrophotometric study.

Solutions of each of the *N*-benzyl-5-nitroisoquinolinium cations (8) in the presence of 0.02 M KOH have a long wavelength absorption maximum in the vicinity of 455 nm (Table I). Such spectra are quite different from the spectra of these cations in neutral solution and are typical[30] of the presence of the pseudobase **9**. The pK_{R^+} values for pseudobase formation from the cations 8 in aqueous solution (24.6 °C, ionic strength 0.1) vary[30] from 10.50 for 8 (X = 4-CN) to 11.62 for 8 (X = 4-CH_3O). The neutral pseudobase species **9** can be expected to be further stabilized relative to the cations 8 by the presence of 20% acetonitrile, so that in the present study the pseudobase should be the predominant species present in the presence of 0.02 M KOH.

In more basic solutions, the spectrum of each of the pseudobases **9** undergoes further spectral changes; a typical case is illustrated in Figure 1 for **9** (X = 4-Br). These spectral changes result in a bathochromic shift of the longest wavelength peak by 42–49 nm in 1 M KOH, as indicated in Table I. These spectral changes are readily reversible, and the presence of clean isosbestic points indicates that the pseudobases **9** are involved in a pH-dependent equilibrium with another species. The simplest rapid reversible reaction that **9** could undergo with hydroxide ion is deprotonation of the OH group to give the alkoxide ion **11**. The spectra in 0.02 M and 1 M KOH solutions also suggest formation of **11** since these spectra are consistent with relatively little electronic reorganization on equilibration in 1 M KOH solution. Equilibrium constants, $K_d = [11]/[OH^-][9]$, were calculated from the dependence of these spectra on hydroxide ion concentration and are given in Table I. The values of K_d appear to be almost independent of the substituent X in the benzyl ring. Electronic effects of X would be expected to have little influence on the equilibrium between **9** and **11** since such effects have to be transferred from the aromatic ring to oxygen through three saturated atoms.

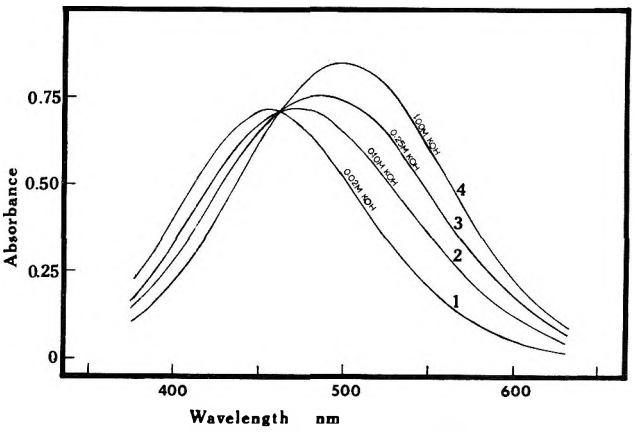
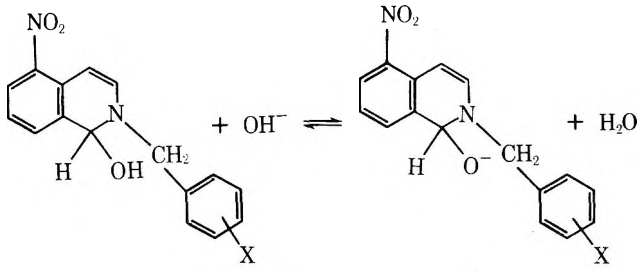


Figure 1. Spectra of 8 (X = 4-Br) in 20% CH_3CN/H_2O (ionic strength = 1.0) at various hydroxide ion concentrations: curve 1, 0.02 M KOH; 2, 0.10 M KOH; 3, 0.25 M KOH; 4, 1.0 M KOH.



9 **11**

In the presence of potassium ferricyanide, basic solutions of the cations 8 undergo spectral changes consistent with the oxidation of the heterocyclic species to the 1-isoquinolinones (**10**) and the reduction of ferricyanide to ferrocyanide. At equilibrium, the absorption spectrum of a basic solution that initially contained 8 and ferricyanide ion in a 1:2 molar ratio is identical to the spectrum of a solution of **10** and ferrocyanide ion in a 1:2 molar ratio. This is a clear indication that **10** is the only major organic product of this oxidation reaction. The time dependence of the absorption spectrum of a solution of 8 (X = H) and potassium ferricyanide in a 1:2 molar ratio in 0.02 M KOH is shown in Figure 2. The long wavelength peak that is due to **9** gradually disappears during the course of the reaction, and at equilibrium the absorbance at wavelengths greater than 450 nm is 0. Since neither ferricyanide anion,

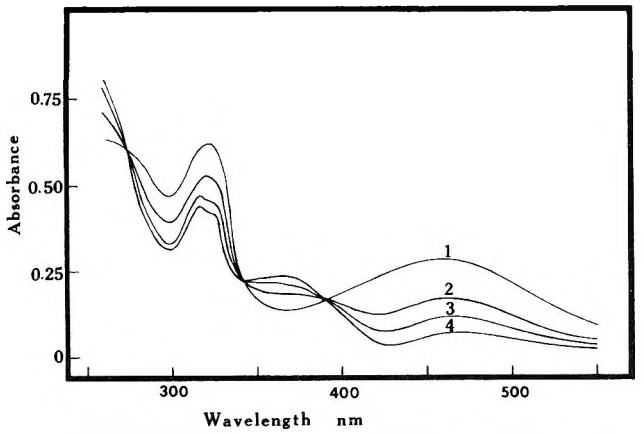


Figure 2. Time dependence of the spectrum of 8 (X = H) (7.5×10^{-5} M) and $K_3Fe(CN)_6$ (1.5×10^{-4} M) in 0.02 M KOH (25 °C, 20% CH_3CN/H_2O, ionic strength 1.0): curve 1, 1 min; 2, 6 min; 3, 15 min; 4, 45 min.

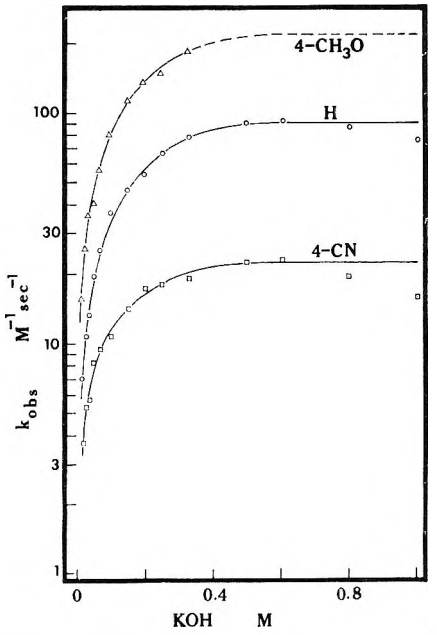


Figure 3. Dependence of k_{obsd} on [OH⁻] for the oxidation of 8 (X = 4-CH_3O, H, 4-CN) by $K_3Fe(CN)_6$ (25 °C, 20% CH_3CN/H_2O, ionic strength 1.0).

ferrocyanide anion, nor **10** shows appreciable absorption at 500 nm, the absorbance at this wavelength during the course of the oxidation reaction is a direct reflection of the concentration of unoxidized heterocycle (i.e., a mixture of **9** and **11**) at all times. Since the stoichiometry of the reaction requires the reduction of two ferricyanide ions per heterocyclic molecule oxidized, the concentration of ferricyanide at any time can also be calculated from the absorbance change at 500 nm as the reaction progresses.

All reactions studied were found to be first order in both heterocycle and ferricyanide ion (i.e., a second-order reaction overall) for at least the first 85% of the complete reaction. Observed second-order rate constants (k_{obsd}) were calculated from the slopes of second-order rate plots at at least ten different base concentrations in the range 0.02–1 M KOH. For the fastest reactions investigated, only the final 70% of the reaction was sometimes accessible, owing to the manual mixing of solutions that was used.

Values of k_{obsd} are plotted as a function of [OH⁻] in Figure 3 for several substituents X. In all cases a rapid increase in k_{obsd} is observed for low [OH⁻]; k_{obsd} tends to reach a plateau at higher concentrations and then decrease slightly in the most

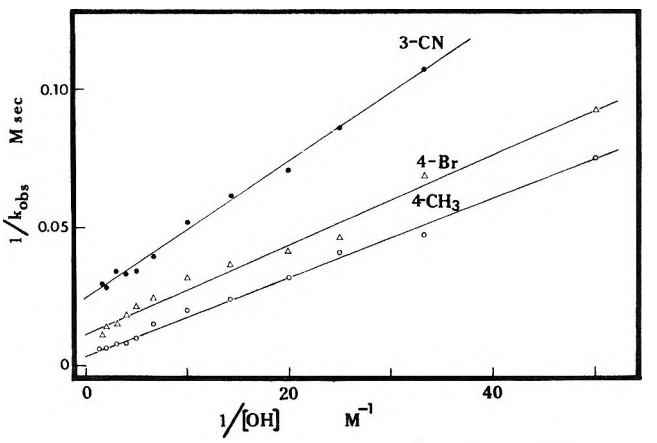


Figure 4. Dependence of $1/k_{obsd}$ on $1/[OH^-]$ for the oxidation of 8 (X = 4-CH_3, H, 3-CN) by $K_3Fe(CN)_6$ (25 °C, 20% CH_3CN/H_2O, ionic strength 1.0).

Table II. Kinetic Parameters for Oxidation of 8 and 12 by Ferricyanide Ion[a]

Cation	X	Registry no.	k_2, M^{-1} s^{-1}	K, M^{-1}
8	4-CN	64840-42-2	27.1 ± 0.7	8.0 ± 0.3
	4-CN[b]		32.4 ± 1.9	7.8 ± 0.7
	4-CN[c]		48.8 ± 4.1	9.2 ± 1.1
	4-CN[d]		71.6 ± 6.0	10.0 ± 1.2
	4-CN[e]		120 ± 6	13.1 ± 1.0
	3-CN	64840-43-3	40.4 ± 1.4	10.1 ± 0.6
	4-Br	64840-44-4	84.2 ± 8.4	7.4 ± 1.0
	3-F	64840-45-5	65.0 ± 4.5	5.8 ± 0.6
	H	52166-52-6	238 ± 80	1.7 ± 0.6
	4-CH_3	64840-46-6	262 ± 54	2.6 ± 0.6
	4-CH_3O	64840-47-7	490 ± 100	1.9 ± 0.4
12	4-CN	64840-48-8	19.2 ± 0.8	11.9 ± 0.8
	3-F	64840-49-9	42.3 ± 3.2	9.3 ± 1.0
	H	64840-50-2	84 ± 10	3.9 ± 0.6
	4-CH_3O	64840-51-3	151 ± 13	4.7 ± 0.6

[a] All data in 20% acetonitrile–water at 25 °C, ionic strength 1.0 (KCl + KOH), unless indicated otherwise; initial $[Fe(CN)_6^{3-}]$/[heterocycle] = 2:1. [b] Initial $[Fe(CN)_6^{3-}]$/[heterocycle] = 10:1. [c] At 35 °C. [d] At 45 °C. [e] At 55 °C.

basic solutions. Plots of $1/k_{obsd}$ vs. $1/[OH^-]$ are quite linear at all [OH⁻] up to the maximum in k_{obsd} for each X (Figure 4). Extrapolation of these plots to $1/[OH^-] = 0$ gives $1/k_2$, where k_2 is a second-order rate constant that is independent of [OH⁻]. Values of k_2 evaluated in this way for each of the cations 8 at 25 °C, and also for 8 (X = 4-CN) at three further temperatures, are recorded in Table II. An Arrhenius plot based on the temperature dependence of k_2 for 8 (X = 4-CN) is quite linear and gives $\Delta H^{\ddagger} = 8.4 \pm 0.5$ kcal/mol and $\Delta S^{\ddagger} = -24 \pm 2$ eu at 25 °C.

The observed dependence of k_{obsd} on [OH⁻] in Figures 3 and 4 suggests that the pseudobase **9** is involved in a rapid pH-dependent equilibrium with a species Z, which then reacts with a ferricyanide ion in a rate-determining step of second-order rate constant k_2. Such a scheme leads to the rate equation

$$\frac{d(\text{products})}{dt} = k_2[Fe(CN)_6^{3-}][Z]$$

$$= k_{obsd}[Fe(CN)_6^{3-}]([\mathbf{9}] + [Z])$$

$$= k_{obsd}[Fe(CN)_6^{3-}][Z](1 + 1/K[OH^-])$$

where $K = [Z]/[\mathbf{9}][OH^-]$. Thus, $1/k_{obsd} = 1/k_2 + 1/k_2K[OH^-]$, and K can be calculated from the slope of the linear plots in

Table III. Isotope Effects for the Oxidation of 8 and 12[a]

X	k_2^H/k_2^D	K^H/K^D
4-CN	1.41 (1.38)[b]	0.67
3-F	1.54 (1.78)	0.62
H	2.84 (2.29)	0.44
4-CH_3O	3.25 (2.82)	0.40

[a] Calculated from data in Table II. [b] Data in parentheses based on log $(k_2^H/k_2^D) = -0.33\sigma + 0.36$, which is derived from the correlations lines in Figure 6. This data is more reliable than k_2^H/k_2^D based on Table II since k_2^H values for X = 4-CH_3O and H in Table II have relatively large experimental errors.

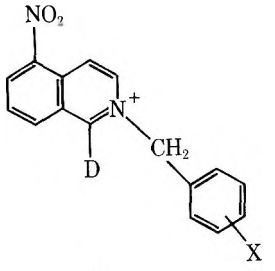
Table IV. Influence of Added $Fe(CN)_6^{4-}$ on Oxidation of 8 (X = 4-CN)[a]

Initial $[Fe(CN)_6^{4-}]$, M	Initial $[Fe(CN)_6^{3-}]$, M	$[Fe(CN)_6^{4-}]/[Fe(CN)_6^{3-}]$	k_{obsd}, M^{-1} s^{-1}
0	1.5×10^{-4}	0.0	18.6 ± 0.5
7.5×10^{-5}	1.5×10^{-4}	0.5	21.2 ± 0.2
1.5×10^{-4}	1.5×10^{-4}	1.0	22.0 ± 0.3
3.0×10^{-4}	1.5×10^{-4}	2.0	18.3 ± 0.1

[a] At 25 °C, ionic strength 1.0, in 20% acetonitrile–water; [KOH] = 0.25 M.

Figure 4. Values of K obtained in this way from the kinetic data for each cation are included in Table II.

The dependence of k_{obsd} on $[OH^-]$ in the oxidation of the 1-deuteroisoquinolinium cations (12: X = 4-CN, 3-F, H, 4-



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CH_3O) was also determined. Values of k_2, K, and K_d for these cations at 25 °C are included in Tables I and II. The isotope effects for these constants as a function of X are given in Table III.

In Figure 5, k_2 is plotted as a function of the Hammett σ constant for the substituent X for 8 and 12. These plots are correlated by the lines from eq 2 and 3.

$$\log k_2^H = -1.29\sigma + 2.29 \text{ (correction coeff = 0.989)} \quad (2)$$

$$\log k_2^D = -0.96\sigma + 1.93 \text{ (correction coeff = 0.999)} \quad (3)$$

A study of the influence of added potassium ferrocyanide in the initial reaction solution is summarized in Table IV. It is clear that ferrocyanide ion present at concentrations up to 2-fold that of the initial ferricyanide concentration has little effect on k_{obsd}. This observation is consistent with the strict second-order kinetics that are observed over at least the first 85% of these reactions. A significant effect of the product ferrocyanide ions on these oxidations would cause marked deviations from second-order behavior.

Discussion

The observation that the kinetics of oxidation of the isoquinolinium cations 8 are first order in both heterocycle and ferricyanide ion requires a rate-determining step as indicated in Scheme I. This scheme also is consistent with the observed dependence of the rate of oxidation on hydroxide ion concentration and the required stoichiometry of two ferricyanide ions per heterocyclic molecule oxidized. The identification of the species Z, introduced above, as the alkoxide ion 11 is discussed further below.

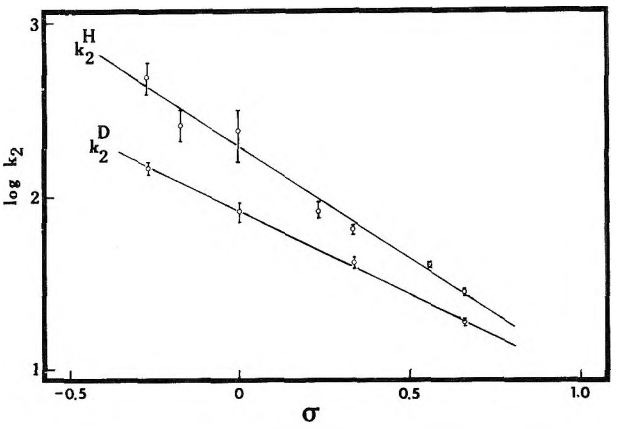
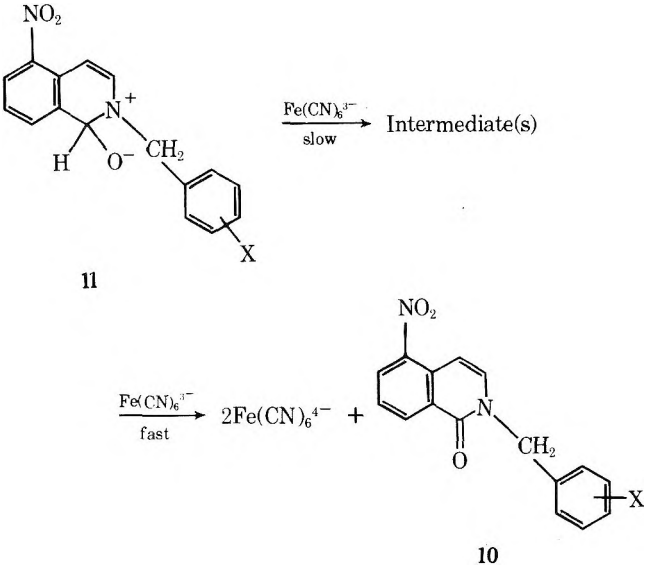


Figure 5. Hammett plots for k_2 for the oxidation of 8 and 12 by $Fe(CN)_6^{3-}$ (25 °C, 20% CH_3CN/H_2O, ionic strength 1.0).

Scheme I, requiring the presence of at least one intermediate, is typical of schemes which have often been proposed for a wide range of ferricyanide oxidations.[32,33] Most commonly, the intermediate has been proposed to be a radical species of some type on the assumption that since ferricyanide ion is a one-electron oxidant the rate-determining step probably involves a one-electron transfer from reductant to oxidant. A radical intermediate could then reduce a second ferricyanide ion in a second one-electron transfer step. Although there have been occasional claims[32,33] for nonradical ferricyanide oxidations, the mechanisms of such reactions have usually been written in terms of vaguely defined intermediate complexes.

Wiberg and co-workers[34] have conclusively ruled out the presence of intermediates which involve displacement of one of the cyanide ions from ferricyanide by another ligand. These workers established that for a number of ferricyanide oxidation reactions there is no incorporation of labelled free cyanide into the ferrocyanide product. This observation is also consistent with observations of the extreme difficulty in exchanging cyanide ions in ferricyanide with free cyanide from solution;[35,36] e.g., at pH 10, less than 2% of the cyanide substituents in $Fe(CN)_6^{3-}$ exchange with aqueous CN^- in 100 h

Scheme I



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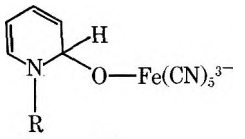
at 25 °C. Thus, a structure such as **13**, which was proposed by Abramovitch and Vinutha[22] for the ferricyanide oxidation of pyridinium ions, can be ruled out for the intermediate in Scheme I.



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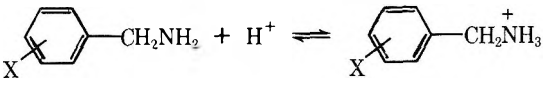
The most direct evidence in the present study which bears on the nature of the intermediate in Scheme I is contained in the observed magnitude of the ρ values for k_2^H and k_2^D. These values ($\rho(k_2^H) = -1.29$ and $\rho(k_2^D) = -0.96$) are similar to the equilibrium ρ values for protonation of ring-substituted benzylamines (**14**) ($\rho = -1.05$ in water at 25 °C)[37] and for the



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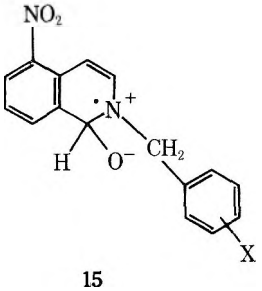
dissociation of the pseudobase **9** to the isoquinolinium ions **8** ($\rho = -1.14$ in water at 25 °C).[30] Thus, the sign and magnitude of $\rho(k_2)$ clearly indicate that the transition state for the rate-determining step in Scheme I must bear close to a full unit positive charge on the ring nitrogen atom. If the assumption is made that this transition state is quite product-like (see later discussion), then this requires that the (first) intermediate after the rate-determining transition state should also bear a positive charge on the ring nitrogen atom. Under this constraint, there would seem to be only two reasonable structures that can be proposed for the rate-determining transition state. These are (i) the transition state for the transfer of one of the lone-pair electrons on N to ferricyanide ion to generate the zwitterionic radical **15**, (ii) the transition state **16** for transfer of hydride ion to ferricyanide



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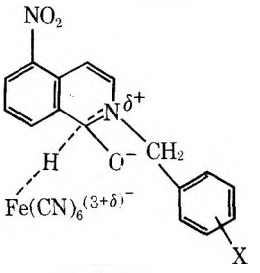
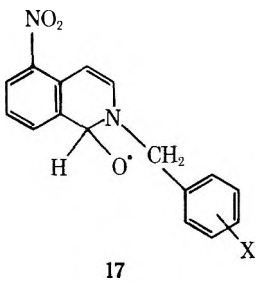


16

ion. For **16**, $\rho(k_2^H) = -1.29$ would require the lone-pair electrons on nitrogen to be so completely involved in the transition state that the nitrogen atom would bear close to a full +1 charge in **16**. Such a situation also requires a large amount of C–H bond breaking in **16**.

A rate-determining transition state for electron abstraction from the anion **11** to give the oxygen radical **17**, which is analogous to the radical species suggested as intermediates in the ferricyanide oxidation of phenols,[38] can certainly be ruled out on the basis of $\rho(k_2)$. Although the reaction **11** → **17** does formally involve an increase of +1 in the charge on oxygen, this process would be expected to have a very small ρ value since the oxygen atom is separated from the substituted phenyl ring by three saturated atoms (C(1)–N(2)–CH_2). The ρ value for **11** → **17** would be expected to be very similar to the equilibrium ρ value for **11** + H^+ ⇌ **9**. From the data for the substituent dependence of K_d in Table I it is clear that $\rho \approx 0$ for this latter process.



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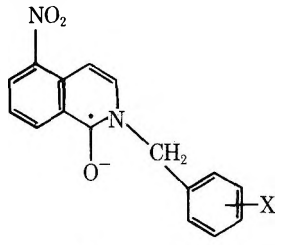
Another rate-determining transition state that is formally possible for the ferricyanide oxidation of **11** is associated with hydrogen atom abstraction from C-1 to give the carbon radical **18**. It is difficult to conceive of any anchimeric assistance to



18

the formation of **18** from the ring nitrogen atom so as to allow the generation of close to a full unit positive charge on nitrogen. Without such assistance the ρ value for generation of **18** would be expected to be quite small since bond breaking occurs at a carbon atom that is separated from the substituent phenyl ring by two saturated atoms (N(2)–CH_2).

Thus, assignment of a mechanism for the ferricyanide oxidation of **11** and of a structure to the first-formed intermediate in Scheme I seems to simply require a distinction between a radical mechanism involving rate-determining formation of **15** and a hydride-abstraction mechanism via the rate-determining transition state **16**. This latter mechanism, unlike the radical mechanism, involves breaking the C(1)–H bond in the rate-determining step. Thus, for transition state **16** a primary kinetic isotope effect is predicted when this hydrogen atom is replaced by deuterium, whereas for a mechanism proceeding through **15** such isotopic substitution should only lead to a very small secondary kinetic isotope effect. The values for k_2^H/k_2^D in Table III are considerably larger than can be accounted for in terms of a secondary isotope effect on the formation of **15**, and so the hydride-transfer mechanism via **16** is indicated.

Of particular interest is the observation that k_2^H/k_2^D in Table III is quite dependent on the nature of the substituent X in the phenyl rings of **8** and **12**. There is a smooth decrease in k_2^H/k_2^D as X becomes increasingly more electron withdrawing. This variation in k_2^H/k_2^D is over twofold between X = 4-OCH_3 and X = 4-CN and is so uncharacteristic of secondary kinetic isotope effects that the possibility of a radical mechanism via **15** may be confidently eliminated. The substituent dependence of k_2^H/k_2^D can, however, be readily rationalized in terms of the hydride-abstraction mechanism involving transition state **16** by reference to Figure 6. In Figure 6, it is assumed that the immediate products of the rate-determining transition state are the isoquinolinones **10** (written as the resonance contributors **19**) and the species $HFe(CN)_6^{4-}$, which is the result of hydride addition to ferricyanide ion. The formal representation $HFe(CN)_6^{4-}$ is not meant to bear any implication as to the exact structure of this species (see later discussion). As pointed out above, $\rho(k_2)$ is only consistent with close to a full unit positive charge on the ring nitrogen atom in the transition state, and this in turn suggests that this transition state is quite product-like. The influence of X on the stabilities of **19** would be expected to exactly parallel the substituent effects on the transition states leading to **19**. On the other hand, X will exert almost no influence on the relative

stabilities of the anions **11**, consistent with K_d (Table I) being effectively independent of X. Thus, in the reaction profiles in Figure 6 we have a situation where the stabilities of the starting materials are independent of the substituent X, but the stabilities of the products are strongly influenced by X. In such a situation the Hammond postulate[39] may be applied to predict that the transition states will vary as X is varied and be most product-like for the most unstable product (i.e., X = 4-CN in the present study).

Theoretical treatments[40] of primary kinetic isotope effects for asymmetric transition states predict that k_2^H/k_2^D decreases as the transition state becomes more product-like. When viewed in this way, our data for k_2^H/k_2^D as a function of X (Table III) are completely consistent with the reaction diagrams which we have derived in Figure 6 on the basis of the observed value for $\rho(k_2)$ and so further support our conclusion that the rate-determining step in these reactions involves hydride ion transfer to ferricyanide ion. It should also be noted that the k_2^H/k_2^D values in Table III are similar to the primary deuterium kinetic isotope effects which have been reported for two other reactions which are generally considered to involve hydride transfer. Thus, for the Cannizzaro reaction, k^H/k^D = 1.8 for benzaldehyde (C_6H_5CHO vs. C_6H_5CDO),[41] while k^H/k^D is in the range 1.8–2.6 for the reduction of the triphenylmethyl cation by isopropyl alcohol [$(CH_3)_2CHOH$ vs. $(CH_3)_2CDOH$].[42]

The independence of the rate of oxidation on the presence of ferrocyanide ions up to at least a 12-fold[43] excess of ferrocyanide over ferricyanide is also atypical of those ferricyanide oxidations in which radical mechanisms have been firmly established. Ferricyanide oxidations which appear to be genuine examples of one-electron transfer processes involving radical intermediates are typically significantly inhibited by even small concentrations of ferrocyanide ions.[32,33] For example, McDonald and Hamilton[38] reported a radical oxidation of a phenol for which ferrocyanide inhibition is observed even under conditions where ferricyanide ion is in 100-fold excess over ferrocyanide ion. Such reactions show marked deviations from true first-order behavior in ferricyanide ion and are in sharp contrast to the clean overall second-order behavior observed over at least the first 85% of reaction in the current study. The deviations from second-order behavior which we do observe in this study when greater than a 12-fold excess of ferrocyanide over ferricyanide has built up are probably ascribable to specific ion effects rather than any true inhibition of the reaction by ferrocyanide ion. The rates of ferricyanide oxidations are well-known[32,33] to be susceptible to a wide range of specific ion effects from both cations and anions. The slight decreases in rate that are observed at high concentrations of KOH in Figure 4 are probably also attributable to specific ion effects arising from the replacement of chloride ion by hydroxide ion in these media. We have taken care to use only potassium salts in the current study so that cationic specific ion effects can have no influence on the interpretation of our results.

The structure of the ferricyanide hydride adduct, represented above as $HFe(CN)_6^{4-}$, can only be speculated upon at the present time. Clearly, this species is very unstable toward oxidation by the second ferricyanide ion that is required by the overall reaction stoichiometry. Formally, this reaction can be represented as in eq 4.

$$HFe(CN)_6^{4-} + Fe(CN)_6^{3-} \rightarrow 2Fe(CN)_6^{4-} + H^+ \quad (4)$$

Structures for $HFe(CN)_6^{4-}$ can be formally written in which hydride attack has occurred at either Fe, C, or N of the $Fe(CN)_6^{3-}$ unit. One possibility is that this species is hexacyanohydridoiron(III), which involves a 7-coordinate Fe(III) complex. Several stable 7-coordinate Fe(III) complexes are known.[44-48] Many hydride mixed complexes of iron are known,[49] although it is not surprising that none of these are iron(III) complexes since such species are expected to be rapidly converted to iron(II) species.

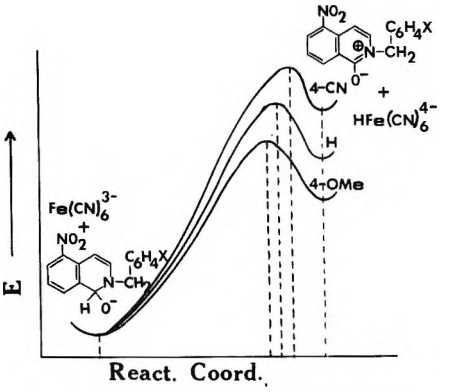


Figure 6. Energy profiles for the rate-determining step in the oxidation of isoquinolinium cations by $Fe(CN)_6^{3-}$. Profiles are derived as described in text.

An alternative attractive structure for $HFe(CN)_6^{4-}$ can be suggested on the basis of the recent observation by Casey and Neumann[50] that $Na^+HB(OCH_2)_3^-$ reacts with $Fe(CO)_5$ to give the $[Fe(CO)_4CHO]^-$ anion. This reaction involves hydride attack on the carbon atom of a coordinated CO molecule and suggests that a similar hydride attack on carbon in $Fe(CN)_6^{3-}$ might occur since CN^- and CO are isoelectronic. This analogy is even further strengthened by the observation[51-54] that both BH_4^- and $HB(OCH_3)_3^-$ rapidly reduce $Fe(CN)_6^{3-}$ to $Fe(CN)_6^{4-}$. These reactions presumably must involve hydride attack on ferricyanide ion and may be considered to be simple models for the ferricyanide ion abstraction of hydride ion from **11** via transition state **16**. It seems likely that the same $HFe(CN)_6^{4-}$ species, whatever its structure, is involved in each of the above three reactions.

As discussed above, the value of $\rho(k_2)$ requires close to a full unit positive charge on the ring nitrogen atom in the transition state **16**. This requirement indicates extensive delocalization of the lone-pair electrons on nitrogen into the ring and a resulting essentially "aromatic" transition state. The requirement for a product-like transition state (see above) then suggests that a large amount of positive charge also exists on N-2 in the isoquinolinone product **10**. This requires major contributions from the Kekulé pyridinium resonance structures **19–21** to the true resonance-hybridized isoquinolinone product. The amount of aromatic character present in such isoquinolinones has been a matter of considerable dispute, and the situation has been reviewed recently.[55] The recent ex-

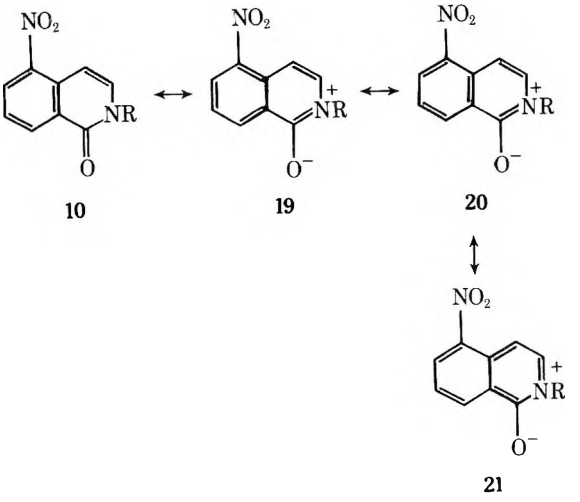


Table V. Characterization of 10 and 12

Compd	X	Registry no.	Mp, °C	^{1}H NMR,[a] δ →	λ_{max}, nm (log ε)[b]
10	4-CN	64840-52-4	188–189	5.30 (s, 2 H), 7.3–7.8 (m, 7 H), 8.45 (d, 1 H), 8.80 (d, 1 H)	261 (4.07), 313 (3.84), 372 (3.67)
	H	64840-53-5	155–156[c]	5.22 (s, 2 H), 7.3–7.7 (m, 8 H), 8.38 (d, 1 H), 8.80 (d, 1 H)	261 (4.06), 313 (3.83), 372 (3.69)
	4-CH_3	64840-54-6	145–146	2.33 (s, 3 H), 5.20 (s, 2 H), 7.25 (m, 6 H), 7.53 (t, 1 H), 8.38 (d, 1 H), 8.80 (d, 1 H)	262 (4.06), 314 (3.83), 372 (3.70)
	4-CH_3O	64840-55-7	137–139[d] (dec)	3.80 (s, 3 H), 5.16 (s, 2 H), 6.87 (d, 2 H), 7.29 (s, 2 H), 7.32 (d, 2 H), 7.55 (t, 1 H), 8.38 (d, 1 H), 8.80 (d, 1 H)	262 (4.07), 313 (3.82), 367 (3.65)
12 (Br^-)	4-CN	64840-56-8	260–261 (dec)	6.37 (s, 2 H), 7.7–8.1 (m, 4 H), 8.37 (t, 1 H), 8.8–9.5 (m, 4 H)	
	3-F	64840-57-9	222–224 (dec)	6.20 (s, 2 H), 7.2–7.7 (m, 4 H), 8.30 (t, 1 H), 8.7–9.5 (m, 4 H)	
	H	64840-58-0	203–204 (dec)	6.08 (s, 2 H), 7.55 (s, 5 H), 8.20 (t, 1 H), 8.7–9.4 (m, 4 H)	
	4-CH_3O	64840-30-8	193–194 (dec)	4.08 (s, 3 H), 6.11 (s, 2 H), 7.21 (d, 2 H), 7.65 (d, 2 H), 8.25 (t, 1 H), 8.6–9.4 (m, 4 H)	

[a] Solvents: **10**, $CDCl_3$; **12** (Br^-), CF_3CO_2H. [b] In 20% CH_3CN/H_2O. [c] Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 10.20. Found: C, 68.19; H, 4.41; N, 10.34. [d] Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 66.08; H, 4.74; N, 9.33.

perimental estimate[56] of a difference of only 4.4 kcal/mol in the resonance energies of isoquinoline and 1-isoquinolinone is consistent with our conclusion of major contributions from the structures **19–21** to the resonance hybrid.

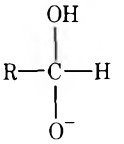
There seems to be no obvious alternative choice to the pseudobase anion **11** for the structure of the species Z introduced above on the basis of kinetic considerations. As discussed in detail above, the identification of Z as **11** allows a satisfying rationalization of the substituent effects and kinetic isotope effects observed in the present study. In particular, the formation of the 1-isoquinolinones in the rate-determining transition state via hydride abstraction from **11** is an essential feature of the rationalization via Figure 6 of the observed substituent dependence of the kinetic isotope effects. However, a comparison of the equilibrium constant for formation of **11** by deprotonation of **9** as determined by a thermodynamic method (K_d in Table I) and kinetically (K in Table II) reveals a discrepancy. Thus, the kinetically determined values of K are consistently smaller than the spectroscopically determined K_d values. Such a trend indicates that the formation of the pseudobase anion **11** from the neutral pseudobase **9** is apparently more difficult in the presence of $Fe(CN)_6^{3-}$ than in its absence (i.e., in the spectroscopic determination of K_d). Furthermore, there appears to be a substituent and isotope dependence on the difference between K and K_d. The overall trend is for the difference between K and K_d to become larger as the X substituent becomes less electron withdrawing, although the exact magnitude of this trend is masked by the experimental errors involved. K^D is considerably larger than K^H (Table III) and shows less deviation from K_d than K^H does for all X substituents.

The simplest rationalization for the observations of deviations between K and K_d seems to be the assumption of a rapid formation of a 1:1 complex between neutral pseudobase **9** and ferricyanide ion. The strength of this complex is required to be dependent on the substituent X and to involve some type of interaction between the C(1) hydrogen atom of **9** and ferricyanide in order to account for $K^H/K^D \approx 0.5$ (Table III). Clearly, alkoxide ion formation within a complex species of this type would be more difficult than in the neutral pseudobase because of the negative charge borne by the ferricyanide ion. We have no basis at the present time for further speculation as to the exact structure of such a 1:1 complex, but we note that there are precedents for the complexation of iron(III) species with dihydropyridine derivatives.[57–59]

In an earlier attempt at a mechanistic study of ferricyanide oxidation of heteroaromatic cations, Abramovitch and Vinutha[22] found that the ratio of 2- to 6-pyridone product was the same for the 1,3-dimethylpyridinium cation and its C(2) and C(6) deuterated derivatives. They therefore concluded that cleavage of the C–H bond was not involved in the rate-determining step. An isotope effect of the size that we have found for **12** (X = 4-CN) ($k_2^H/k_2^D = 1.41$) could easily have been missed in this previous study since such an isotope effect could be hidden in the experimental error in the determination of the observed 3–4% of 6-pyridone in the mixture of oxidation products.[60]

In a very recent study[23] of the oxidation of pyridinium cations, Tomilenko has apparently observed the same pH dependence and first-order ferricyanide dependence for the oxidation kinetics as we report herein. However, the postulated mechanism via two consecutive one-electron transfers is not consistent with the substituent and isotope effects observed in our study.

The Cannizzaro reaction of nonenolizable aldehydes is generally considered[41,61] to involve hydride transfer from either the mono- or dianion of the aldehyde hydrate (i.e., **22** or **23**) to the carbonyl group of another aldehyde molecule. The anions **22** and **23** are clearly quite similar electronically to the



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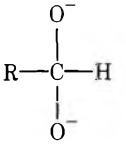
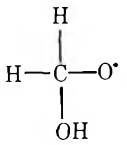


23

pseudobase anion **11**, which is deduced in the present study to be the species susceptible to ferricyanide attack. Thus, the current oxidation reaction may be formally considered as being analogous to the Cannizzaro reaction with hydride transfer to ferricyanide instead of to another organic molecule.

Ferricyanide ion is well-known[62,63] to oxidize aldehydes to carboxylate anions in basic solution, and so the question arises as to whether hydride transfer from **22** and/or **23** to ferricyanide ion is also involved in this reaction. Such reactions have been generally interpreted as proceeding through ferricyanide attack on the enolate anion for enolizable aldehydes. Since ketones which cannot react by hydride transfer appear to be oxidized by ferricyanide ion at similar rates to related aldehydes,[63–65] this route via the enolate ion seems to be indicated for enolizable aldehydes. However, for nonenolizable

aldehydes oxidation via hydride transfer from **22** and/or **23** seems to be the most attractive route. A detailed kinetic study of the oxidation of formaldehyde has been reported.[66] The interpretation of this reaction as passing through the radical **24** is not, however, consistent with the observed first-order



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dependence on hydroxide ion concentration in the region 0.5–2.0 M NaOH. In this region formaldehyde exists essentially as its hydrated anion (**22**, R = H) since the pK_a for formation of this anion from the neutral hydrate is 13.3.[67] Thus, the observed pH dependence suggests reaction via the dianion **23** (R = H). On the basis of the current study, hydride transfer from this dianion to ferricyanide ion is clearly the most likely mechanism.

Experimental Section

Salts of the cations **8** were available from an earlier study.[30] Potassium chloride, potassium ferrocyanide, potassium ferricyanide, and acetonitrile (spectroscopic) were all the best commercially available grades.

1-Deuterio-5-nitroisoquinoline. 1-Deuterioisoquinoline was prepared from isoquinoline via 1-isoquinolinecarboxylic acid[68,69] by the method of Schleigh[70] and nitrated by the general method of Le Fèvre and Le Fèvre.[71,72] Mass spectral and ^1H NMR spectral analyses indicated >96% of the 1-deuterio derivative.

***N*-Benzyl-1-deuterio-5-nitroisoquinolinium bromides (12)** were prepared by refluxing 1-deuterio-5-nitroisoquinoline with a slight excess of the appropriate ring-substituted benzyl bromide in acetone. The crude salts precipitated from solution and were treated with decolorizing charcoal and recrystallized from ethanol–diethyl ether. ^1H NMR spectral data and melting points are given in Table V.

Isolation of 1-Isoquinolinone Products. The bromide salt of the cation **8** (0.25 g) and a large excess of potassium ferricyanide (5 g) were dissolved in water (50 mL). Aqueous 1 M KOH (5 mL) was added dropwise with vigorous stirring until precipitation was complete. The aqueous mixture was extracted with chloroform, and the combined chloroform layers were dried over anhydrous $MgSO_4$. The solvent was removed on the rotary evaporator, and the residue was decolorized (charcoal) and recrystallized from methanol with addition of water to the hot solution to promote crystallization. Yields of **12** were in the range of 50–80%. Spectral and mp data are given in Table V.

Kinetic Studies. All oxidation rates were measured at 25 °C in 20% (v/v) acetonitrile–water at ionic strength 1.0 (KOH + KCl) with heterocyclic cation and ferricyanide present in the molar ratio 1:2. Typical reaction solutions (total volume 3 mL) contained heterocyclic cation (7.5×10^{-5} M), potassium ferricyanide (1.5×10^{-4} M), acetonitrile (0.6 mL), and appropriate concentrations of potassium hydroxide and potassium chloride. Appropriate modifications were made for studying the influence of ferrocyanide ion on reaction rates. Reference cells contained all components of the reaction mixture, except the heterocyclic cation. All rates were measured from recorded traces of the absorbance at 500 nm as a function of time (Unicam SP1800 spectrophotometer equipped with Unicam AR25 linear recorder). Second-order rate constants were calculated from the slopes of plots of $\frac{1}{2}(1/C - 1/C_0)$ vs. t (where C_0 is the initial concentration of heterocycle and C is the concentration at time t) using at least ten data points over the first 85% of reaction. Least-squares lines were fitted to the data points, and the computed and experimental data points were visually checked for fit and linearity.

Equilibrium constants (K_d) were evaluated from the dependence of the absorption spectrum on $[OH^-]$ in the range 0.02–1 M KOH (25 °C, ionic strength 1.0, 20% acetonitrile–water).

Registry No.—1-Deuterio-**11** (X = 4-CN), 64840-32-0; 1-deuterio-**11** (X = 3-F), 64840-33-1; 1-deuterio-**11** (X = 4-CH_3O), 64840-34-2; 4-cyanobenzyl bromide, 17201-43-3; 3-fluorobenzyl bromide, 456-41-7; benzyl bromide, 100-39-0; 4-methoxybenzyl bromide, 2746-25-0; 1-deuterio-5-nitroisoquinoline, 64840-31-9; $Fe(CN)_6^{3-}$, 13408-62-3; $Fe(CN)_6^{4-}$, 13408-63-4.

References and Notes

(1) Supported by an operating grant awarded to J.W.B. by the National Research Council of Canada.
(2) National Research Council of Canada Postdoctoral Fellow, 1975–1977.
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Mechanism for the Reaction Involving Dimethyl Sulfoxide and Acetyl Chloride Studied by Nuclear Magnetic Resonance Spectroscopy

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The kinetics of the reaction between dimethyl sulfoxide (Me_2SO) and acetyl chloride (AcCl) have been studied using the nuclear magnetic resonance spectroscopy of both static and flowing liquids at 30 °C in either benzene or methylene chloride solutions. The decay of Me_2SO and AcCl follows mainly second-order kinetics, first order each in Me_2SO and AcCl. The growth of the main products, acetic acid and chloromethyl methyl sulfide, appears to be mainly second order also, although the overall reaction is complicated by several side reactions that compete to a lesser extent with the main path. These side reactions generate three previously unreported compounds in small amounts, namely, acetoxymethyl methyl sulfide, acetic anhydride, and chlorodimethylsulfonium chloride. Both the anhydride and the sulfonium salt are unstable under the reaction conditions and eventually disappear, with the salt having the faster rate. When Me_2SO-d_6 replaces Me_2SO, a primary deuterium isotope effect is observed, indicating the presence of an intermediate. This conclusion is supported by the observation that acetic anhydride and the sulfonium salt appear to be generated by trapping reactions. A mechanism to account for these observations is proposed.

Introduction

The chemistry of dimethyl sulfoxide (Me_2SO) has been under study for a number of years, and much is known about its nucleophilic properties.[1b] However, in the case of addition to acyl halides, conclusions concerning the reaction mechanism are based on only the nature of the products that could be identified.[2] No kinetic data seem to be available, and none of the proposed intermediates have been detected in solution at room temperature. In the present paper, we report a study of the kinetics of the reaction between Me_2SO and acetyl chloride (AcCl) in benzene and in methylene chloride, studied using nuclear magnetic resonance spectroscopy (NMR). In each solvent the rate of reaction appears to be second order, first order each in Me_2SO and ACT. The main products of this reaction are acetic acid (AcOH) and chloromethyl methyl sulfide (CMMS), as reported earlier.[2] However, small amounts of two other compounds, acetoxymethyl methyl sulfide (AMMS) and acetic anhydride (Ac_2O), are also generated during the reaction, and their amounts depend on the reaction conditions. In addition, a transient signal is observed in the frequency region expected for a dimethylsulfonium salt. A mechanism is proposed to account for these observations as well as the occurrence of a primary deuterium isotope effect for the disappearance of the reactants and the growth of the products.

Experimental Section

Chemicals. Me_2SO, Me_2SO-d_6, AcCl, benzene, and methylene chloride were obtained from commercial sources. Me_2SO and AcCl were distilled immediately before solution preparation. Benzene and methylene chloride were dried over molecular sieves, distilled, and stored over additional molecular sieves.

Kinetic Studies. The time dependence of the proton NMR spectrum was measured at 30 ± 2 °C using a Varian A-60 or HA-100-15 for the slower rates and an HA-100-15 equipped with a flow system[3] for the faster rates. Solutions of each reactant were prepared gravimetrically, and equal volumes were mixed (outside the magnet for the static runs and inside the magnet via a mixing chamber for the flow runs). Temperature regulation was not as precise as for other studies using the HA-100 flow system because the thermostated reservoir was left out to decrease solution volume.

In a complementary study, a Beckman IR-12 was used to measure the time dependence of infrared absorption bands due to Me_2SO-d_6 (1050 cm^{-1}) and ACT (950 and 1900 cm^{-1}) at about 25 °C after mixing equal volumes of a benzene solution containing 0.4 M Me_2SO-d_6 and one containing 0.4 M ACT.

Results

The CH_3 region of the proton NMR spectra of a nonspinning sample obtained at 100 MHz after mixing but before completion of the reaction is given in Figure 1 to illustrate the solvent dependence of the reactant and product signals. The series of spectra given for benzene solvent consists of five consecutive scans from left to right with pauses ranging from 30 s to several minutes. The first scan (labeled 1) gives CH_3-proton resonances for Me_2SO (labeled d) and AcCl (labeled a). Scan 2 illustrates an additional central signal (labeled c,h), which is a superposition of the AcOH (labeled h) and CMMS (labeled c) CH_3-proton resonances. The AcOH signal position as well as its intensity is time dependent moving upfield in scans 2, 3, 4, and 5, in which it is at higher field than the ACT signal. Its final position is upfield from the AcCl

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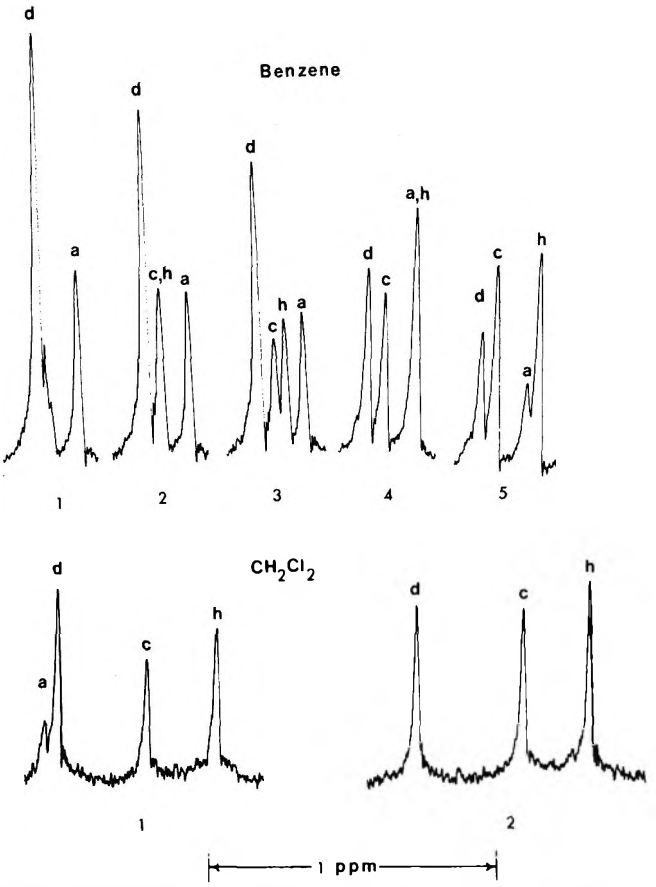


Figure 1. Successive scans of the CH_3-proton resonance region at 30 °C and 100 MHz during the reaction after the flow had been stopped with pauses from 30 s up to several minutes obtained without spinning. For each solvent, the first scan is labeled 1. For benzene, the initial concentrations were 0.070 M Me_2SO and 0.066 M AcCl. For methylene chloride, the initial concentrations were 0.103 M Me_2SO and 0.091 M AcCl, and the spectra were obtained at lower rf power than that used for the benzene solution. The assignments of these CH_3-proton resonances are: Me_2SO, d; AcCl, a; CMMS, c; add AcOH, h.

Table I. Chemical-Shift Values (Hz) for the CH_3-Proton Resonances of Me_2SO and AcOH Relative to *tert*-Butyl Alcohol in Benzene at 30 °C

[AcOH], M	[Me_2SO], M	δ_{AcOH}	δ_{Me_2SO}
0.202		83	
	0.07		93.2
	0.31		99.5
	0.92		108.4
0.100	0.146	98	102.5
0.104	0.501	103	111.2
0.106	0.820	104	115.8

position by about 10 Hz. This time dependence for the AcOH signal position results from the fact that the AcOH chemical shift in benzene depends on the concentration of Me_2SO, as illustrated in Table I, which lists the chemical shifts for Me_2SO and AcOH relative to *tert*-butyl alcohol. Thus, as the reaction progresses the concentration of Me_2SO decreases and the AcOH signal moves upfield. This conclusion is also supported by the fact that the position of the CH_3-proton resonance of AcOH is fixed downfield if a sufficient excess of Me_2SO-d_6 is present.[4] The CH_3- and CH_2-proton resonances due to CMMS appear to be independent of Me_2SO concentration, and the CH_2-proton resonance is observed at lower field at 2.43 ppm from the CH_3-proton resonance. In addition

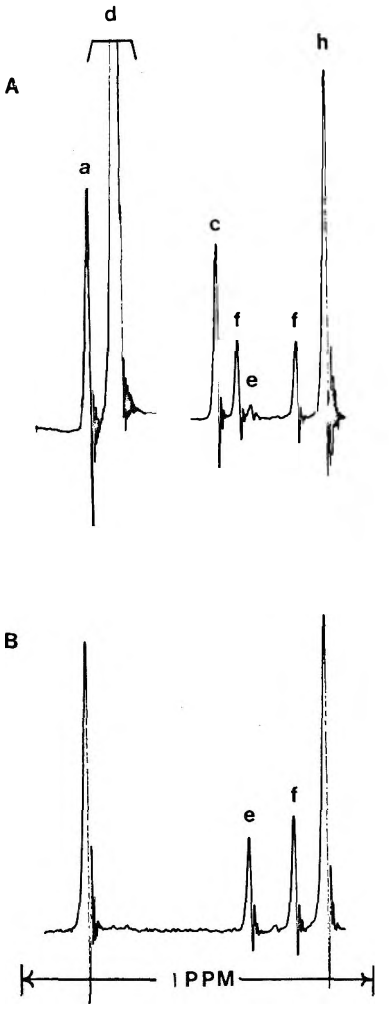


Figure 2. Spectra of the CH_3-proton resonance region obtained at 30 °C and 100 MHz during the reaction using spinning samples for methylene chloride solutions having substantially larger initial concentrations of reactants than Figure 1, namely, 0.64 M Me_2SO and 0.32 M AcCl. The signal labeled e is due to the CH_3-proton resonance of Ac_2O and those labeled f are due to acetoxymethyl methyl sulfide with the upper-field signal assigned to the acetoxy CH_3. The field strength increases from left to right. See Figure 1 for the other assignments.

a transient signal is observed 1.48-ppm downfield from the CH_3-proton resonance of CMMS. No other transient signals were observed. Because the AcOH signal moves into other signals, its time dependence could not be determined accurately in benzene. For this reason, the reaction was also studied in methylene chloride, a solvent in which the AcOH signal position is only slightly dependent on Me_2SO concentration. As illustrated in Figure 1, the chemical shifts for AcCl and Me_2SO are very close in this solvent. In fact, the Me_2SO signal position is somewhat concentration dependent and it moves into the AcCl signal as the reaction progresses. However, the time dependence for the Me_2SO and AcCl signals could still be determined as accurately as in benzene when spinning samples were used to provide better resolution. The proton resonance (not illustrated) of a transient could also be observed 1.48-ppm downfield from the CMMS CH_3 signal. The CMMS CH_2-proton signal could be observed, although it is close to the methylene chloride signal, 0.6-ppm upfield. The higher resolution spectra obtained with spinning samples permit the observation of additional signals. Sample spectra obtained during the reaction are illustrated in Figure 2 for the reaction of AcCl with Me_2SO (Figure 2A) and with Me_2SO-d_6 (Figure 2B). In addition to the signals identified above, three

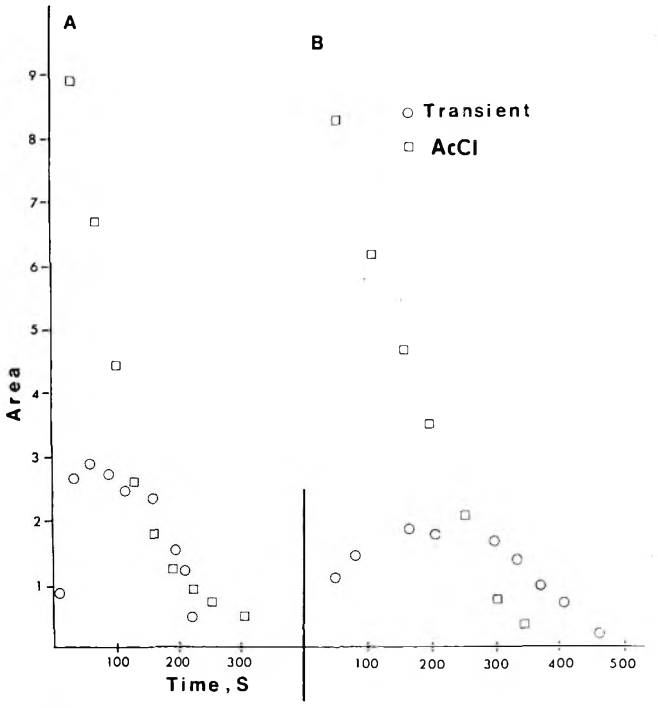


Figure 3. Integrated areas of the signals due to AcCl and the transient at various times during the reaction in methylene chloride at 30 °C. The initial concentrations were: A, 0.64 M Me_2SO and 0.32 M AcCl; B, 0.256 M Me_2SO and 0.128 M AcCl.

new signals are observed, and they are assigned to the CH_3-proton resonances of acetic anhydride (Ac_2O) (labeled e) and acetoxymethyl methyl sulfide (labeled f) (AMMS). The assignment for AMMS was confirmed by reacting Me_2SO with Ac_2O. Di-*tert*-butyl ketone is used as an internal reference. The intensity of these signals depends on the conditions employed. Thus, the intensity of the signals due to AMMS increase relative to the AcOH signal as the concentration of Me_2SO is increased. For example, if the initial AcCl concentration is held constant at 0.126 M, the intensity ratio, AMMS/AcOH, after AcCl has disappeared is 0.06 and 0.10 for initial Me_2SO concentrations of 0.146 and 0.256 M, respectively. Further, when these solutions contain HCl, AMMS is not detected, and when Me_2SO is replaced by Me_2SO-d_6 the downfield signal of AMMS disappears but the AMMS/AcOH concentration ratio remains about the same as that for undeuterated Me_2SO.

Although acetic anhydride reacts with Me_2SO, a similar intensity comparison is possible because its rate of reaction is substantially slower than that for AcCl; i.e., the AcCl reaction is essentially complete before an appreciable amount of acetic anhydride has reacted. In this case, we find that the acetic anhydride intensity increases relative to the AcOH intensity as the AcCl concentration increases. For example, when the initial Me_2SO concentration is fixed at 0.15 M, the intensity ratio, Ac_2O/AcOH, is 0.020 and 0.048 for initial concentrations of 0.13 and 0.32 M AcCl, respectively. In addition, replacing Me_2SO by Me_2SO-d_6 causes an increase in this ratio from 0.017 to 0.080 when the initial concentrations of AcCl and Me_2SO are held constant at 0.32 and 0.64 M, respectively. As in the case of AMMS, acetic anhydride is not detected when HCl is present in the solution.

The intensity of the transient signal and its time dependence also depend on the initial concentration of each reactant, as illustrated in Figure 3, which presents the area rather than intensity as a function of time. Areas are used because the line width of the transient increases as the concentration of each reactant is increased. As illustrated in this figure,

Table II. AcOH/CMMS Concentration Ratio at Various Times during the Reaction of AcCl with Me_2SO at 30 °C

Time, s	AcOH/CMMS[a]	
	HCl absent[b]	HCl present[c]
20	1.42	
30		2.16
40	1.50	
50		3.11
60	1.25	
80	1.12	
100	1.10	1.61
120	1.05	
150		1.35
200		1.24
300		1.15

[a] Concentration ratio. [b] 0.32 M AcCl, 1.28 M Me_2SO initially. [c] 0.128 M AcCl, 0.256 M Me_2SO initially.

doubling the concentration of each reactant not only increases the maximum area observed for the transient, but also decreases the time period in which the maximum is attained. This rate of growth of the transient appears related to the rate of disappearance of AcCl and Me_2SO, as can be seen from the time dependence for the intensity of AcCl; i.e., AcCl disappears more rapidly at the higher concentration. Furthermore, the rate of disappearance of the transient increases relative to that for AcCl when the excess concentration of Me_2SO is increased. In the presence of HCl, the transient appears to reach a larger maximum in a shorter time, and it disappears faster after AcCl has disappeared. However, the signal is substantially broader than in the absence of HCl and these results must be considered qualitative. The spectrum obtained using Me_2SO-d_6 in place of Me_2SO provides information concerning the structure of the compound responsible for this transient signal. First, the transient signal is not observed in this case. Second, no acetoxy-CH_3 signal is observed for this transient compound under these conditions, which provide a better opportunity for its detection than the Me_2SO mixtures do, since the CH_3 signals due to Me_2SO and CMMS are absent. To further probe the structure of this transient, a spectrum was obtained for a solution of Me_2SO in CH_2Cl_2 containing various amounts of dry HCl. Aside from the CH_2Cl_2 signal and one due to the reference (di-*tert*-butyl ketone), the spectrum consists of only one signal that moves downfield as the concentration of HCl is increased. However, even at the highest concentration of HCl employed, this signal has not reached the same chemical shift as observed for the transient generated by reaction of AcCl with Me_2SO. In addition, under these conditions, in the absence of AcCl Me_2SO appears to react slowly; i.e., after about 2 h approximately 4% of the Me_2SO has been converted to CMMS.

In another control experiment, 0.16 M AcCl was mixed with 0.13 M AcOH. These compounds react with each other to form acetic anhydride. After approximately 5 min equilibrium is attained, and the equilibrium constant is 2.2×10^{-3} at 30 °C.

The time dependence for the growth of AcOH does not coincide exactly with that for the growth of CMMS, as indicated in Table III, which illustrates the ratio (AcOH/CMMS) of concentrations as a function of time. For a solution containing 0.32 M AcCl and 1.28 M Me_2SO, the concentration of AcOH increases more rapidly and reaches it maximum value sooner than the CMMS concentration does, even though the final AcOH/CMMS concentration ratio is close to 1. Thus, AcOH grows at a somewhat larger rate than does CMMS. This difference in rates between AcOH and CMMS is enhanced when HCl is present, as illustrated in Table II, which indicates

Table III. Second-Order Rate Constant for the Reaction of Me_2SO with AcCl at 30 °C

$[Me_2SO]$,[a] M	[AcCl],[a] M	$k_{obsd} \times 10^2$ M^{-1} s^{-1}		
		Me_2SO	AcCl	AcOH
		Benzene		
0.067	0.108	d_6[b]	1.0 ± 0.2	1.1 ± 0.3
0.067	0.216	d_6	1.2 ± 0.2	
0.086	0.069	d_6	1.8 ± 0.4	1.7 ± 0.4
0.127	0.063	d_6	1.6 ± 0.2	1.5 ± 0.4
0.175	0.075	d_6	1.6 ± 0.4	1.6 ± 0.4
0.050	0.038	9 ± 1.5	9.4 ± 0.8	
0.070	0.077	6.0 ± 0.9	5.7 ± 0.9	
0.070	0.173	7.8 ± 0.7	6 ± 1	4.9 ± 0.7[c]
0.103	0.070	6.0 ± 0.8	8 ± 1	
0.125	0.066	9.3 ± 0.8	7.3 ± 0.7	
0.151	0.111	5.4 ± 0.9	5.0 ± 0.7	
0.202	0.156	4.8 ± 0.7	4.5 ± 0.6	
		Methylene chloride		
0.64	0.32	d_6[b]	0.53	0.43
0.146	0.128	2.2	2.5	2.8
0.297	0.128	2.3	2.9	2.7
0.64	0.32			2.6
0.256[d]	0.128	12.3	12.0	8.6
0.256[e]	0.128	0.99	0.80	0.92

[a] Initial concentration after mixing equal volumes of solutions. [b] Me_2SO-d_6. [c] AcOH signal overlaps with several signals during the reaction. Consequently, this value is obtained from only four intensity values and should be considered to be only an approximation. [d] Lower concentration of HCl present. [e] Higher concentration of HCl present. Based on downfield shift of Me_2SO resonance.

that the maximum value for the ratio AcOH/CMMS is substantially larger than that obtained in the absence of HCl. This relative acceleration by HCl may be somewhat larger than indicated in the table because HCl reacts with Me_2SO to form CMMS as mentioned above. In fact, if the solution is allowed to stand overnight, the concentration of CMMS continues to grow and exceeds that for AcOH. In addition, the rate of disappearance of Me_2SO and AcCl as well as the rate of growth of AcOH and CMMS are affected by the presence of HCl in a complicated manner. Thus, when present at a lower concentration, HCl accelerates the rate for the reactants and products relative to that in its absence. On the other hand, at a higher concentration of HCl, the rate is retarded somewhat and becomes smaller than that measured at the lower concentration of HCl, as can be seen from the rate constants presented below. The quantitative effect of HCl on the rates cannot be determined from our results because the absolute concentration of HCl was not measured. Instead, the relative concentration of HCl in each solution was determined qualitatively from the extent of the downfield shift of the Me_2SO CH_3-proton resonance.

The time dependence of the various signals has been used to calculate first- and second-order rate constants. For reasons presented in the discussion, we conclude that the rate has mainly a second-order dependence, and values are listed as k_{obsd} in Table III. The values listed for benzene are averages of at least two runs, whereas those given for methylene chloride are calculated from one each.

Discussion

As mentioned above, the data were analyzed in terms of first- and second-order rate expressions, and the results indicate that the reaction is more consistent with second-order kinetics, first order each in Me_2SO and AcCl. This conclusion is based on the fact that the second-order rate constant exhibits no systematic concentration dependence, whereas the first-order rate constant does. For example, when the initial concentration of Me_2SO is held constant at 0.070 M, doubling the AcCl concentration from 0.077 to 0.173 M has only a slight effect on the value for the second-order rate constant (see Table III) whereas the first-order rate constant increases from 4.4×10^{-3} to 12×10^{-3} s^{-1} when benzene is the solvent. When methylene chloride is the solvent and the initial concentration of AcCl is held constant at 0.128 M, doubling the Me_2SO concentration from 0.146 to 0.297 M has little effect on the second-order rate constant (Table II) but increases the first-order rate constant by a factor of 2.1.

The second-order rate of reaction indicates that the time dependence of the signals assigned to the reactants is, in fact, the dependence for the respective reactants. In other words, the observed CH_3-proton resonances labeled d and a are not due to an intermediate arising from a rapid addition of Me_2SO to AcCl, since the decay of such an intermediate would be expected to exhibit a first-order dependence, which does not appear to be the case. This conclusion is supported by the chemical shifts of the resonances. If an intermediate were formed, the signals labeled d and a should be shifted relative to the Me_2SO and AcCl CH_3 signals. However, as can be seen in Figure 1, no additional signal is observed when Me_2SO is present in excess. Likewise, no additional signal is observed when AcCl is present in excess. As an additional check of this conclusion, the reaction was studied using infrared spectroscopy. One minute after mixing equal volumes of 0.4 M AcCl in benzene with 0.4 M Me_2SO-d_6 in benzene, the infrared spectrum contained the 950- and 1900-cm^{-1} bands for AcCl and the 1050-cm^{-1} band for Me_2SO-d_6. These bands decay with a time dependence that is very close to that observed in the NMR study. To our knowledge, the only reported kinetic study concerning acid halides is one involving the reaction of Me_2SO with 5-dimethylaminonaphthalene-1-sulfonyl chloride in ethyl ether.[5] The ultraviolet spectrum was followed as a function of time for a solution containing a large excess of Me_2SO, and it was concluded that the reaction is bimolecular.

Comparison of the k_{obsd} values for Me_2SO and Me_2SO-d_6 in Table II indicates the occurrence of a deuterium isotope effect in both solvents. Although the values for k_{obsd} fluctuate to some extent for both types of determinations, the ratio k_H/k_D is at least 4 or greater, indicating a primary deuterium isotope effect for the disappearance of the reactants and the formation of AcOH (and also CMMS). Consequently, the rate-limiting step for the disappearance of reactants and the formation of AcOH involve a transfer of the SCH_3 proton. This information along with the time dependence for the transient relative to that for AcCl indicate that the transient is not an intermediate in the main path of the reaction and is generated by a minor competitive pathway. This conclusion is based on the following argument. If the transient is an intermediate resulting from the reaction of AcCl with Me_2SO, the rate-limiting step in the formation of products must occur after the formation step for this transient; i.e., an intermediate would not be observed if its formation were involved in the rate-limiting step. Consequently, the deuterium isotope effect would be associated with the decomposition of the transient. As a result, to account for the fact that the decay of reactants is subject to this isotope effect, the reactants would have to be in equilibrium with the transient if it were an intermediate. However, the reactants are not in equilibrium with the transient, since a fixed relationship is not maintained between their concentrations during the reaction; i.e., the concentrations do not conform to an equilibrium constant during the period of reaction, as can be seen in Figure 3. Thus, at the lower initial concentration of reactants, the transient has a smaller concentration than AcCl during most of the reaction but can still be detected after AcCl has disappeared com-

pletely. This crossover in concentrations would not be expected if the transient were in equilibrium with the reactants. At a higher initial concentration for the reactants, no crossover occurs because the decay of the transient is faster, presumably because it is catalyzed by Me_2SO. For convenience, the structure of this transient will be discussed after the proposed mechanism is presented.

Since this transient is not an intermediate in the main path for product formation, the mechanism given in Scheme I is proposed to account for all of the observations given above. In this scheme, IN1 and IN2 are intermediates that are in equilibrium with the reactants. On the basis of product studies, the possibility that these intermediates could occur in this reaction was suggested previously.[2b] IN1 is suggested to be an ion pair; however, it could have a sulfurane structure similar to that suggested for the analogous *tert*-butoxy compound[6] and no alteration in the mechanism would be required. The ion pair structure indicated for IN2 is suggested because it provides a chemically reasonable route to Ac_2O as discussed below. Neither IN1 nor IN2 are observed, requiring that the equilibrium constant be small. The rate-limiting step in this mechanism, the decomposition of IN2, is consistent with the observations presented above. Thus, the main path is the formation of AcOH plus CMMS according to the left-hand step, which involves the removal of the SCH_3 proton and, therefore, is consistent with the primary deuterium isotope effect observed for the formation of the products. Furthermore, the preequilibrium can explain why this isotope effect is also observed for the decomposition of the reactants.

The reaction steps proceeding to the right can account for the formation of the minor products. Consequently, the observation of these products provides support for the occurrence of an intermediate. The formation of AMMS is accompanied by the formation of HCl, which is probably associated with Me_2SO. That Me_2SO acts as a base in this step is supported by the fact that the concentration ratio, AMMS/AcOH, increases as the concentration of Me_2SO is increased. This result also indicates that a base such as Me_2SO may be less important for proton removal in the main reaction path, i.e., the formation of AcOH plus CMMS. In addition, for the initial concentrations of 0.32 M AcCl and 0.64 M Me_2SO, this concentration ratio is unchanged at 0.19 when Me_2SO is replaced by Me_2SO-d_6, as might be expected for the mechanism in Scheme I since AMMS and AcOH are each formed via rate-limiting steps that involve removal of the SCH_3 proton. The fact that AMMS is not observed in the presence of added HCl provides additional support for an intermediate. Thus, the intermediate is trapped by HCl faster than it can react to form AMMS.

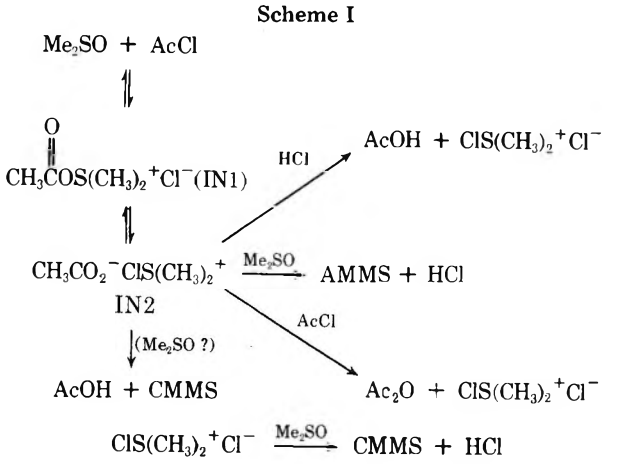
According to Scheme I, Ac_2O is formed by trapping IN2 with AcCl. This path is consistent with the fact that the concentration ratio Ac_2O/AcOH increases as the concentration of AcCl is increased. Furthermore, this path can account for the substantial increase in Ac_2O concentration when Me_2SO is deuterated. Thus, since the reaction of AcCl with IN2 does not involve proton removal, the rate of this reaction should be unaffected when Me_2SO is deuterated, whereas the rates for the formation of AcOH + CMMS and AMMS + HCl are retarded. Consequently, deuteration of Me_2SO makes the trapping of IN_2 by AcCl more competitive with the main path for the decomposition of IN2. Furthermore, at a fixed initial concentration of reactants, the fraction of Ac_2O in the products increases approximately by a factor of the deuterium isotope effect when Me_2SO is deuterated, as would be expected since the Ac_2O path makes a very small contribution in the nondeuterated case; i.e., the rate constant for this path is substantially smaller than those for the other paths in the nondeuterated case. The Ac_2O results are also the reason for the suggested structure for IN2. Thus, since these results indicate that AcCl traps an intermediate to generate Ac_2O, trapping IN2 seems more reasonable than trapping IN1 (or the chlorosulfurane) for which larger steric interactions are expected; i.e., AcO^- is expected to be better than IN1 as a nucleophile for AcCl.

The possibility that Ac_2O is formed via reaction between AcOH and AcCl must also be considered. As indicated above, this reaction proceeds to equilibrium, and it is possible to estimate an upper limit to the concentration ratio Ac_2O/AcOH.[7] For a solution containing 0.64 M Me_2SO and 0.32 M AcCl initially, this upper limit (0.022) is comparable to the observed value (0.017). Although the calculated and experimental results appear to agree in this case, the agreement is very poor when Me_2SO is replaced by Me_2SO-d_6 for which the observed ratio is 0.08, a factor of 3.6 larger than the calculated value. Furthermore, the disparity is larger if this analysis is made using data obtained earlier in the Me_2SO-d_6 reaction. Thus, after about 100 s of reaction, the calculated Ac_2O concentration is a factor of 4.6 smaller than the observed value, i.e., 0.0038 vs. 0.0173 M, indicating that the Ac_2O is formed somewhat more rapidly at the beginning of the reaction when AcCl is present in higher concentration, a result expected for a trapping reaction. Consequently, a reaction path involving AcCl and AcOH can, at best, account for only a small part of the Ac_2O formed when Me_2SO-d_6 is a reactant. Its contribution in the Me_2SO case may be smaller than indicated above, since the Me_2SO–AcCl reaction is almost complete in 3 min, a time shorter than the 5-min time period observed for the AcCl–AcOH–Ac_2O equilibration at comparable concentration, namely, 0.13 M AcOH and 0.16 M AcCl.

As indicated in Scheme I, chlorodimethylsulfonium chloride is generated in the same step as Ac_2O is generated. We suggest that the transient signal is due to the methyl protons of this sulfonium salt and will discuss the reasons for this conclusion below. This salt may also be generated along with AcOH via reaction of HCl with IN2 as indicated in Scheme I. This path is proposed to account for the observations that AcOH is generated slightly more rapidly than CMMS and that the presence of added HCl enhances this difference in rate (Table III). As indicated, the overall scheme is self-consistent, since HCl is generated in another step.[8] Furthermore, the bottom step in this scheme can account for the fact that CMMS eventually attains the same concentration as AcOH. Thus, the chloromethylsulfonium salt reacts more slowly than IN2 to form CMMS. Me_2SO is indicated as a base in this step, since the transient signal seems to disappear more rapidly at higher concentrations of Me_2SO (Figure 3). The effect of HCl on the overall rate of disappearance of reactants will be discussed below.

The assignment of the CH_3-protons of the chloromethyl-

Scheme I



sulfonium salt to the transient signal is based mainly on the fact that only one transient signal is observed with a chemical shift comparable to those for oxysulfonium salts. Thus, relative to tetramethylsilane, the transient chemical shift is 3.75 ppm in methylene chloride, and for the methyls of dimethyl-*tert*-butoxysulfonium salts they range from 3.43 to 3.78 ppm.[6] Although the SCH_3 proton resonance of IN1 is expected to lie in the same region, this structure is precluded because the corresponding acyl-CH_3 resonance expected for this structure is not observed. Furthermore, assignment of this structure to the transient is not consistent with the kinetic results discussed above, e.g., isotope effect and concentration dependence of some of the minor products. In addition, it is unlikely that the resonance assigned to Ac_2O could, in fact, be due to the acyl CH_3 of IN1. First, the ratio of intensities is not 2 to 1. Second, the Ac_2O signal remains long after the transient has disappeared. Third, the time period for this disappearance is similar to that observed when Ac_2O is mixed with Me_2SO. Thus, the chlorosulfonium salt seems more consistent with the experimental results than IN1 does. Furthermore, this type of salt has been suggested to be the intermediate isolated when sulfuryl chloride is allowed to react with an aryl methyl sulfide below 0 °C.[2b]

As mentioned above, the line width of the transient signal depends on the experimental conditions. Thus, it increases as the initial concentration of reactants is increased. The fact that the line width for each of the other signals remains unaffected by concentration changes indicates that the protons in the transient signal are undergoing an exchange process. The nature of this exchange process cannot be expressed conclusively. However, since the line width of the transient also increases as the concentration of HCl is increased, one possible explanation is that the methyl protons of the chlorosulfonium salt are exchanging with those of $(CH_3)_2S(OH)^+ Cl^-$ via a mechanism in which the OH group is replaced by Cl. The details of this mechanism must await the results of further investigation.

Since the presence of HCl alters the overall rate of reaction, it probably alters the mechanism in Scheme I to some extent. Thus, the initial increase in rate observed in the presence of small amounts of HCl could result from protonation of IN1 as well as trapping IN2. The retardation at higher concentrations of HCl may be due to a substantial reduction in the amount of unprotonated Me_2SO and, therefore, a reduction in the amount of IN1 since it is in equilibrium with the reactants.

Because of the low polarity of the solvents (as indicated by their dielectric constants), salts are expected to exist in the form of ion pairs or larger ion aggregates. For this reason, the sulfonium salts are indicated to be ion pairs in Scheme I. The polarity of the solvent also appears to affect the rate of reaction. Thus, methylene chloride, which has a larger dielectric constant than benzene (9.08 vs. 2.26) has a rate constant that is smaller by about a factor of 2 than the one for benzene. The proposed mechanism is consistent with this result, since the charge is destroyed when AcOH and CMMS are formed. However, a more extensive solvent study is needed to test this proposal. In addition, on the basis of the above discussion, it is clear that the reaction is not cleanly second order except at low concentration for which the minor products cannot be observed. However, even at the higher concentrations, the contribution made by the minor reaction paths is sufficently small to make a second-order fit possible. Finally, as also noted by other workers,[9] CMMS reacts with Me_2SO. Since this reaction is slower than the one involving Me_2SO and AcCl, it, therefore, was not studied.

Finally, because of the relatively low concentrations employed, no precautions were necessary. However, concentrated solutions of Me_2SO plus AcCl have been known to explode.[1a]

Acknowledgment. We are grateful to the National Research Council of Canada for support of this study.

Registry No.—Me_2SO, 67-68-5; AcCl, 75-36-5; AcOH, 64-19-7; CMMS, 23372-58-9; AMMS, 16437-69-7; Ac_2O, 108-24-7.

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(6) C. Johnson and J. Rigan, *J. Am. Chem. Soc.*, **91**, 5398 (1969).
(7) This ratio is calculated at a time in the reaction when AcCl and AcOH have equal concentrations using the equilibrium constant ($K = 2.2 \times 10^{-3}$) and assuming the approach to equilibrium is instantaneous, which is not the case. Equilibration takes approximately 5 min with comparable concentrations of AcCl and AcOH whereas the reaction between Me_2SO and AcCl is essentially over in about 3 min at these concentrations. In addition, this ratio is probably slightly overestimated, since HCl is also generated in the step that produces AMMS.
(8) The downfield shift of the Me_2SO signal during the reaction is consistent with the formation of HCl, since addition of HCl causes a downfield shift.
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Mechanism of Thermolysis of Diketene in the Gas Phase

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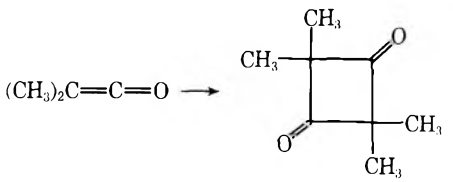
The mechanism of diketene thermolysis is investigated by isotopic double-labeling experiments and the thermolysis of cyclobutane-1,3-dione. The results of these experiments suggest that the thermolysis reaction is concerted. An activation energy of 50 kcal/mol was obtained for the thermolysis of diketene. This leads to an estimate of 31 kcal/mol as an activation energy for the dimerization of ketene in the gas phase. The heats of combustion (ΔH_c) and sublimation of cyclobutane-1,3-dione were measured and values of -450.7 ± 0.5 and 17.6 ± 0.5 kcal/mol were calculated. A comparison of $\Delta H_c^{25}(g)$ for diketene and cyclobutane-1,3-dione suggests that both compounds are thermodynamically accessible from dimerization of ketene in the gas phase.

The dimerization reaction of ketenes has been an area of considerable interest for over half a century. Initial attention was focused on the structure of ketene dimers[2,3] and more recent attention has been concerned with the mechanism of the reaction.[4,5] Orbital symmetry considerations of Woodward and Hoffman have stimulated the most recent interest in these (2 + 2) cycloaddition reactions.[6]

We became interested in the dimerization of ketene to diketene for a variety of reasons. First, despite the commercial importance of both ketene and diketene, very little concerning the mechanism of this reaction has been reported; the work of Rice and Greenberg appears to be the only mechanistic study reported which relates to this reaction.[4] In addition, regiospecific head-to-tail dimerization of ketene is anomalous in comparison to the cyclobutane-1,3-diones which are obtained in the dimerization reaction of other ketoketenes.[2] Finally we have recently reported some calculations using a semiempirical molecular orbital method to calculate potential energy surfaces for ketene dimerization.[7] The results of these calculations suggested the concerted ($_\pi 2_s + _\pi 2_s$) cycloaddition pathway to be preferred. The course of this reaction was governed by both electronic factors as well as by nuclear repulsion. In addition, a barrier of only 6 kcal (using configuration interaction) was calculated for the dimerization reaction. This report summarizes our efforts to obtain experimental verification of these calculations.

Rice and Greenberg found an activation energy of only 11 kcal for the rate of disappearance of ketene in acetone. The rough parallelism between the rate of reaction and the dielectric constant of the solvent has been interpreted by some workers as evidence of an ionic mechanism.[2a] Similar experimental results have been obtained for the dimerization of dimethylketene although the results in this case were interpreted to involve a cycloaddition reaction with unequal bond formation and partial charge separation.[5a] To avoid the ambiguities brought about by the solvent, we decided to examine the dimerization reaction in the gas phase. However, as described in the Experimental Section, the dimerization of ketene at pressures below 1 atm could not be accomplished.



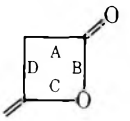
$\Delta H^{\ddagger} = 10.8$ kcal

$\Delta S = -42$ eu

(benzonitrile)

The thermolysis of diketene in a flow system at 500 °C has been reported to produce ketene quantitatively.[3a] Failing to achieve gas-phase dimerization of ketene, the thermolysis of diketene was investigated next. We were specifically interested in determining whether this thermolysis reaction was a homogeneous unimolecular process, and if so, in measuring the activation parameters for this process. To the extent that it is possible, we were also interested in determining whether this reaction is concerted as suggested by our calculations.

The thermolysis of diketene has recently been shown to be a homogeneous unimolecular process by demonstrating that the intermolecular secondary deuterium isotope effect is pressure dependent, decreasing with decreasing pressure. In addition, a kinetic isotope effect k_H/k_D of 1.04 (140 mm, 420 °C) was obtained, suggesting that carbon–carbon bond



breaking is a rate-determining factor in the thermolysis of diketene.[9] The sole product of the pyrolysis is ketene, and this suggests that bonds B or D are broken sequentially or concertedly. The rapid and reversible formation of diradical intermediates involving rate-determining bond cleavage at A, B, or C was effectively eliminated on the basis of the following experiment.

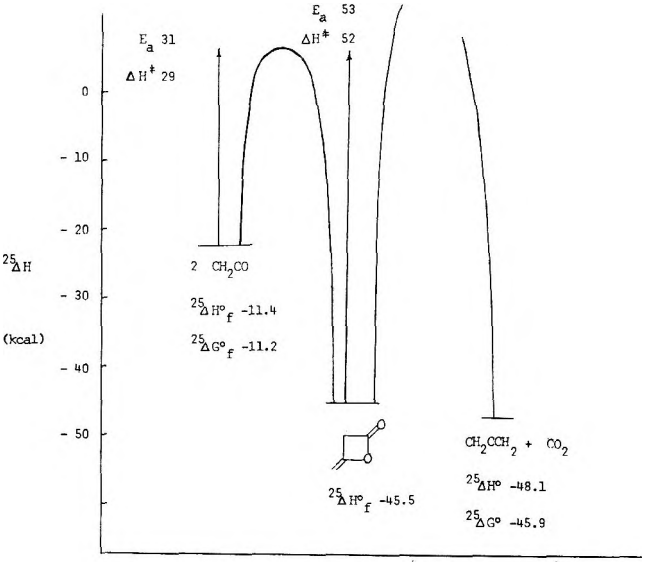


Figure 1. Enthalpy differences between diketene and possible thermolysis products.[20]

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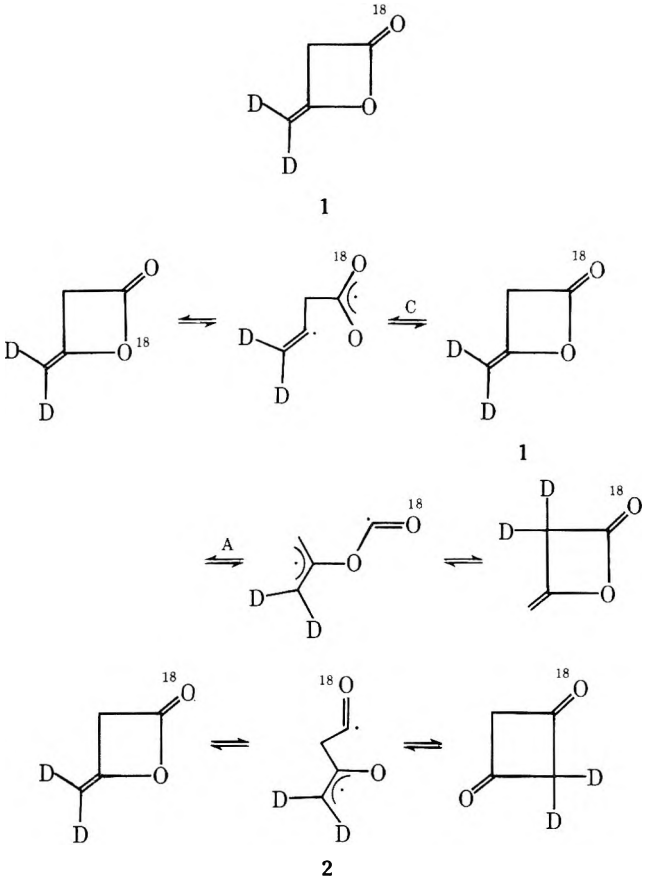
Table I. Heats of Combustion of Diketene and Cyclobutane-1,3-dione

Diketene[a]		Cyclobutane-1,3-dione[b]	
ΔH_c^{25}	−457.11	ΔH_c^{25}(s)	−450.7 ± 0.5
ΔH_v^{25}	10.25	ΔH_s^{25}	+17.6 ± 0.5
ΔH_c^{25}(g)	−467.36	ΔH_c^{25}(g)	−468.3 ± 1.0

[a] M. Mansson, Y. Nakasi, and S. Sunner, *Acta Chem. Scand.*, **22**, 171 (1968). [b] Cyclobutane-1,3-dione exists as the dione tautomer in the solid phase and in solvents of moderate to low polarity.[19] Similar behavior would be expected in the gas phase.

Diketene was prepared from a mixture of ^{18}O-labeled ketene and D_2 labeled ketene. Approximately equal amounts of ketene-^{18}O (26.6% ^{18}O) and ketene-d_2 (98.5%) were allowed to dimerize in a sealed tube. The diketene isolated was pyrolyzed at 380 °C in a nitrogen stream. Mass analysis of the product did not reveal any ketene doubly labeled with ^{18}O and deuterium, thus ruling out all of the scrambling processes summarized in the equations below, *both in the dimerization and subsequent thermolysis reactions.*



The labeling experiment mentioned above does not conclusively eliminate rapid cleavage of bond B as a possibility. However, it does require that a substantial barrier be present to prevent the isomerization to cyclobutane-1,3-dione. Evidence that cyclobutane-1,3-dione is thermodynamically accessable from diketene was obtained by determining the heat of combustion of cyclobutane-1,3-dione at 25 °C. The results are listed in Table I along with the known heats of combustion of diketene. The results within experimental error indicate similar ground-state stabilities.

Thermolysis of cyclobutane-1,3-dione in a flow system using a nitrogen carrier (140 mm) at 400 °C affords a 53% yield of ketene. No diketene could be detected. Thermolysis of diketene under similar conditions affords ketene in 83%, the remainder being starting material. Failure to observe isomerization of diketene and cyclobutane-1,3-dione in either direction leads to the conclusion that there is no common intermediate in the thermolysis of cyclobutane-1,3-dione and diketene. Thus either both reactions are concerted or one is concerted and the other occurs in a stepwise fashion through a diradical intermediate, **2**, which is not capable of surmounting the barrier to lead to isomerization. The simplest explanation is that both reactions are concerted.[17]

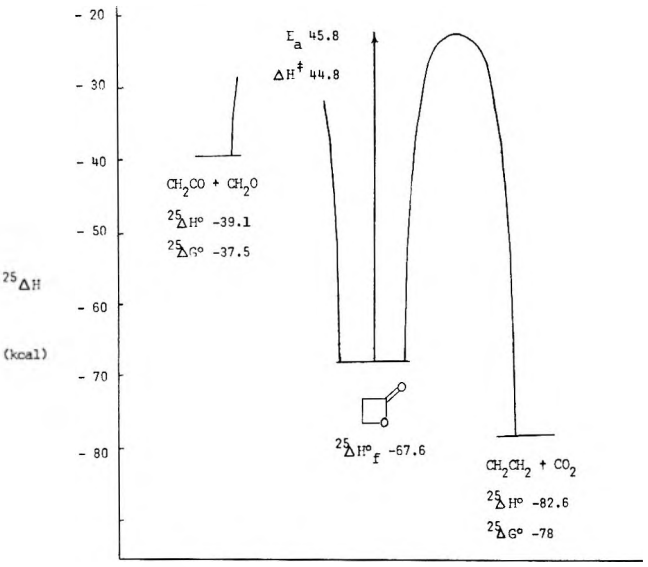


Figure 2. Enthalpy differences between propiolactone and possible thermolysis products.[20,24]

If it is assumed that the entropies of both isomers are comparable ($\Delta S°$), the similar ground-state stabilities ($\Delta G°$) and yields of ketene at 400 °C suggest that the barriers to thermolysis of both, $\Delta G^{\ddagger}$, must also be similar in magnitude. This leads to an interesting conclusion regarding the regioselectivity of the gas-phase dimerization of ketene (presumable at pressures above 1 atm). Both diketene and cyclobutane-1,3-dione should be accessible from direct dimerization of ketene, similar to what is observed in the low-temperature (liquid phase) dimerization of aldoketenes.[12]

The activation energy for thermolysis of diketene was obtained in a flow system by competitive co-thermolysis of acetic-d_6 anhydride and diketene at 294–417 °C using N_2 (42, 142 mm) as a carrier gas. The results are given in Table III. An activation energy of approximately 50 kcal was obtained. (For further discussion see Experimental Section.) Combining this with the heats of formation of ketene and diketene (Table I) leads to an estimate of the activation enthalpy for the dimerization reaction in the gas phase of approximately 30 kcal. This number is considerably larger than the 6-kcal barrier calculated for this reaction.[7]

It is immediately evident from examination of Figure 1 that the regiospecific thermolysis of diketene to ketene must be the result of kinetic control. Even at 350 °C, the formation of allene and carbon dioxide is thermodynamically preferred by 21 kcal/mol ($\Delta\Delta G°$). The thermolysis of β-propiolactone which cleaves thermally to carbon dioxide and ethylene provides an interesting comparison to the diketene thermolysis (Figure 2). The free-energy difference between the products resulting from thermodynamic control and kinetic control, $\Delta\Delta G°$, in β-propiolactone (40.5 kcal/mol) is larger than the similar $\Delta\Delta G°$ for diketene (23.5 kcal/mol) by 17 kcal at 25 °C. This additional difference in free energy is presumably the cause for the change in the orientation of cleavage. It would be interesting to determine whether this is also accompanied by a change in mechanism.

Table II. Calculation of the $^{18}O, d$ Label in Diketene

A. Distribution of Label in Reacting Ketenes[a]

Fraction of ketene (K)	[diketene-$^{16}O_2$/total diketene]$^{1/2}$	$[0.09]^{1/2}$	0.3
Fraction of ketene-^{18}O (K_{18})	[ketene-^{18}O/ketene-^{16}O] × K	[0.266/(1 − 0.266)][0.3]	0.109
Fraction of ketene-d_2 (K_2)	[1 − K − K_{18}]	[1 − 0.409]	0.509

B. Distribution of Label in Diketene[b]

			Calcd	Found
m/e 74	Diketene	$[K]^2$		0.09
m/e 76	Diketene-^{18}O	$2[K_{18}][K]$	0.065	0.41
	Diketene-d_2	$2[K_2][K]$	0.355	
m/e 78	Diketene-$^{18}O_2$	$[K_{18}]^2$	0.011	0.50
	Diketene-$^{18}O,d_2$	$2[K_{18}][K_2]$	0.129	
	Diketene-d_4	$[K_2]^2$	0.345	

[a] Based on the unlabeled diketene content and ^{18}O, D_2 content in ketene: ketene-^{18}O, ^{18}O content, 26.6%; ketene-d_2, deuterium content, 98%; mass spectrum of diketene-^{18}O, -d_2, m/e 74, 9.0; 76, 41.2; 78, 49.7. [b] Assuming a statistical distribution with no isotope effect.

Table III. Co-thermolysis of Acetic-d_6 Anhydride (AA) with Diketene (DK)[a]

Run	Temp, °C	Total mmol of reactants	Fraction reacted	Initial ratio of reactants DK^0/AA^0	mmol of ketenes isolated[b] (m/e 74/76)	Ketene/ ketene-d_2	k_{AA}/k_{DK}	K_{DK}[b]
1	760	0.431	1.0	2.78	0.750	5.56		
2	690	0.398	0.80	2.78	0.556	4.78	1.6	2.2
3	654	0.403	0.35	2.78	0.243	1.96	4.6	0.2
4	621	0.438	0.12	2.78	0.088	0.50	15.2	1.7×10^{-2}
5	597	0.449	0.05	2.78	0.039	0.28	22.7	4.0×10^{-3}
6	567	0.444	0.012	2.78	0.0097	0.23	24.9	8.6×10^{-4}
7	727	0.706	1.0	2.27	0.706	4.54		
8	664	0.358	0.72	2.27	0.437	3.75	1.54	2.5
9	652	0.336	0.51	2.27	0.296	2.88	3.01	0.92
10	618	0.361	0.20	2.27	0.122	0.750	9.05	7.71×10^{-2}
11	595	0.367	0.097	2.27	0.0602	0.321	17.9	1.41×10^{-2}
12	569	0.264	0.026	2.27	0.0117	0.206	23.8	3.04×10^{-3}

[a] Conditions used in thermolysis: (runs 1–6) carrier gas N_2 (42 ± 1 mm), flow (measured at the exhaust of pump) 0.27 ± 0.02 mL/s; (runs 7–12) carrier gas N_2 (142 ± 1 mm), flow 0.34 ± 0.02 mL/s. [b] Ketene analyzed as methyl acetate.

The thermolysis of diketene to the kinetically controlled product, ketene, in a concerted manner is a good indication that orbital topology does play an important factor in the reaction. Yet to be determined is whether the reaction is best described as a ($_\pi 2_a + _\pi 2_s$) or ($_\pi 2_s + _\pi 2_s$) cycloaddition.

Experimental Section

Thermolysis of Ketene and Diketene in a Static System. The experiments performed in a static system were performed in an untreated 3 L Pyrex bulb suspended in an air bath maintained at ±5 °C. The products were identified by comparison of their infrared spectra to authentic samples. During the course of these studies a carbonaceous material was deposited on the surface of the bulb. In addition a tarry liquid was also formed from which an undetermined amount of 4-acetoxy-6-methyl-2-pyrone could be isolated. Typically, several hundred millimeters of ketene were pyrolyzed at 250 °C for 24 h. The products were condensed in liquid nitrogen and analyzed. In addition to the unreacted ketene, acetic anhydride, and acetic acid which were transferred to the trap, a white crystalline material was deposited during evacuation along the cooler portions of the tube connecting the 3-L flask. This material was identified as 4-acetoxy-6-methyl-2-pyrone: mp 45–46 °C; λ_{max} (KBr) 5.55, 5.65, 6.0, 6.2, 6.3, and 8.3 μm; NMR ($CDCl_3$, Me_4Si) 2.28, 2.32 (6 H), 6.0, 6.05 ppm (1.96 H); m/e 168; calcd for $C_8H_8O_4$, 168.[10] The acetic acid, acetic anhydride are most likely the result of surface promoted processes leading to the carbonaceous deposit and release of water. The thermal homogeneous decomposition of ketene at higher temperatures is known to give mixtures of gases including carbon monoxide, ethylene, and methane.[8]

Preparation of 4-Acetoxy-6-methyl-2-pyrone. 4-Hydroxy-6-methyl-2-pyrone (3.32 g), acetic anhydride (4 mL), and a few drops of sulfuric acid were warmed to 75 °C for 1 h. Upon cooling, ether was added and the solution was washed with water. Evaporation of the ether afforded a solid (2.41 g) which was sublimed and then recrystallized from cyclohexane–ethyl acetate (2:1) (1.44 g), mp 45–6 °C, the infrared and NMR spectra were identical to that obtained above. There was no depression of the mp upon admixture.

Preparation of Ketene-^{18}O. Acetone-^{18}O was prepared by hydrolyzing 2-methoxypropene[13] (22.6 mmol) with $H_2{}^{18}O$ (22.6 mmol) and a crystal of p-toluenesulfonic acid (hydrate). After stirring for approximately 2 h the methanol was derivatized with phenyl isocyanate (2.74 g, 2.3 mmol). The mixture was allowed to stand overnight at room temperature. After cooling to −20 °C, the acetone was removed by bulb-to-bulb distillation: yield 17.6 mmol; 78.5%.

Ketene-^{18}O was prepared by the pyrolysis of acetone under conditions of low conversion by passing the acetone through a heated quartz tube at 500 °C using nitrogen gas (1 atm) as a carrier. After three passes, 5.04 mmol of ketene-^{18}O was obtained. Ketene-^{18}O (.59 mmol) was converted to methyl acetate and analyzed by mass spectrometry for the ^{18}O content. Analysis of the parents indicated that 26.6% of the ketene was labeled with ^{18}O.

Codimerization of Ketene-^{18}O with Ketene-d_2. Ketene-d_2 (~99.5% isotopic purity, prepared from thermolysis of acetic-d_6 anhydride (Aldrich Chem. Co.) in an evacuated hot tube (500 °C, 4.78 mmol)) and ketene-^{18}O (4.808 mmol) were combined and sealed in a glass tube. The tube was cooled to −78 °C and then allowed to warm slowly to 0 °C. The tube was opened, the contents were transferred, and the diketene was isolated by bulb-to-bulb distillation on a vacuum line. The diketene had the following analysis: m/e 74 (9.0), 76 (41.2), 78 (49.7). Since the ketene-^{18}O was known to be impure (methane and other impurities), the composition of the reacting ketenes was determined by using the isotopic distribution of both diketene and ketene-^{18}O (26.6% ketene-^{18}O). This in turn was then used to calculate the isotopic composition of the diketenes. This is shown in Table II. The calculated results are very close to the experimental values. Of all the isotopically labeled diketenes, only diketene-$^{18}O,d_2$,

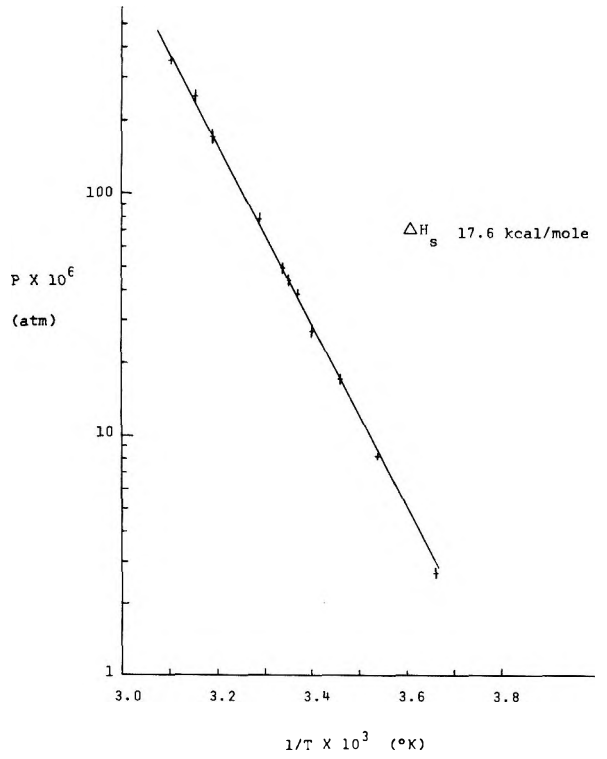
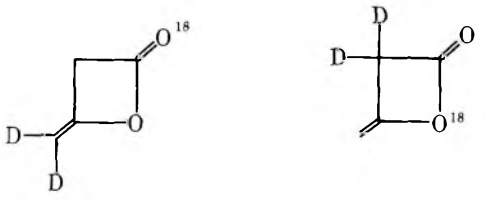


Figure 3. Vapor pressure–temperature relationship for cyclobutane-1,3-dione. Each entry determined in triplicate.

amounting to 12.9% of the total, is of interest. This material consists of a mixture of the following:



Thermolysis of Diketenes-$^{18}O,d_2$. The diketenes (0.44 mmol) were thermolyzed at 380 °C. The ketene and diketene were trapped and separated as previously described.[9] The ketene (0.632 mmol, 72%) was derivatized with methanol and analyzed. The following results were obtained: *m/e* 74 (28.89), 76 (71.02), 78 (0.08). Calcd for no exchange and ignoring isotope effects: *m/e* 74 (30), 76 (70). Calcd assuming complete scrambling, no isotope effects: *m/e* 74 (30), 76 (63.6), 78 (6.5).

As an upper limit, the amount of scrambing which can be accounted for by the experimental data is 1.2% (0.08/6.5). Mass analysis of the diketene at *m/e* 42, 44, 46 (ketene fragmet) of both starting material and residue from thermolysis (0.1 mmol) did not reveal any changes in the *m/e* 44/46 ratio. Thermolysis of diketene to 90% completion gave essentially the same results.

Heat of Combustion of Cyclobutane-1,3-dione. The heats of combustion were determined in a Parr Oxygen Bomb calorimeter. The energy equivalent of the calorimeter was determined by combustion of benzoic acid (AR grade). The reagents used were pelleted and fuse wire, 2.3 cal/cm, was purchased from Parr Instrument Co., Molene, Ill. Calculations were according to Manual 130 "Oxygen Bomb Calorimetry and Combustion Methods", Parr Instrument Co. The results were corrected for formation of nitric acid and for the heat of combustion of the fuse.

The heat of sublimation of cyclobutane-1,3-dione was determined by measuring vapor pressure as a function of temperature by a method previously described.[15] Concentrations of cyclobutane-1,3-dione were determined by ultraviolet spectroscopy (ethanol). The results of these measurements are given in Figure 3. The combined results of both the heats of combustion and sublimation are given in Table I. Errors reported are average deviations.

Measurement of the Activation Energy for Thermolysis of Diketene. The activation energy for thermolysis of diketene (DK) was determined by competition with the thermolysis of acetic-d_6 anhydride (AA) in flow system. The temperature dependence on the rate of thermolysis of acetic anhydride is given by $k = 10\ \exp(-32194/TR)\ s^{-1}$ over the temperature range 197–370 °C.[16] No correction for the kinetic isotope effect was included. In the calculation of the activation energy of diketene, it was necessary to extrapolate to 417 °C. The results of these experiments are given in Table III. The products, ketene (k) and ketene-d_2 (k_{d_2}), were derivatized with methanol and analyzed as methyl acetate. Although a temperature gradient of about 25 °C existed in the tube, the temperature at each point of the tube was maintained to ±2 °C. The rate constants for thermolysis of diketene were calculated from the following equation.

$$\frac{\ln [DK°/(DK° - (1/2)K)]}{\ln [AA°/(AA° - K_{d_2})]} = \frac{k_{DK}}{k_{AA}}$$

The initial concentrations of reactants were determined by analysis of the amount and composition of the ketenes obtained from complete thermolysis (runs 1 and 7).

Competitive thermolyses of acetic-d_6 anhydride with diketene were performed at two pressures, approximately 40 and 140 mm. A plot of ln *k* vs. y_I gave rise to two sets of data from which activation energies of 50.2 and 53 kcal/mol were calculated (correlation coefficient: 0.9924, 0.996, respectively). Differences in the intercepts are probably due to the fact that even at 40 mm, diketene is still in the falloff region. Although activation energies in the low-pressure region are known to decrease anywhere from 5 to 10 kcal/mol, the differences in this instance should probably be attributed to experimental error.[22,23]

Cyclobutane-1,3-dione. Cyclobutane-1,3-dione was prepared according to the procedure of Wasserman-Piper and Dehmlow.[19] We have found that in the preparation of 3-ethoxy-2-cyclobutenone, a more convenient manner of purifying this material is to molecularly distill the dark liquid at low temperatures. The cyclobutenone obtained on the cold finger (−10 °C) was obtained in approximately 50–70% yield; mp 25 °C (lit. 26–27.5 °C). Hydrolysis as reported gave cyclobutane-1,3-dione, mp 116–120 °C (lit. 119–120 °C).

Thermolysis of Cyclobutane-1,3-dione. Thermolysis experiments with cyclobutane-1,3-dione were performed in the same flow apparatus as the diketene thermolysis at 140 mm (N_2). The vapor pressure of cyclobutane-1,3-dione is quite low at room temperature (~20 μm). It is improbable that the thermolysis of cyclobutane-1,3-dione occurs by anything other than a first-order process. Consistent with this conclusion was the observation that the fractional conversion to ketene was not affected when the pot temperature was increased above room temperature (~35 °C) and the time required for transfer was significantly reduced. If the thermolysis of cyclobutane-1,3-dione was conducted in the absence of a carrier gas, considerably less ketene was obtained and significant amounts of decomposition on the surface of the quartz tube were observed. No unreacted starting material was recovered nor was any diketene detected in both the high- and low-pressure experiments. The effect of carrier gas on the decomposition of cyclobutane-1,3-dione suggests that the thermolysis reaction to give ketene is a homogeneous process. The yield of ketene may be considerably higher at these temperatures in the absence of the surface-promoted process. Characterization of the tarry residue or other products was not attempted. Characterization of the products was conducted by infrared spectroscopy in the gas phase.

Acknowledgments. We would like to thank Ted Windsor for technical assistance and Tom Goodwin and James Ketchum for performing some of the experiments. J.S.C. would also like to thank the University of Missouri-St. Louis for financial support and for a Summer Research Fellowship.

Registry No.—Cyclobutane-1,3-dione, 15506-53-3; propiolactone, 57-57-8; diketene, 674-82-8; 2-methyl-1-propen-1-one, 598-26-5; ketene, 463-51-4; 4-acetoxy-6-methyl-2-pyrone, 22073-80-9; 4-hydroxy-6-methyl-2-pyrone, 675-10-5.

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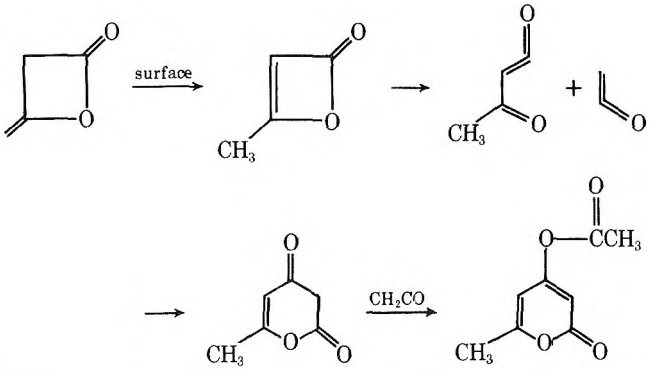
(10) We currently believe that gas-phase polymerization of ketene (including dimerization) will occur at ketene pressures in excess of 1 atm. 4-Acetoxy-6-methyl-2-pyrone is probably formed from low-level concentrations of diketene present. A possible mechanism for its formation is shown below. This mechanism is similar to the one postulated for the dimerization of diketene to dehydroacetic acid.



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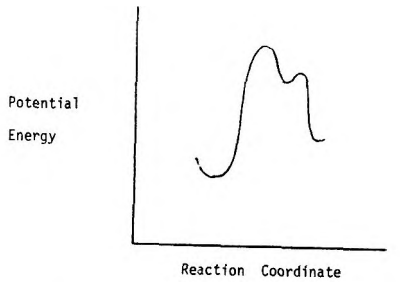
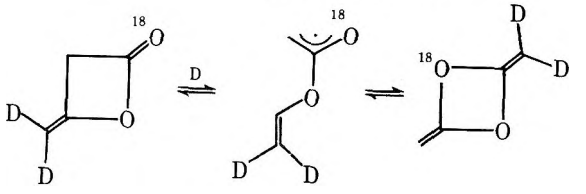
(17) We specifically ignored a potential energy surface such as shown below for the thermolysis of diketene. The small size of the molecule (ten atoms) decreases the likelihood that the system could sustain an intermediate in such a situation. The large internal energy necessary to overcome the initial barrier would most likely transform the intermediate directly to product.[18] Should the lifetime of intermediate be increased by collisional deactivation, scrambling of label would be possible by way of the following 1,3-dioxetane intermediate providing no significant barrier separates the diradical and the dioxetane. Our experimental results are also incapable of discriminating between the concerted process and a situation in which transition state and intermediate are essentially isoergic (as calculated for tetramethylene[25]) and lifetimes are short compared to bond rotations.





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Bridged Polycyclic Compounds. 86. Multiple Mechanisms in the Reactions of Some Bridged Alcohols with Triphenylphosphine and Carbon Tetrachloride[1]

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Reactions of several isomeric benzobicyclooctadienyl alcohols and dibenzobicyclononatrienyl alcohols with triphenylphosphine–carbon tetrachloride reagent demonstrate that these alcohol to chloride transformations are much more complex than originally proposed. Products from these and from deuterium-labeled alcohols show that direct displacements, Wagner–Meerwein rearrangement displacements, and allylic rearrangement displacements all occur. The reactions are rationalized as involving competitions between S_N2, S_N1, and S_Ni' or S_N2' processes.

Since the discovery[2] of the use of triarylphosphine dihalides in the ready conversion of alcohols to alkyl halides without rearrangement,[2,3b] and with clean inversion of configuration in the reaction of menthol to give neomenthyl halides, there has been considerable use of these reagents.[3] A mixture of triphenylphosphine and carbon tetrachloride was found[4] to cause transformations analogous to triphenylphosphine dichloride, under rather mild conditions. Although the initial papers[2] describing the use of the dichloride reported clean stereochemistry and thus the intervention of a direct displacement mechanism in the attack of chloride ion on the $ROPPh_3Cl$ intermediate,[2,3c] later work suggested alternative mechanistic possibilities. Thus, the lack of inversion (and loss of optical activity) in treatment[3e] of (+)-*exo*-norborneol with

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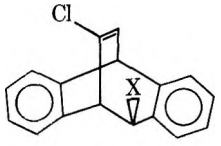
triphenylphosphine dibromide makes clear the possibility of intervention of carbenium ion processes in some cases. Similarly, while it has been found[5] that treatment of alcohols with triphenylphosphine–carbon tetrachloride generally leads to reaction with inversion, in certain cases[5] evidence for carbenium ion intermediates was again noted.

Snyder[5d] showed that the triphenylphosphine–carbon tetrachloride reagent could be utilized with allylic alcohols and that crotyl alcohol was converted cleanly (without allylic rearrangement) to crotyl chloride. α-Methylallyl alcohol did not lead to as clean a product, giving 89% α-methylallyl chloride (allylic retention) and 11% crotyl chloride (allylic inversion).

Our interest in the chemistry and photochemistry of organic halides[6] and our associated need to prepare isotopically labeled compounds of known structure and/or stereochemistry prompted us to investigate this reagent in a number of systems prone to give mixtures and/or rearrangements, in the hope that carbenium ion processes could be avoided. The results and our rationalization of these results are reported in this paper.

Complete reaction of the exo alcohol 1-OH with triphenylphosphine–carbon tetrachloride required 36 h at 65 °C and gave a product that, by ^{1}H NMR analysis, contained about 20% exo chloride 1-Cl, but was principally the endo chloride 2-Cl. Thus inversion of configuration was the principal stereochemical outcome. When the reaction was carried out in 50:50 (by volume) carbon tetrachloride–acetonitrile, the rate, as anticipated,[4c] increased markedly, and the reaction was complete in 2 h at room temperature. The reaction similarly gave mostly (ca. 80%) inverted chloride 2-Cl. When the endo alcohol (2-OH) was used, the product mixture comprised 75% exo chloride 1-Cl and 25% endo chloride 2-Cl in CCl_4–acetonitrile. In none of these cases was the Wagner–Meerwein product 3-Cl or the cyclopropylcarbinyl chloride 4-Cl observed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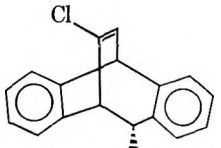
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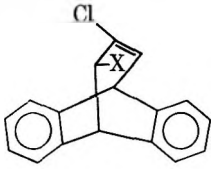
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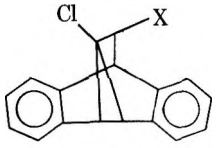
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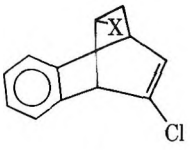
(these are thermodynamically more stable than 1-Cl and 2-Cl[7]).

When the allylic alcohol 3-OH, which is related by a Wagner–Meerwein shift to 1 and to 2, was treated with the reagent, the principal product (55–75%) was the allylic chloride 3-Cl, but substantial amounts of the rearranged isomer 2-Cl (and lesser amounts of 1-Cl) were found. It has been noted[7] that kinetically controlled capture of the cationic manifold produced from species related to 1, 2, 3 (and 4, as well) gives mixtures of the benzylic species 1 and 2. This is consistent with the results we now report, if we assume that the allylic product 3-Cl comes from some direct displacement process or processes, while the benzylic products are the result of some cationic-intermediate process (see below for further elaboration).

We have also studied the system represented by the isomers 5, 6, and 7. In this system,[8] carbenium ions produced from 5, 6, or 7 are captured predominantly as 6 species, thermodynamic control leads predominantly to 5 species, and mixing of this system with 8 and 9 species is not observed in cationic processes. When 5-OH was treated with the reagent in 50:50 carbon tetrachloride–acetonitrile at room temperature, we observed (^{1}H NMR) the alkoxychlorotriphenylphosphorane,[9] 5-OPPh$_3$Cl, that is, the intermediate with unrearranged carbon skeleton.[10] Warming to 70 °C gave clean conversion to 6-Cl, the result of anti bond migration and exo capture of chloride ion. When 6-OH was treated with triphenylphosphine in carbon tetrachloride at reflux, the reaction similarly gave only 6-Cl, no epimeric 7-Cl (or 5-Cl) being formed. With 7-OH at room temperature only 6-Cl was formed, as was the case when the reaction was carried out at 70 °C. Again no 5-Cl or 7-Cl was found.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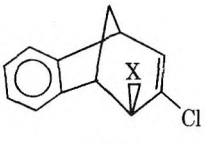
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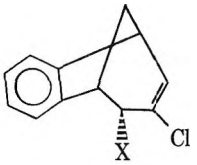
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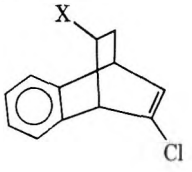
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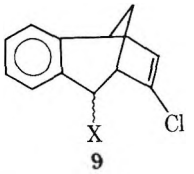
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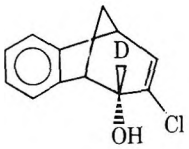
In order to develop our knowledge of these reactions further, and in the hope of preparing labeled compounds for our other work, we investigated the reactions of the deuterated alcohols 10 and 11. 10 was prepared by reaction of the corresponding ketone with lithium aluminum deuteride; the deuterium transfer was completely from the exo side; no exo alcohol was produced.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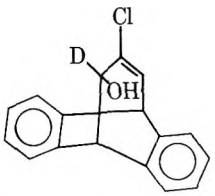
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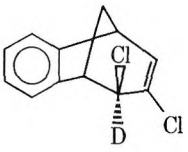
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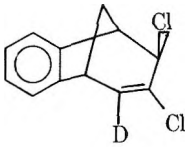
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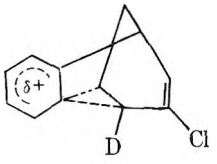
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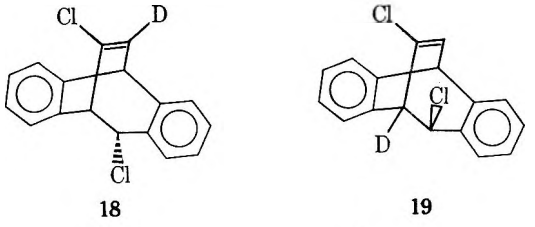
When 10 was treated with triphenylphosphine in carbon tetrachloride, as with the undeuterated alcohol 7-OH, only the exo chloride resulted. It was a mixture comprising about 80% of 12 and 20% of 13. The reaction thus does not exhibit either the clean inversion without allylic rearrangement anticipated for an S_N2 reaction or the relatively complete scrambling of deuterium anticipated for a free allylic cationic intermediate. The absence of endo chloride rules out any S_Ni' process.[12] We conclude therefore that the reaction involves a combination of S_N2 and S_N1 processes or perhaps includes some process involving a delocalized ion such as 14, to rationalize the preponderance of 12 over 13.

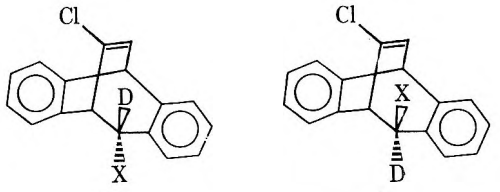
Use of 11 as substrate offers the advantage over 10 that carbenium ion reactions lead to Wagner–Meerwein rearrangement products, but has the drawback that the two faces

of the allylic cation are indistinguishable. When **11** was treated with triphenylphosphine in carbon tetrachloride at reflux, the product mixture was largely allylic chloride, with some replacement at the initial carbinol carbon atom, but principally with replacement by allylic rearrangement (i.e., about 3:1 of **16**:**15**). Little deuterium scrambling was seen in the benzylic chlorides, as well, where bond migration to the initial carbinol carbon atom to give **17** rather than to the other end of the allylic system to give **18** predominated by a large factor. Just as with **3**-OH, the endo chloride **17** was produced in greater amount than the exo chloride **19**.

15 **16** **17**

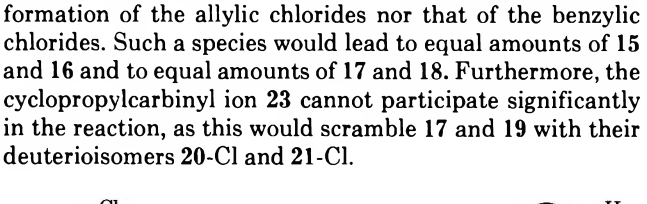


18 **19**



20 **21**

Lack of stereochemical information on the reactions of **11**, that is, whether the formations of **15** and **16** proceed with stereochemical retention or inversion, precludes precise definition of reaction mechanisms. Nevertheless, certain aspects are clear. First, a symmetrical free allylic ion **22** (or a set of ion pairs that mimic such a species) is involved in neither the formation of the allylic chlorides nor that of the benzylic chlorides. Such a species would lead to equal amounts of **15** and **16** and to equal amounts of **17** and **18**. Furthermore, the cyclopropylcarbinyl ion **23** cannot participate significantly in the reaction, as this would scramble **17** and **19** with their deuterioisomers **20**-Cl and **21**-Cl.

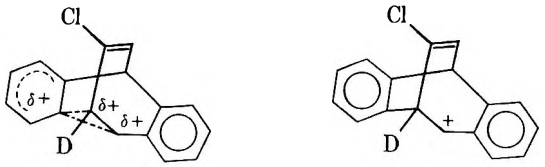


22 **23** **24**

When **20**-OH was treated with the reagent in acetonitrile, it was converted to a 1:3 mixture of **20**-Cl and **21**-Cl. Again the deuterium label was retained at C-4 (within experimental error, **17** and **19** were absent), so that ion **23** was not involved in these transformations either.

It would appear to us most conservative to assume that **15** is produced via an S_N2 reaction on the phosphorane from **11** (and that it probably has a configuration opposite to that shown) and that **16** results from an S_Ni' reaction (and that the configuration shown is correct). When the S_Ni' reaction, which has been noted earlier with allylic alcohols and thionyl chloride, was first discussed,[12] the question was raised about whether the reaction was concerted, with a six-membered transition state, or involved a carbocationic intermediate. We favor the former (**24**) in our example, since, as mentioned above, we assume that the cationic intermediate would lead almost exclusively to benzylic isomers. Clearly we cannot distinguish this mechanism from an S_N2' process[13] in which the phosphorus–chlorine bond is ionized prior to carbon–chlorine bond formation.[14]

We suggest ion **25** as the intermediate leading from the phosphorane of **11**, either as a real species or as the incipient carbocationic portion of the transition state leading to ion **26**. The formation of much more **17** than **19** indicates that **26** is the principal product-forming intermediate in the benzylic system. Again, it would be useful to have stereochemical information to corroborate the assumed migration of the anti bond in **11** in the transformations to **17** and **19**.



25 **26**

Experimental Section

^{1}H NMR spectra were taken with either a Varian Associates A-60A, T-60, EM-390, or HA-100 spectrometer. ^{2}D NMR spectra were obtained with a JEOL JNM-PS-100 spectrometer. HPLC separations were carried out on a Waters Associates Model 6000A pump with a Beckamn Model 25 ultraviolet spectrometer detector using two Waters Associates μ-porasil columns connected in series. The mobile phase was 0.25% tetrahydrofuran–hexane. The hexane was obtained from Burdick and Jackson Laboratories, Inc. Melting points were determined on a Thomas-Hoover Unimelt apparatus. Triphenylphosphine was obtained from Eastman Kodak Co. and used without further purification.

In the reactions described below, we were able to obtain reaction product ratios from ^{1}H NMR by using the benzo ring(s) protons as internal standards. Thus, we obtained product ratios by integrating a unique resonance for each product and comparing it to the integration for the benzo ring(s) protons.

Preparation of *exo*-4,6-Dichloro-2,3:8,9-dibenzo-2,6,8-bicyclo[3.2.2]nonatriene (1-Cl). A solution of 1-OH[7] (1.0 g, 3.7 mmol), in 30 mL of anhydrous ethyl ether, was cooled to 0 °C. Three milliliters of thionyl chloride was added and the stirred solution was slowly warmed to room temperature. After the solution had been stirred for 3 h, it was poured into 50 mL of cold water and extracted with three 30-mL portions of ethyl ether. The combined ether extracts were washed with saturated aqueous sodium bicarbonate and water and then dried ($MgSO_4$). Evaporation to dryness left a pale yellow oil (900 mg, 85%). ^{1}H NMR analysis of this oil indicated 53% **2** and 47% **1**. These two isomers were separated by low-pressure liquid chromatography (2.5 cm × 100 cm glass column packed with 0.032–0.063-mm silica gel supplied by ICN Pharmaceuticals. The mobile phase was hexane pumped at 9.0 mL/min). A fraction was cut between 1090 and 1280 mL of elution volume which was evaporated to dryness and crystallized from ethanol to produce 170 mg (16%) of white crystals (1-Cl): mp 131–132.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.10–7.65 (m, 8, aromatic), 6.96 (dd, 1, H-7, $J_{7,1}$ = 7.2 Hz, $J_{7,5}$ = 2 Hz), 5.33 (d, 1, H-4, $J_{4,5}$ = 4 Hz), 4.40 (d, 1, H-1, $J_{1,7}$ = 7.2 Hz), 4.27 (dd, 1, H-5, $J_{5,4}$ = 4 Hz, $J_{5,7}$ = 2 Hz). Anal. Calcd for $C_{17}H_{12}Cl_2$: C, 71.12; H, 4.18. Found: C, 71.02; H, 4.25.

Preparation of 3-Chloro-6,7-benzobicyclo[3.2.1]octa-3,6-dien-2-one. A solution of the exo alcohol 6-OH[16] (2.10 g, 10.2 mmol) in 40 mL of acetone was titrated with 2.67 N Jones reagent[17] (~3 mL) until a red tint remained. Excess Jones reagent was destroyed with isopropyl alcohol. The reaction mixture was then diluted with brine and extracted with three 30-mL portions of ethyl ether. The combined ether extracts were washed with saturated aqueous sodium bicarbonate and brine. The solution was then dried ($MgSO_4$), filtered, and evaporated to dryness. The ketone product (1.87 g of white solid, 90%) could be used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.0

(m, 5, aromatic and H-4), 3.8 (m, 1, H-1), 3.5 (m, 1, H-5), 2.5 (m, 2, H-8 syn + H-8 anti). Sublimation (85 °C, 1 Torr) afforded pure ketone: mp 102.5–104 °C. Anal. Calcd for $C_{12}H_9ClO$: C, 70.43; H, 4.43. Found: C, 70.46; H, 4.33.

Preparation of 3-Chloro-6,7-benzobicyclo[3.2.1]octa-3,6-dien-*exo*-2-ol Acetate (6-OAc). A solution of 6-Cl[16] (1.00 g, 4.44 mmol) in 20 mL of glacial acetic acid was placed in a round-bottom flask equipped with a reflux condenser and magnetic stirring bar. Silver acetate (1.5 g, 9.0 mmol) was added, and the solution was heated at reflux for 2 h. The silver chloride precipitate was filtered off, and the clear solution was diluted with 200 mL of water. The mixture was extracted with three 30-mL portions of ethyl ether. The combined ether extracts were washed with water, saturated aqueous sodium bicarbonate, and brine. The solution was dried ($MgSO_4$), filtered, and evaporated to dryness. The product, 6-OAc, could be used without further purification: yield, 1.1 g (99%); ^1H NMR ($CDCl_3$) δ 7.3 (m, 4, aromatic H), 6.55 (d, 1, H-4, $J_{4,5}$ = 7 Hz), 5.2 (d, 1, H-2, $J_{2,1}$ = 2 Hz), 3.4 (m, 2, H-1 and H-5), 2.2 (m, 2, H-8 syn and H-8 anti), 2.1 (s, 3, CH_3). Crystallization from hexane afforded pure product: mp 92–93 °C. Anal. Calcd for $C_{14}H_{13}ClO_2$: C, 67.61; H, 5.27. Found: C, 67.71; H, 5.25.

Preparation of 6-Chloro-7,8-benzobicyclo[2.2.2]octa-5,7-dien-*anti*-2-ol (5-OH). 6-OAc (1.1 g, 4.2 mmol) was dissolved in 16.5 mL of 0.1 M perchloric acid–acetic acid and placed in a round-bottom flask equipped with a reflux condenser and magnetic stirring bar. The deep red solution was heated at reflux for 1 h, followed by dilution with water and extraction with three 30-mL portions of ethyl ether. The ether extracts were combined and washed with water, aqueous sodium bicarbonate, brine, and then dried ($MgSO_4$). Evaporation to dryness left a pale yellow oil (0.9 g, 82%). ^1H NMR analysis indicated that the acetate mixture contained at least 70% 5-OAc. The mixture was then methanolyzed in 0.1 M sodium methoxide–methanol followed by separation using preparative TLC (silica gel–15% ethyl ether–hexane). The slowest band was collected. Alternatively, the mixture could be dried over P_2O_5 and recrystallized to purity from CCl_4. The ^1H NMR spectrum was consistent with that expected for 5-OH: ($CDCl_3$) δ 7.1 (m, 4, aromatic H), 6.55 (dd, 1, H-5, $J_{5,4}$ = 7 Hz, $J_{5,1}$ = 2 Hz), 4.1 (m, 2, H-1 and H-2), 3.85 (dt, 1, H-4, $J_{4,5}$ = 7 Hz, $J_{4,3syn}$ = 3 Hz, $J_{4,3anti}$ = 3 Hz), 2.0 (ddd, 1, H-3 syn, $J_{3anti,3syn}$ = 13.5 Hz, $J_{3syn,2}$ = 8 Hz, $J_{3syn,4}$ = 3 Hz), 1.4 (dt, 1, H-3 anti, $J_{3syn,3anti}$ = 13.5 Hz, $J_{3anti\,2}$ = 3 Hz, $J_{3anti,4}$ = 3 Hz). Spin–spin couplings for H-2 and H-1 were obtained from the methanesulfonate ester[8b] (5-OMs): δ 5.0 (dt, 1, H-2 anti, $J_{2,3anti}$ = 3 Hz, $J_{2,3syn}$ = 8 Hz, $J_{2,1}$ = 3 Hz), 4.35 (dd, 1, H-1, $J_{1,2}$ = 3 Hz, $J_{1,5}$ = 2 Hz). Recrystallization of 5-OH from carbon tetrachloride afforded small white needles: mp 130–131 °C. Anal. Calcd for $C_{12}H_{11}ClO$: C, 69.74; H, 5.36. Found: C, 69.55; H, 5.45. That the stereochemistry of the hydroxyl in 5-OH is anti to the benzene ring was demonstrated by the fact that acetolysis of 5-OMs gave only 6-OAc and acetolysis of 8-OMs gave only 9-OAc.[8b]

Preparation of 3-Chloro-6,7-benzobicyclo[3.2.1]octa-3,6-dien-*endo*-2-ol (7-OH) and the Corresponding Deuterium-Labeled Alcohol (10). A predried round-bottom flask equipped with a magnetic stirring bar, reflux condenser, and calcium chloride drying tube was charged with lithium aluminum hydride (or lithium aluminum deuteride) (0.22 g, 5.8 mmol) in 15 mL of anhydrous ethyl ether. The ketone 3-chloro-6,7-benzobicyclo[3.2.1]octa-3,6-dien-2-one (1.58 g, 7.72 mmol) dissolved in 25 mL of ether was slowly added by syringe. After the addition was complete (10 min), the reaction mixture was stirred for 2 h at room temperature. Excess lithium aluminum hydride was destroyed with a saturated aqueous solution of sodium potassium tartrate. The reaction mixture was then filtered and dried ($MgSO_4$). Evaporation to dryness yielded 1.54 g (96%) of white crystals whose ^1H NMR spectrum was consistent with that expected for 7-OH: ($CDCl_3$) δ 7.2 (m, 4, aromatic H), 6.4 (dd, 1, H-4, $J_{4,5}$ = 7 Hz, $J_{4,2}$ = 1 Hz), 4.4 (dd, 1, H-2, $J_{2,1}$ = 5 Hz, $J_{2,4}$ = 1 Hz), 3.5 (m, 2, H-1 and H-5), 2.3 (m, 2, H-8 syn and H-8 anti), 1.8 (s, 1, hydroxyl). The stereochemistry at C-2 was determined to be *endo*-OH by comparison of $J_{2,1}$ to the analogous benzobicyclo[3.2.1]octadiene derivatives.[8a] Very pure 7-OH was obtained by recrystallization from carbon tetrachloride: mp 104–105 °C. Anal. Calcd for $C_{12}H_{11}ClO$: C, 69.74; H, 5.36. Found: C, 69.75; H, 5.25.

Treatment of 3-Chloro-6,7-benzobicyclo[3.2.1]octa-3,6-dien-*exo*-2-ol (6-OH) with Triphenylphosphine–Carbon Tetrachloride. The exo alcohol 6-OH (43.2 mg, 0.209 mmol), prepared using Goldschmidt's procedure,[16] was dissolved in 0.5 mL of carbon tetrachloride and placed in a 5-mm NMR tube. Triphenylphosphine (78 mg, 0.300 mmol) was added and the tube was sealed and left to stand at room temperature for 24 h. A ^1H NMR spectrum indicated only the presence of starting material. The solution was heated at reflux for 3 h to give a mixture whose ^1H NMR spectrum indicated a composition of 70% 6-Cl and 20% starting material. The remaining product(s) could not be identified; however, neither 5-Cl nor 7-Cl was detected.

Treatment of 3-Chloro-6,7-benzobicyclo[3.2.1]octa-3,6-dien-*endo*-2-ol (7-OH) with Triphenylphosphine–Carbon Tetrachloride at Room Temperature. 7-OH (83.2 mg, 0.486 mmol) was dissolved in 1.5 mL of carbon tetrachloride and placed in a 5-mm NMR tube. Triphenylphosphine (131 mg, 0.500 mmol) was added; the tube was sealed and allowed to stand at room temperature for 5 days. At that time, a ^1H NMR spectrum indicated the presence of 20% 7-Cl with the remaining 80% being 7-OH.

Treatment of 3-Chloro-6,7-benzobicyclo[3.2.1]octa-3,6-dien-*endo*-2-ol (7-OH) with Triphenylphosphine–Carbon Tetrachloride at 70 °C. 7-OH (24.8 mg, 0.120 mmol) was dissolved in 0.25 mL of carbon tetrachloride and placed in a 5-mm NMR tube. Triphenylphosphine (49.4 mg, 0.188 mmol) was added; the tube was sealed and heated for 25.5 h at 70 °C. The contents were eluted through a short silica gel column with hexane. Evaporation of solvent left 18.4 mg (68%) of colorless oil which crystallized upon standing. The ^1H NMR spectrum was consistent with that reported[16] for 6-Cl.

Treatment of 3-Chloro-*exo*-2-deuterio-6,7-benzobicyclo-[3.2.1]octa-3,6-dien-*endo*-2-ol (10) with Triphenylphosphine–Carbon Tetrachloride. The endo alcohol (10) (32.2 mg, 0.155 mmol) was dissolved in 0.3 mL of carbon tetrachloride and placed in a 5-mm NMR tube. Triphenylphosphine (64.1 mg, 0.245 mmol) was added; the tube was sealed and heated to 70 °C for 25 h. The resulting yellow oil was eluted through a short silica gel column with hexane. Evaporation of the solvent left 29 mg (80%) of colorless oil. The ^1H NMR spectrum was consistent with that of a mixture of 80% 12 and 20% 13.

Treatment of 6-Chloro-7,8-benzobicyclo[2.2.2]octa-5,7-dien-*anti*-2-ol (5-OH) with Triphenylphosphine–Carbon Tetrachloride–Acetonitrile. 5-OH (100 mg, 0.48 mmol) was dissolved in carbon tetrachloride–acetonitrile (1:1 v/v) and placed in a 5-mm NMR tube. Triphenylphosphine (120 mg, 0.46 mmol) was added and the tube was sealed. After 1 h at room temperature, analysis by NMR indicated that some starting material still remained. Additional triphenylphosphine was added (30.0 mg, 0.114 mmol) and the reaction mixture was allowed to stand at room temperature for an additional 1.75 h. A TLC (silica gel–hexane) of the reaction mixture demonstrated that neither 6-Cl nor starting material was present. A ^1H NMR spectrum of the product indicated a new ethylenic proton (H-5) whose absorption resonance was about 0.4 ppm downfield from that of H-5 in 5-OH. The carbinol proton (H-2) resonance had also shifted about 1 ppm downfield from its location in 5-OH. The ^1H NMR and TLC evidence leads us to believe that the product of the reaction is the alkoxychlorotriphenylphosphorane (5-OPPh_3Cl). The reaction mixture was then heated to 70 °C for 1 h. The ^1H NMR spectrum then obtained showed that the phosphorane had been completely converted to the exo chloride (6-Cl).

Treatment of 3-Chloro-6,7:8,9-dibenzobicyclo[3.2.2]nona-2,6,8-trien-4-ol (3-OH) with Triphenylphosphine–Carbon Tetrachloride. 3-OH[7] (48 mg, 0.18 mmol) was dissolved in 0.33 mL of carbon tetrachloride and placed in a 5-mm NMR tube. Triphenylphosphine (71 mg, 0.27 mmol) was added and the tube was sealed. After 19 h of heating at 45–50 °C, the following ratio of products was observed (^1H NMR): 75% 3-Cl, 20% 2-Cl, and 5% 1-Cl.

Treatment of 3-Chloro-4-deuterio-6,7:8,9-dibenzobicyclo-[3.2.2]nona-2,6,8-trien-4-ol (11) with Triphenylphosphine–Carbon Tetrachloride. 11[7] (51 mg, 0.19 mmol) was dissolved in 0.5 mL of carbon tetrachloride and placed in a 5-mm NMR tube. Triphenylphosphine (65 mg, 0.25 mmol) was added and the tube was heated at 65 °C for 17 h. The contents of the tube were eluted with hexane through a short silica gel column. Evaporation of solvent left 41 mg (80%) of colorless oil. HPLC analysis of the resulting oil indicated the following ratio: 68% 3-Cl-d_1, 27% 2-Cl-d_1, and 5% 1-Cl-d_1. ^1H NMR analysis of the allylic chloride (3-Cl-d_1) indicated that the ratio of 16:15 was about 3:1, while ^2H NMR analysis of 2-Cl-d_1 indicated about 93% 17 and about 7% 18. 18 was measured by the peak intensity 0.3 ppm upfield from deuteriochloroform and 17 by a peak 3.2 ppm upfield from deuteriochloroform.

Treatment of 6-Chloro-2,3:8,9-dibenzobicyclo[3.2.2]nona-2,6,8-trien-*exo*-4-ol (1-OH) with Triphenylphosphine–Carbon Tetrachloride–Acetonitrile. 1-OH[7] (1.4 g, 5.2 mmol) was dissolved in 16 mL of carbon tetrachloride–acetonitrile (1:1 v/v) and placed in a round-bottom flask equipped with a magnetic stirring bar. Triphenylphosphine (1.4 g, 5.3 mmol) was added and the mixture was stirred at room temperature for 3 h.

The reaction mixture was eluted through a silica gel column with

hexane. A ^1H NMR spectrum of the resulting pale yellow oil (1.75 g) indicated the presence of **2**-Cl and 1-Cl in a ratio of 4:1.

Treatment of 6-Chloro-2,3:8,9-dibenzobicyclo[3.2.2]nona-2,6,8-trien-exo-4-ol (1-OH) with Triphenylphosphine–Carbon Tetrachloride. 1-OH[7] (1.08 g, 4.00 mmol) was dissolved in 7 mL of carbon tetrachloride and 1.06 g (4.0 mmol) of triphenylphosphine was added. The solution was heated at 65–70 °C for 36 h. The reaction mixture was cooled and filtered. The yellow solution was chromatographed over a silica gel column and eluted with hexane. The solution was evaporated to dryness and crystallized from 95% ethanol, producing 0.80 g (70%) of a white crystalline solid (**2**-Cl): mp 113 °C; ^1H NMR ($CDCl_3$) δ 7.13–7.67 (m, 8, aromatic), 6.96 (dd, 1, H-7, $J_{7,1}$ = 7.3 Hz, $J_{7,5}$ = 2 Hz), 5.60 (d, 1, H-4, $J_{4,5}$ = 4 Hz), 4.38 (d, 1, H-1, $J_{1,7}$ = 7.3 Hz), 4.13 (dd, 1, H-5, $J_{5,4}$ = 4 Hz, $J_{5,7}$ = 2 Hz). Anal. Calcd for $C_{17}H_{12}Cl_2$: C, 71.12; H, 4.18. Found: C, 71.06; H, 4.18.

In a similar experiment, the crude reaction mixture was analyzed (^1H NMR) and found to contain 80% **2**-Cl and 20% 1-Cl.

Treatment of 6-Chloro-4-deuterio-2,3:8,9-dibenzobicyclo[3.2.2]nona-2,6,8-trien-*endo*-4-ol with Triphenylphosphine–Carbon Tetrachloride–Acetonitrile. The alcohol[7] (**20**-OH) (500 mg, 1.9 mmol) was dissolved in 8 mL of carbon tetrachloride–acetonitrile (1:1 v/v) and triphenylphosphine (655 mg, 2.50 mmol) was added. The solution was stirred for 2 h at room temperature. A preparative scale TLC was run (silica gel–10% tetrahydrofuran–hexane) on the product to remove triphenylphosphine oxide. Evaporation of solvent gave 410 mg (82%) of a yellow oil which by ^1H NMR integration of resonances at δ 4.13 and δ 4.27 contained 25% **20**-Cl and 75% **21**-Cl. The oil was crystallized from carbon tetrachloride to produce 250 mg (50%) of a white solid (**21**): mp 130–132 °C; ^1H NMR ($CDCl_3$) δ 7.10–7.65 (m, 8, aromatic), 6.96 (dd, 1, H-7, $J_{7,1}$ = 7.2 Hz, $J_{7,5}$ = 2 Hz), 4.40 (d, 1, H-1, $J_{1,7}$ = 7.2 Hz), 4.27 (d, 1, H-5, $J_{5,1}$ = 2 Hz).

Mixture melting point and spectral comparison with the nondeuterated chloride (1-Cl) proved this compound to be **21**-Cl.

Acknowledgments. This work was supported in part by Grant CA-13199, awarded by the National Cancer Institute, Department of Health, Education and Welfare, and in part by National Science Foundation Grant CHE74-24348.

Registry No.—1-OH, 20887-64-3; **1**-Cl, 64600-09-5; **2**-Cl, 64626-00-2; **3**-OH, 20851-76-7; **5**-OH, 64600-10-8; **5**-OAc, 64600-11-9; **6**-OH, 54647-01-7; **6**-Cl, 54647-00-6; **6**-OAc, 64600-12-0; **7**-OH, 64626-01-3; **10**, 64600-13-1; **11**, 64600-14-2; **20**-OH, 64600-15-3; **21**-Cl, 64600-16-4; thionyl chloride, 7719-09-7; 3-chloro-6,7-benzobicyclo[3.2.1]octa-3,6-dien-2-one, 57020-95-8; silver acetate, 563-63-3; carbon tetrachloride, 56-23-5; triphenylphosphine, 603-35-0.

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(9) Such compounds have been noted earlier.[3b,5c,e]
(10) It is of considerable interest that Aneja and co-workers[5e] report that treatment of cholesterol with the reagent at 20 °C leads to large amounts of a phosphorane which they believe is that of 3,5-cyclo-6β-cholestanol. It is known,[11] of course, that derivatives of the latter alcohol are greatly unstable thermodynamically with respect to those of cholesterol. If this result is correct, and if the phosphorus derivative is similar to other derivatives of the alcohol, some mechanism for the formation of the alkoxycholorotriphenylphosphorane other than one involving simple replacement of chlorine on phosphorus by oxygen must be involved. Put another way, it must be necessary to assume that carbon–oxygen cleavage in the alcohol *precedes* the formation of the alkoxyphosphorane. We are at a loss to suggest how this could be true.
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(14) Whether the pentavalent phosphorus compounds are best considered as pentacoordinated phosphoranes or as phosphonium chlorides seems still to be in question although recent papers favor the latter.[4c,15]
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Prostanoid Endoperoxide Model Compounds: Preparation of 1,2-Dioxolanes from Cyclopropanes[1]

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A synthesis of 1,2-dioxolanes from cyclopropanes, which potentially could be adapted to prepare prostanoid endoperoxide model compounds, is reported. Cyclopropanes with 1-aryl, 1,1-diaryl, and 1-alkyl-1-aryl substituents, readily prepared by 1,1-dichlorocyclopropanation of the corresponding olefins with chloroform and sodium hydroxide under tetraalkylammonium chloride phase-transfer catalysis and subsequent sodium metal/*tert*-butyl alcohol in THF reduction, were hydroperoxybrominated with *N*-bromosuccinimide or 1,3-dibromo-5,5-dimethylhydantoin. The labile γ-hydroperoxy bromides were subsequently cyclized into their respective 1,2-dioxolanes with silver oxide. The substitution pattern of the original olefin in this sequence dictates the substitution pattern of the resulting 1,2-dioxolane.

Prostaglandin endoperoxides (PEP) serve as biosynthetic precursors to the physiologically potent prostaglandins PGF and PGE,[4] thromboxane A_2,[5] and prostacyclin.[6] So far these biologically important intermediates have been accessible through natural sources, but isolation and purification have been tedious and limiting in view of the labile nature of the endoperoxides and their scarce abundance.[7] In fact, until recently even the basic endoperoxide skeleton, i.e., the 2,3-dioxobicyclo[2.2.1]heptane ring system, was unknown. We prepared[8] this novel bicyclic peroxide by in situ, selective

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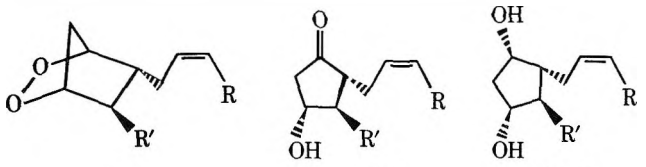
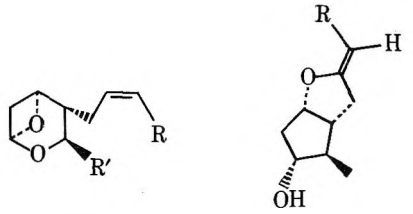
diimide reduction of cyclopentadiene endoperoxide (eq 1, path a), Salomon and Salomon[9] by peroxide bond transfer from bis(trialkylstannyl) peroxide to the ditriflate of 1,3-dihydroxycyclopentane (eq 1, path b), and Porter and Gilmore[10]



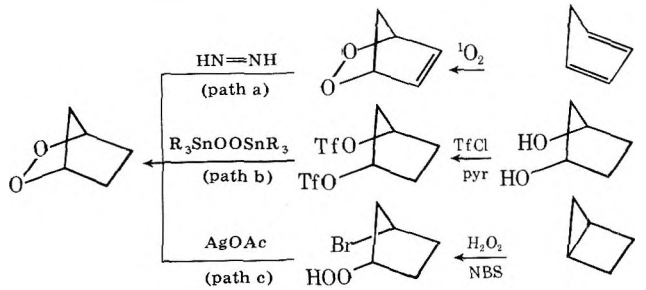
PEP PGE PGF



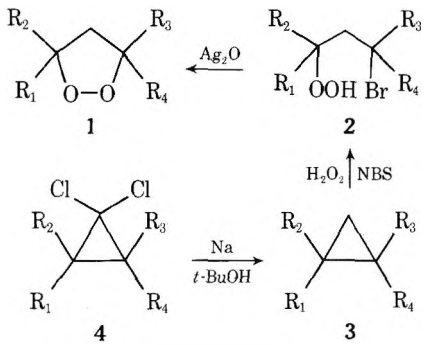
thromboxane A_2 prostacyclin

by bicyclization of 3-bromocyclopentyl hydroperoxide with silver acetate (eq 1, path c).

We also reported on the latter synthetic route (eq 1, path c, with silver oxide instead of silver acetate) earlier;[11] however, we found the hydroperoxybromination reaction of bicyclo[2.1.0]pentane and the subsequent bicyclization with silver oxide erratic, affording the impure and labile endoperoxide product in low yield. In view of our interest in prostanoid



endoperoxide model compounds,[12] we decided, therefore, to investigate in detail the hydroperoxybromination of cyclopropanes **3** and the cyclization of the γ-hydroperoxy bromides



2, to assess whether cyclopropanes **3** could serve as efficient and convenient synthons for the preparation of the simpler 1,2-dioxolanes **1**. The synthetic strategy is outlined in eq 2. Herewith we report our results on this sequence.

Experimental Section

Melting points, taken on a Thomas-Hoover melting point apparatus, and boiling points are not corrected. Refractive indices were measured on a Bausch and Lomb refractometer, supplied with a Haake temperature regulator. Infrared spectra were taken on a Perkin-Elmer Model 237 Infracord and ^1H-NMR spectra on a Hitachi Perkin-Elmer R-24B spectrometer. Elemental analysis were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Reagents and solvents were purchased from standard commercial sources and when necessary purified to match literature physical data. The olefin starting materials were either purchased or prepared according to literature procedures and purified to match reported physical and spectral data.

1,2-Dioxolanes 1 were prepared and purified according to the general method outlined below:

In a 100 mL, one-necked, round-bottomed flask, provided with magnetic spinbar, was placed ca. 20 mmol of freshly prepared and purified γ-hydroperoxy bromide **2** contained in 50 mL CCl_4 (A.R.) and cooled to 0 °C by means of an ice bath. The reaction flask was protected from light by wrapping with aluminum foil and while the solution was being magnetically stirred and cooled with an ice bath, ca. 40 mmol of freshly precipitated and thoroughly water-washed silver oxide was added all at once and the reaction progress of the heterogeneous mixture was monitored by following the hydroperoxy band in the 3500–3200-cm^{-1} region of the infrared. After completion of the reaction (usually 1–7 h), the silver bromide was removed by filtration and the solvent was rotoevaporated at 0–5 °C (10 mm) and the crude product purified by column chromatography on Silica Gel (ca. 1:100 ratio of substrate to adsorbant) at −20 °C, eluting with hexane and/or bulb-to-bulb distillation at the minimum possible bath temperature. When feasible as for 1,2-dioxolanes **1a** and **1c**, rigorous purification was achieved through fractional recrystallization from hexane and sublimation. The results are summarized in Table I.

γ-Hydroperoxy bromides 2 were prepared and purified according to the general method outlined below:

A stoppered 50-mL Erlenmeyer flask, provided with magnetic spinbar, was charged with 10 mmol of cyclopropane **3** in 20 mL of anhydrous ether and cooled to 0 °C by means of an ice bath. The flask was protected from light by wrapping with aluminum foil and while the solution was being stirred 4 mL of 98% H_2O_2 (CAUTION!) was added by means of a CHENG-tube.[13] To this cooled and stirred mixture was added by means of a spatula in portions of 10 mmol of brominating agent, either *N*-bromosuccinimide (NBS) or 1,3-dibromo-5,5-dimethylhydantoin (DDH), waiting for disappearance of the yellow bromide color between additions. After complete addition (2–5 days), intermittantly storing the reaction flask in the refrigerator (0–5 °C) overnight to avoid detrimental warm-up, the reaction mixture was washed with cold water (3 × 25 mL), with cold saturated $NaHCO_3$ (1 × 15 mL), with cold saturated $(NH_4)_2SO_4$ (1 × 15 mL), and finally again with cold water (2 × 20 mL), always placing crushed ice into the separatory funnel to prevent warm-up. The ether layer was dried over anhydrous $MgSO_4$ (60 min at 0–5 °C), the solvent was rotoevaporated (0–5 °C (10–15 mm)), and the crude product was immediately chromatographed on methanol-deactivated silica gel (ca. 1:100 ratio of substrate to adsorbant) at −10 °C, eluting with hexane–ether (19:1) and collecting fractions on the onset of a positive KI test by monitoring the eluant periodically. Relatively pure fractions (better than 80% by iodometry) were combined and rechromatographed affording material of better than 90% (by iodometry). Attempts to purify the material further by fractional low-temperature recrystallization, or column chromatography on silica gel or alumina, or DABCO precipitation led to decomposition. On storing neat in the freezer the hydroperoxides deteriorated by turning brown within a few days, but stored as CCl_4 solutions they could be preserved for longer periods. The results are summarized in Table II.

Cyclopropanes 3a, 3b, and 3d were prepared according to the general procedure (method A) outlined below:

A 1000-mL, three-necked, round-bottomed flask, provided with a reflux condenser, and efficient mechanical stirrer, was charged with 80 mmol of metallic sodium, ca. 500 mmol of *tert*-butyl alcohol, and 200 mL of THF. While stirring, 60 mmol of dichlorocyclopropane **4** was added in portions and the mixture was vigorously refluxed and high-speed stirred for ca. 60 h. To destroy the large excess of sodium metal, small portions (2 mL) of water were added while stirring and cooling the reaction vessel by means of an ice bath. The reaction mixture was extracted with hexane (3 × 100 ml), the combined extracts were washed with water (1 × 100 mL) and dried over anhydrous $MgSO_4$, the solvent was rotoevaporated (ca. 30 °C (ca. 10 mm)), and the residue was purified by fractional distillation at reduced pressure. The results are given in Table III.

Cyclopropanes 3c and 3e were isolated as by-products in the hydroperoxybromination of cyclopropanes **3b,d** by column chromatography on silica gel at 0 °C of the crude reaction mixture, collecting hexane-eluted fractions until appearance of a positive KI test for peroxide. The combined hexane eluants were rotoevaporated (ca. 30 °C (20 mm)) and the product was purified by recrystallization (**3c**) or fractional distillation (**3e**). An analytical sample of **3c** was prepared by preparative GC, using a 6 ft × ¼ in. stainless steel column packed

Table I. Yields and Physical and Spectral Properties of 1,2-Dioxolanes 1[a]

	Registry no.	R_1	R_2	R_3	R_4	Crude yield, %	bp, °C (mm)	NMR (CCl_4, Me_4Si) Type	δ, ppm	No. of H	Multiplicity (J, Hz)	IR (CCl_4) ν_{max},[b] cm^{-1}
1a	64884-60-2	Ph	Ph	H	H	93	mp 85–86[c]	$R_1 + R_2$	6.8–7.3	10	m	3085 (m), 3065 (s), 3025 (s), 2995 (m), 2965 (m), 2877 (s), 1592 (w), 1487 (s), 1444 (s), 1025 (m), 1003 (m)
								$R_3 + R_4$	4.05	2	t (6.7)	
								CH_2	3.08	2	t (6.7)	
1b	64884-61-3	Ph	Me	H	H	94	66–68 (0.2)[c]	R_1	7.0–7.4	5	m	3080 (m), 3055 (m), 3025 (m), 2978 (vs), 2925 (s), 2875 (s), 1598 (w), 1480 (s), 1445 (vs), 1368 (s), 1280 (s, broad)
								$R_3 + R_4$	3.8–4.2	2	m	
								CH_2	2.4–2.9	2	m	
								R_2	1.54	3	s	
1c	64884-62-4	pBrPh	Me	H	H	91	mp 63.5–64[c]	R_1	7.39; 7.26	4	AB (9)	3085 (w), 3025, 2980 (s), 2935 (s), 2870 (s), 1590 (m), 1482 (vs), 1448 (s), 1278 (s, broad)
								$R_3 + R_4$	3.9–4.2	2	m	
								CH_2	2.5–2.9	2	m	
								R_2	1.54	3	s	
1d	64884-63-5	Ph	H	H	H	72	50–55 (10^{-3})[d]	R_1	7.20	5	s	3060 (s), 3030 (s), 2990 (s), 2955 (s), 2910 (s), 2875 (vs), 1600 (m), 1485 (s), 1450 (vs), 1360 (m), 1325 (m), 1310 (m), 1280 (m)
								R_2	5.04; 5.16	1	AB (6.0)	
								$R_3 + R_4$	4.15	2	t (7.0)	
								CH_2	2.2–3.2	2	m	
1e	64884-64-6	pBrPh	H	H	H	86	*d*	R_1	7.04; 7.32	4	AB(9.9)	3080 (w), 3060 (w), 3025 (m), 2990 (s), 2955 (s), 2930 (s), 2875 (vs), 1485 (s), 1400 (s), 1068 (s)
								R_2	5.07; 4.98	1	AB(6.0)	
								$R_3 + R_4$	4.04	2	t (6.6)	
								CH_2	3.1–2.3	2	m	

[a] No parent ions could be observed on mass spectral analysis. [b] Relative intensities are given as very strong (vs), strong (s), medium (m), and weak (w). [c] Satisfactory elemental analyses. [d] Ca. 90% pure (by NMR) after low temperature silica gel chromatography; resisted all attempts of further purification by fractional distillation, low temperature crystallization, or gas chromatography.

Table II. Yields and Spectral Properties of γ-Hydroperoxy Bromides 2

	Registry no.	R_1	R_2	R_3	R_4	Brominating agent[a]	Yield, %	Iodide[b] titer, %	NMR (CCl_4, Me_4Si) Type	δ, ppm	No. of H	Multiplicity (J, Hz)	IR (CCl_4)[c] ν_{max}, cm^{-1} OOH	C–O
2a	64884-65-7	Ph	Ph	H	H	NBS	60	95	$R_1 + R_2$ + OOH	7.02–7.48	11	m	3500–3700 (m)	1070 (m)
									$R_3 + R_4$ + CH_2	2.7–3.5	4	m		
2b	64884-66-8	Ph	Me	H	H	DDH	50	91	R_1	7.07	5	s (broad)	3590–3200 (m)	1080 (s)
									OOH	3.95	1	s (broad)		
									$R_3 + R_4$	3.18	2	t (6.6)		
									CH_2	2.37	2	t (6.6)		
									R_2	1.50	3	s		
2c	64884-67-9	pBrPh	Me	H	H	DDH	65	92	R_1	7.00; 7.25	4	AB (9.0)	3570–3200 (m)	1078 (s)
									$R_3 + R_4$	3.16	2	t (10)		
									CH_2	2.31	2	t (10)		
									R_2	1.50	3	s		
2d	64884-68-0	Ph	H	H	H	NBS	50	96	OOH	7.53	1	s (broad)		
									R_1	7.00	5	s (broad)	3550–3300 (m)	1020 (m)
									R_2	5.02; 4.80	1	AB (5.7)		
									$R_3 + R_4$	3.0–3.2	2	m		
									CH_2	1.7–2.4	2	m		
2e	64884-69-1	pBrPh	H	H	H	NBS	85	92	OOH	8.13	1	s (broad)	3530–3130 (s)	1065 (s)
									R_1	7.33; 7.02	4	AB (10.8)		
									R_2	4.95; 4.85	1	AB (6.0)		
									$R_3 + R_4$	3.0–3.6	2	m		
									CH_2	1.8–2.6	2	m		

[a] *N*-Bromosuccinimide (NBS); 1,3-dibromo-5,5-dimethylhydantoin (DDH). [b] After silica gel chromatography at −10 °C; resisted all attempts of further purification by column chromatography or low-temperature recrystallization. [c] Relative intensities are given as strong (s), medium (m), and weak (w).

with 10% Carbowax 20M on Chromosorb W. The results are included in Table III.

1,1-Dichlorocyclopropanes 4 were prepared according to the general procedure outlined below:

A 250-mL, three-necked, round-bottomed flask, equipped with a reflux condenser and efficient mechanical stirrer, was charged with 75 mmol of olefin, 78 mmol of chloroform (A.R.), and 2.0 mmol of methyltri-*n*-caprylammonium chloride in 4.1 g of chloroform. While

Table III. Yields and Physical and Spectral Properties of Cyclopropanes 3

	Registry no.	R_1	R_2	R_3	R_4	Method[b]	Yield, %	Obsd bp, °C (mm), n_D [°C]	Reported bp, °C (mm), n_D [°C]	NMR (CCl_4, Me_4Si) Type	δ, ppm	No. of H	Multiplicity (J in Hz)
3a	3282-18-6	Ph	Ph	H	H	A	80	108–109 (1.3), 1.5850 [25]	110–111 (1.3), 1.5847 [25][c]	$R_1 + R_2$	7.08	10	s (broad)
										$R_3 + R_4 + CH_2$	1.24	4	s (broad)
3b	2214-14-4	Ph	Me	H	H	A	84	60 (13), 1.5156 [20]	66 (11), 1.5159 [20][d]	R_1	7.18	5	s (broad)
										R_2	1.39	3	s
										$R_3 + R_4 + CH_2$	0.80; 0.69	4	AB (1.8)
3c	40780-08-3	pBrPh	Me	H	H	B	87	93–94 (13.5), 1.5596 [20]	104–105 (18),[e] 1.5610 [20][f]	R_1	7.25; 6.97	4	AB (7.8)
										R_2	1.38	3	s
										$R_3 + R_4 + CH_2$	0.78; 0.70	4	AB (1.2)
3d	873-49-4	Ph	H	H	H	A	40	71.5 (22), 1.5306 [25]	69 (22), 1.5309 [25][c]	R_1	6.6–7.0	5	m
										R_2	1.5–2.0	1	m
										$R_3 + R_4 + CH_2$	0.5–1.3	4	m
3e	1124-14-7	pBrPh	H	H	H	B	68	92–93 (5.1), 1.5766 [20]	101–102 (11), 1.5773 [20][g]	R_1	7.24; 6.83	4	AB (8.4)
										R_2	1.6–2.1	1	m
										$R_3 + R_4 + CH_2$	0.5–1.1	4	m

[a] Cyclopropane skeletal deformation at ν_{max} 1020 cm^{-1} (strong). [b] Sodium reduction of 1,1-dichlorocyclopropane (method A); side product of hydroperoxybromination. [c] Reference 14a. [d] Reference 14b. [e] Reference 14c. [f] Reference 14d. [g] Reference 14e.

Table IV. Yields and Physical and Spectral Properties of 1,1-Dichlorocyclopropanes 4

	Registry no.	R_1	R_2	R_3	R_4	Yield (%)	Obsd bp, °C (mm), n_D [°C]	Reported bp, °C (mm), n_D [°C]	NMR (CCl_4, Me_4Si)[d] Type	δ, ppm	No. of H	Multiplicity (J, Hz)
4a	3141-42-2	Ph	Ph	H	H	80	mp 111–112 °C	*a*	$R_1 + R_2$	6.9–7.3	10	m
									$R_3 + R_4$	2.11	2	s
4b	3591-42-2	Ph	Me	H	H	79	92–93 (7), 1.5404 [25]	68–69 (1.3), 1.5400 [25][b]	R_1	7.06	5	s (broad)
									R_2	1.60	3	s
									R_3	1.76	1	d (6.6)
									R_4	1.47	1	d (6.6)
4d	2415-80-7	Ph	H	H	H	51	100 (10), 1.5514 [20]	103 (10), 1.5514 [20][c]	R_1	7.01	5	s (broad)
									R_2	2.75	1	t (18.6)
									$R_3 + R_4$	1.85; 1.68	2	AB (3.0)

[a] Satisfactory elemental analysis; MS (70 eV) *m/e* (rel intensity) 263 (30), 265 (18), 230 (22), 228 (14), 193 (100). [b] Reference 14f. [c] Reference 14c. [d] Cyclopropane skeletal deformation at ν_{max} 1040–1080 cm^{-1} (strong).

stirring vigorously, 40 mL of a solution of 50% aqueous NaOH was added and the two-phase mixture was stirred for 4–6 h at 50–55 °C; the exothermic reaction mixture was cooled with a water bath. The reaction mixture was extracted with ether (3 × 50 mL), the combined ether extracts were washed with water (3 × 50 mL) and dried over anhydrous $MgSO_4$, and the solvent was rotoevaporated (ca. 30 °C (ca. 10 mm)). The crude product was purified by recrystallization or fractional distillation at reduced pressure. An analytical sample of **4a** was prepared by repetitive, alternating recrystallization from hexane and sublimation (78 °C (0.15 mm)). The results are summarized in Table IV.

Discussion

The cyclopropanes **3a,b,d** required in this work were conveniently prepared in good yields by dichlorocyclopropanation (Table IV) of the corresponding olefins with chloroform and NaOH, using methyltri-*n*-caprylammonium chloride as phase transfer catalyst,[15] followed by sodium metal/*tert*-butyl alcohol dechlorination[16] in THF (Table III), as illustrated in eq 2. The *p*-bromophenylcyclopropanes **3c,e** (Table III) were isolated as by-products in the hydroperoxybromination of the corresponding cyclopropanes **3b,d.**

The last fact already brings out the problematic nature of the hydroperoxybromination of cyclopropanes **3.** While olefins hydroperoxybrominate swiftly even at −20 °C,[17] ring opening of cyclopropanes is slow at 0–10 °C even for activated cyclopropanes, requiring long reaction times (20–150 h). Higher temperatures cannot be tolerated since the labile γ-hydroperoxy bromides **2** decompose. Thus, at least one aryl substituent was essential for reasonable reactivity since monoalkylated and 1,2-dialkylated cyclopropanes were inert, while 1,1-dialkylcyclopropanes reacted too sluggishly to be useful.

Best results were obtained with 1,1-diphenylcyclopropane (**3a**), cf. Table II. The hydroperoxybromination of this substrate proceeded moderately fast (ca. 20 h) at 0 °C, thus suppressing the competing electrophilic aromatic bromination.[18] The latter process is favored at elevated temperatures; however, we found it to be quite unpredictable. Even rigorously purified reagents, substrates, and solvent and conducting the brominations in the dark gave variable amounts of aromatic bromination vs. ring opening from run to run. Careful moni-

toring of the reaction revealed that in the early stages only hydroperoxy bromides **2** were formed, provided the temperature was rigorously controlled at 0–5 °C and the brominating agent never allowed to accumulate by too fast addition. Only the stoichiometrically required amount of the brominating agent could be tolerated. Furthermore, 1,3-dibromo-5,5-dimethylhydantoin (DDH), a more powerful brominating agent, was more problematic than NBS. Molecular bromine was also used, but the liberated HBr would catalyze the decomposition of the hydroperoxybromination product **2**. Aromatic bromination did not take place when the hydrogen peroxide was left out or substituted by methanol.

The purification of the unstable γ-hydroperoxy bromides **2** presented formidable problems. They decomposed on silica gel TLC plates or on attempted precipitation as DABCO complexes.[17] Efforts to crystallize them failed, which is not surprising in view of their unsymmetrical nature. The only viable purification method, affording material of >90% purity (by iodometry), was by column chromatography on methanol-deactivated silica gel[19] at −10 °C, eluting with hexane–ether (19:1), cf. Table II. All operations, even solvent removal, had to be conducted at sub-ambient temperatures since even the chromatographically purified substances deteriorate on standing in the freezer, losing their peroxide titer within a few days. Consequently, immediately after purification the γ-hydroperoxides were cyclized.

The cyclization worked well if freshly precipitated silver oxide was used and the substrate **2** was employed immediately after chromatography. However, purification again presented problems. At room temperature these materials decomposed on attempted silica gel chromatography. Working at −20 °C and on deactivated silica gel reasonably pure (ca. 90%) 1,2-dioxolanes could be obtained which were further purified by recrystallization and sublimation or by bulb-to-bulb distillation at reduced pressure (Table I). The pure materials deteriorate on standing within a few months. This should be contrasted with the 1,2-dioxolanes with tertiary α-carbons at the peroxide linkage, which are indefinitely stable.[12a] The reason for this is, of course, the propensity of 1,2-dioxolanes with primary or secondary α-carbons to isomerize readily, as demonstrated for the prostaglandin endoperoxides.[4]

In conclusion, the synthetic sequence developed here for 1,2-dioxolanes, modelled after Kopecky's synthesis of 1,2-dioxetanes,[20] works well for 1,1-diaryl- and 1-alkyl-1-arylcyclopropanes but is already problematic for 1-arylcyclopropanes and ineffective for 1,1-dialkyl- and 1-alkylcyclopropanes. The reactivity of the bicyclo[2.1.0]pentane toward hydroperoxybromination (eq 1) is enhanced due to the additional ring strain. A definite advantage is the fact that the substitution pattern of the starting olefin dictates the substitution pattern of the final 1,2-dioxolane.

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Registry No.—H_2O_2, 7722-84-1; NBS, 128-08-5; DDH, 77-48-5; chloroform, 67-66-3; 1,7-diphenylethene, 530-48-3; 1-methyl-1-phenylethene, 98-83-9; 1-phenylethene, 100-42-5.

References and Notes

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(2) NIH Career Development Awardee (1975–80).
(3) (a) Undergraduate Participant in the Support for University Biomedical Education (SUBE) program, funded by NIH. (b) Graduate Research Fellow in the SUBE program.
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Synthesis of α-Hydroperoxy Esters by Singlet Oxygenation of Ketene Acetals[1]

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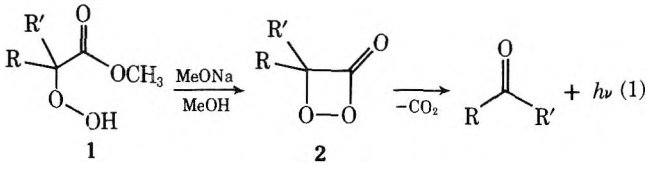
tert-Butyl-(**4a**) and 1-adamantylketene methyl trimethylsilyl acetals (**4b**) quantitatively singlet-oxygenate under photosensitization to their respective methyl trimethylsilyl peroxyacetates **3a** and **3b**. Desilylation with methanol affords the corresponding α-hydroperoxy esters **1a** and **1b** in high yield. The dimethylketene methyl trimethylsilyl acetal (**4c**) suffers competitive ene reaction on photooxygenation, but under controlled conditions good yields of the corresponding α-silylperoxy ester **3c** can be obtained. Similarly, the diphenylketene acetal **4d** leads also to the expected α-silylperoxy ester **3d**, but some (2 + 4) cycloaddition takes place concurrently. In both cases the corresponding α-hydroperoxy esters **1c** and **1d** were isolated and purified after methanolysis.

α-Hydroperoxy esters **1** have been shown to undergo base-catalyzed decomposition with enhanced chemiluminescence in the presence of fluorescers presumably energized by the "high-energy" α-peroxylactones **2** (eq 1)[3]. In view of



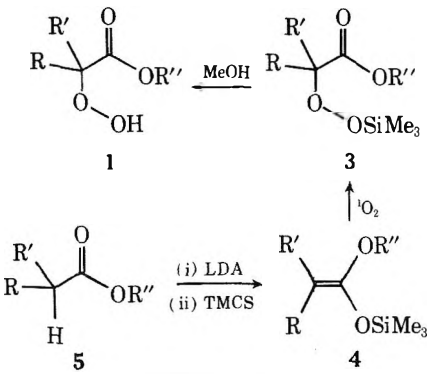
1 **2**

our interest in developing efficient and convenient preparative methods for α-peroxylactones **2**,[4] we considered exploiting the sequence in eq 1 as a potential route to α-peroxylactones. Of course, α-hydroperoxy esters **1** with active leaving groups would be required which would permit running the base-catalyzed cyclization under sufficiently mild conditions, e.g., subambient temperature, nonprotic media, etc., to isolate the labile α-peroxylactones.

Present methods of preparation of α-hydroperoxy esters **1** either involve direct base-catalyzed oxygenation of carboxylic esters or esterification of α-hydroperoxy acids with diazoalkanes.[5] Both methods are of limited value for our purpose since with esters containing activated leaving groups, the intermediary α-peroxy anion, formed on α-oxygenation of the ester enolate, would cyclize in situ to the α-peroxylactones. Their isolation from this complex reaction mixture would be expected to be difficult. In the esterification of the α-hydroperoxy acids with diazoalkanes or other mild esterification agents, the α-hydroperoxy acids are labile compounds which are not very readily available.[5b,6] We required, therefore, a general and convenient method for the preparation of α-hydroperoxy esters **1**.

We reported previously[4] that ketene bis(trimethylsilyl) acetals singlet-oxygenate with silatropic rearrangement to the corresponding trimethylsilyl α-trimethylsilylperoxy esters in high yield. Desilylation with methanol at subambient temperatures releases the free α-hydroperoxy acid quantitatively. In principle, it should be possible to adapt this synthetic sequence for the preparation of α-hydroperoxy esters **1** from their corresponding esters **5** via their ketene alkyl trimethylsilyl acetals **4** (eq 2). In fact the alkyl α-trimethylsilylperoxy esters **3** in their own right are attractive precursors to α-peroxylactones since the corresponding α-peroxy anion should be readily accessible by fluoride ion-catalyzed desilylation in neutral, nonprotic media.[7] We now report on the feasibility of this synthetic strategy, constituting a convenient preparation of methyl α-hydroperoxy esters **1** and methyl α-trimethylsilylperoxy esters **3**. The results are collected in Tables I–III.

The ketene methyl trimethylsilyl acetals **4a–d** were prepared from their corresponding methyl esters by α-lithiation with lithium diisopropylamide (LDA), followed by silylation with excess chlorotrimethylsilane.[8] As Table I shows, the yields are high, except for **4c** which due to its great volatility was lost in part during solvent (THF) removal.



a, R = *t*-Bu; R′ = H; R″ = Me
b, R = 1-Ad; R′ = H; R″ = Me
c, R = Me; R′ = Me; R″ = Me
d, R = Ph; R′ = Ph; R″ = Me

As expected,[4b] the singlet oxygenation of ketene acetal **4a** (R = *t*-Bu, R′ = H, R″ = Me) worked quantitatively, giving on fractional distillation at reduced pressure the α-silylperoxy ester **3a** in 93% yield and 99.9 ± 0.5% purity by iodometry. It was characterized on the basis of its spectral data (Table II) and correct elemental analysis. Furthermore, on desilylation with methanol the expected methyl α-hydroperoxy ester **1a** was obtained essentially quantitatively (Table III), identical with an authentic sample prepared by methylation of the corresponding α-hydroperoxy acid with diazomethane.

The singlet oxygenation of the 1-adamantyl derivative **4b** also proceeded well (Table II), but in view of the low volatility of the α-silylperoxy ester **3b**, on attempted purification by fractional distillation at reduced pressure it decomposed. However, desilylation with methanol and subsequent fractional recrystallization from CH_2Cl_2/pentane (1:4) gave the analytically pure α-hydroperoxy ester **1b** in 69%, correct elemental analysis, and the expected spectral data (Table III).

In the case of the dimethylketene acetal **4c** the competing ene reaction with singlet oxygen[9] presented difficulties. Employing a variety of solvents such as CCl_4, $CFCl_3$, $CDCl_3$, CH_2Cl_2, CD_3CN, C_6D_6, and CS_2, a temperature range from −78 to +10 °C, and the sensitizers tetraphenylporphyrin (TPP) and Rose Bengal, optimal yields (by NMR monitoring) of 80% silatropic singlet oxygenation were achieved with CH_2Cl_2 at −5 °C and TPP as sensitizer (Table II). The remaining 20% was mainly peroxymethacrylic acid (**6**) and unidentified decomposition products, formed by ene singlet oxygenation and hydrolytic desilylation by adventitious water

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Table I. Yields and Physical and Spectral Data of Ketene Methyl Trimethylsilyl Acetals 4

	Registry no.	$R_1R_2CC(OMe)OSiMe_3$ (4) R^1	R^2	Yield, %	bp, °C (mm),[a] $n^{25}D$	IR(CCl_4)[b] $\nu_{C=O}$, cm^{-1}	NMR (60 MHz) δ (CCl_4, Me_4Si) $OSiMe_3$	OMe	R^1	R^2
4a	40195-22-0	*t*-Bu	H	86	79–81 (31), 1.4094	1660	0.30 (9 H, s)	3.55 (3 H, s)	3.70 (1 H, s)	1.15 (9 H, s)
4b	64771-60-4	1-Ad	H	84	88–92 (0.1), 1.4842	1660	0.30 (9 H, s)	3.50 (3 H, s)	3.40 (1 H, s)	1.5–2.1 (15 H, m)
4c	31469-15-5	Me	Me	62[c]	54 (46), 1.4146	1700	0.30 (9 H, s)	3.55 (3 H, s)	1.60 (3 H, s)	1.70 (3 H, s)
4d	31469-19-0	Ph	Ph	92	117–119 (0.15), 1.5541	1630	0.20 (9 H, s)	3.65 (3 H, s)	7.3 (10 H, m)	

[a] Reference 8. [b] Ketene acetal double bond is of medium intensity. [c] Low yield due to volatility loss.

Table II. Yields and Physical and Spectral Data of Methyl α-Trimethylsilyl Peroxyacetates 3

	Registry no.	$R_1R_2C(OOSiMe_3)COOMe$ R^1	R^2	Yield, %	bp, °C (mm)	Peroxide titer, %	IR(CCl_4) $\nu_{C=O}$, cm^{-1},	NMR (60 MHz) δ (CCl_4, Me_4Si) OSiMe	OMe	R^1	R^2
3a	64771-61-5	*t*-Bu	H	93[a]	65 (6)	99.9	1760, 1740	0.25 (9 H, s)	3.75 (3 H, s)	1.05 (9 H, s)	4.1 (1 H, s)
3b	64771-62-6	1-Ad	H	80[b]	*e*	95	1760, 1730	0.25 (9 H, s)	3.75 (3 H, s)	1.6–2.3 15 H, m)	3.95 (1 H, s)
3c	64771-63-7	Me	Me	80[c]	*e*		1745	0.15 (9 H, s)	3.65 (3 H, s)	1.35 (6 H, s)	
3d	64771-64-8	Ph	Ph	70[d]	*e*		1745	0.20 (9 H, s)	3.4 (3 H, s)	7.0–7.6 (5 H, m)	

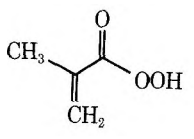
[a] Correct elemental analysis. [b] For conditions of singlet oxygenation consult General Procedure. [c] By NMR; remainder 20% are ene products and unidentified decomposition products; for this optimal yield the photooxygenation was performed in CH_2Cl_2 at −5 °C and TPP as sensitizer. [d] By NMR; remainder 30% are (2 + 4) cycloadducts; for this optimal yield the photooxygenation was performed in CCl_4 at +5 °C and TPP as sensitizer. [e] On attempted purification by fractional distillation product decomposed.

Table III. Yields and Physical and Spectral Data of Methyl Hydroperoxyacetates 1

	Registry no.	$R_1R_2C(OOH)COOMe$ R^1	R^2	Yield, %	bp, °C (mm)	Peroxide titer, %	IR (CCl_4), cm^{-1} ν_{OOH}	$\nu_{C=O}$	NMR (60 MHz) δ (CCl_4, Me_4Si) OOH	OMe	R^1	R^2
1a	64771-65-9	*t*-Bu	H	76	59–60 (2.5)[a]	99	3500	1740	6.65 (1 H, s)	3.7 (3 H, s)	4.1 (1 H, s)	0.95 (9 H, s)
1b	64771-66-0	1-Ad	H	69	mp 95–6 °C[a]	100	3550–3480	1740	8.75 (1 H, s)	3.7 (1 H, s)	3.95 (1 H, s)	1.5–2.1 (15 H, m)
1c	64771-67-1	Me	Me	80	44–5 (15)[b]	95	3100–3600	1740	4.8 (1 H, s)	3.75 (3 H, s)	1.45 (6 H, s)	
1d	57272-44-3	Ph	Ph	72	mp 64–5 °C[b]	99	3200–3600	1730	9.6 (1 H, s)	3.75 (3 H, s)	7.15 (10 H, s)	

[a] Correct elemental analysis. [b] Authentic samples prepared by CH_2N_2 methylation of the corresponding α-hydroperoxy acids (O. Cueto, unpublished results).

and identified by its IR and NMR spectra. Attempted separation of the singlet oxygenated product mixture by fractional distillation at reduced pressure led to vigorous decomposition. Consequently, the product mixture was desilylated with methanol and the α-hydroperoxy ester **1c** was isolated and purified by fractional distillation at reduced pressure (Table III). It was identical with an authentic sample prepared by methylation of the corresponding α-hydroperoxy acid with diazomethane.



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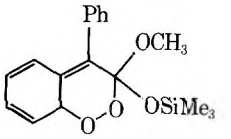

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Also the singlet oxygenation of the diphenylketene **4d** turned out to be problematic in view of the competing (2 + 4) cycloaddition, amply documented for aryl enol ethers.[10] The IR as well as the NMR revealed that the (2 + 4) cycloadduct **7** had formed. An optimal yield (70%) of silatropic singlet oxygenation of **4d** was obtained using carbon tetrachloride at +5 °C and TPP as sensitizer (Table II). Attempted isolation and purification by fractional distillation at reduced pressure led to decomposition. Thus, the singlet oxygenated product mixture was desilylated with methanol and the analytically pure α-hydroperoxy ester **1d** was isolated and purified by fractional recrystallization in 72% yield (Table III). It was

identical with an authentic sample prepared by methylation of the corresponding α-hydroperoxy acid with diazomethane.

Our results show that a variety of α-hydroperoxy esters **1** can be prepared in good to excellent yields via the synthetic sequence outlined in eq 2. We are extending this method to α-hydroperoxy esters with activated leaving groups as synthons for the labile α-peroxylactones **2**.

Experimental Section

Melting points and boiling points are uncorrected. NMR spectra were taken on a Hitachi Perkin-Elmer R-24B instrument and IR spectra on a Perkin-Elmer Infracord 237B. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Reagents, solvents, and starting materials were purchased from standard sources and purified according to literature procedures. Esters **5** were prepared following published methods and purified rigorously to match literature physical constants and spectral data.[11]

Ketene Trimethylsilyl Methyl Acetals 4 (General Preparation). α-Lithiation. A 250-mL, two-necked, round-bottomed flask, provided with a magnetic spinbar and a rubber septum, was connected to a nitrogen manifold and flame-dried while flushing with dry nitrogen. While under a N_2 atmosphere, a solution of 283 mmol of dry diisopropylamine (freshly distilled from CaH_2) in 50 mL of dry THF (freshly distilled from benzophenone ketyl radical) was syringed into the flask and dry ice cooled to −78 °C. While being stirred magnetically 10 mL of *n*-BuLi (2.55 N in hexane) was syringed dropwise into the flask. The solution was stirred 10 min at −78 °C, warmed up to room temperature (ca. 30 °C), and kept at room temperature for 10 min. The lithium diisopropylamide (LDA) solution was again dry ice cooled to −78 °C and 23 mmol of the ester **5** in 10 mL of dry THF was syringed dropwise into the LDA solution while the solution was stirred. The α-lithiocarboxylate solution was kept at −78 °C for 45 min and used for the silylation as described below.

Silylation: Into the freshly prepared (as described above) α-lithiocarboxylate solution was syringed 25.3 mmol of chlorotrimethylsilane (purged rigorously with dry N_2 to displace adventitious HCl) within 45 min while the solution was being stirred at −78 °C. The reaction mixture was allowed to warm up to room temperature (ca. 30 °C) and the THF was rotoevaporated (25 °C (20–30 mm)). The residue was triturated with 2 × 30 mL of dry benzene (freshly distilled from benzophenone ketyl radical) and filtered under a nitrogen atmosphere. The combined benzene triturates were rotoevaporated (25 °C (20–30 mm)) and the crude oil was fractionally distilled at reduced pressure. The yields and physical and spectral data for the ketene acetals **4** are collected in Table I.

Methyl Trimethylsilyl Peroxyacetates 3 (General Photooxygenation). A 100-mL, pear-shaped flask with a side arm which was capped with a rubber septum was connected to a nitrogen manifold. The flask was flame dried under reduced pressure while flushing with nitrogen and charged with a solution of 20 mmol of the acetal **4** in 20 mL of CCl_4, containing 2 mg of tetraphenylporphyrin (TPP). The solution was cooled to 0 °C with an ice bath and while passing a vivid stream of dry oxygen gas by means of a 15G stainless steel capillary, introduced through the rubber septum-capped side arm to the bottom of the flask, the contents were irradiated directly with a 400 W sodium lamp (General Electric). The reaction progress was monitored periodically by IR, following the disappearance of the 1660 cm^{-1} ketene acetal band. Usually within 60–90 min photooxygenation was completed, the solvent rotoevaporated (25 °C (80 mm)) and the residue worked up by fractional distillation at reduced pressure in the case of volatile silylperoxy esters or directly methanolyzed to the hydroperoxy esters in the case of unstable, involatile products. The results are summarized in Table II.

Methyl α-Hydroperoxyacetates 1 (General Methanolysis). A 50-ml, stoppered Erlenmeyer flask, provided with magnetic spinbar, was charged with 20 mL of methanol and cooled to 0 °C by means of an ice bath. While being stirred and cooled 4.64 mmol of silylperoxy ester **3** was syringed into the methanol and allowed to stir overnight. The methanol was rotoevaporated (10 °C (10 mm)) and the crude product was fractionally distilled or recrystallized. The results are summarized in Table III.

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Registry No.—**5a,** 10250-48-3; **5b,** 27174-71-6; **5c,** 547-63-7; **5d,** 3469-00-9; chlorotrimethylsilane, 75-77-4.

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Steric Effects. 11. Substituents at Sulfur

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SX groups, where X is alkyl, were shown to have constant electrical effects. Steric parameters, υ_{SX}, for eight SR groups were calculated from rates of alkaline hydrolysis of alkyl thiolacetates in 40% v/v dioxane–water at 35 °C by the equation: $\upsilon_{SX} = 1.14 \log k_{SX} + 2.06$. The υ_{SX} parameters were used to correlate rate data for the acid- and base-catalyzed hydrolyses of alkyl thiolacetates with the modified Taft equation. The magnitude of the ψ values obtained is discussed. Rate and equilibrium data for an additional 17 sets of reactions involving alkyl groups attached to sulfur have been correlated with the υ_{SX}, υ_X, and υ_X' constants by means of the modified Taft equation. Of the 24 sets studied, 23 gave significant correlations, leading to the conclusion that the effect of alkyl group substitution on sulfur is largely or wholly steric in nature.

In our last two papers in this series, we have developed steric substituent constants for alkoxy groups[1] and for alkylamino and dialkylamino groups.[2] In this paper, we extend our investigation to the problem of the definition of steric substituent constants for alkylthio groups. For this purpose, let us consider the effect of alkyl groups upon the rates of acid-catalyzed and base-catalyzed hydrolysis of alkyl thiolacetates. In addition to the steric effects of interest to us, we

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Table I. Values of Electrical and Steric Constants

X	$\sigma_{I,SX}$	$\sigma_{R,SX}$	$\sigma_{I,X}$	$\sigma_{R,X}$	υ_{CH_2X}	υ_{OX}	υ_{SX}	υ_X	υ_X'
Me	0.30	−0.35	−0.01	−0.16	0.56	0.36	0.64	0.52	0.35
Et	0.26	−0.25	−0.01	−0.14	0.68	0.48	0.94	0.56	0.38
Pr	0.25		−0.01		0.68	0.56	1.07	0.68	0.42
i-Pr	0.26	−0.22	0.01	−0.16	0.98	0.75	1.19	0.76	0.62
Bu	0.26		−0.01		0.68	0.58	1.15	0.68	0.42
i-Bu			−0.01		0.68	0.62	1.15	0.98	0.55
s-Bu	0.25		−0.01		1.00	0.86	1.36	1.02	0.66
t-Bu			−0.01	−0.16	1.34	1.22	1.60	1.24	1.23
Am	0.26				0.73	0.58		0.68	
c-Hex	0.32		0.00	−0.15	0.97	0.81		0.87	
Hex	0.25				0.73	0.61		0.73	
t-$BuCH_2$			0.00	−0.16				1.34	

must also consider the possibility of electrical effects. The localized (field and/or inductive) electrical effect can be described by the σ_I constants of alkylthio groups. Values for a number of these groups are listed in Table I.[4] Inspection of these values shows that they are fairly constant (0.27 ± 0.025), particularly when the error in the values is considered. Unfortunately, the delocalized (resonance) effect cannot be examined as effectively in this manner as σ_R values are available only for the MeS, EtS, and *i*-PrS groups. We can, however, make use of the method of ascertaining the delocalized effect which we have previously used[2] in our study of alkylamino groups. We have previously shown that the σ_p constants of the SX groups can be calculated from the equation[3]

$$\sigma_{p,SX} = m\sigma_{pX} + c \quad (1)$$

and that any composite substituent constant σ_X can be written as

$$\sigma_X = \lambda\sigma_{LX} + \delta\sigma_{DX} \quad (2)$$

where σ_{LX} is the localized effect parameter and σ_{DX} is the delocalized parameter characteristic of the X group, and λ and δ are coefficients. For the localized parameter, σ_L, we will use the σ_I constants[4] and for the delocalized parameter the σ_R constants.[4] Let us apply eq 2 to the case in which σ_X represent the σ_p value of alkyl substituent. For σ_p constants, $\lambda \equiv \delta \equiv 1$. The σ_I and σ_R values for alkyl groups are indeed constant with values −0.01 ± 0.01 for 12 groups and −0.16 for nine groups, respectively. Then σ_{pX} where X is alkyl must be constant, as all of the terms on the right side of eq 2 are constant.

Then, from eq 1, as m and c are constants, σ_{pSX} must be constant. Writing eq 2 for the $\sigma_{p,SX}$ values and rearranging gives

$$\sigma_{R,SX} = \sigma_{p,SX} - \sigma_{I,SX} \quad (3)$$

Then as $\sigma_{p,SX}$ and $\sigma_{I,SX}$ have been shown to be constant, $\sigma_{R,SX}$ must also be constant. It follows, then, that the electrical effect of alkylthio groups is independent of the nature of the alkyl group and will remain constant throughout the sets studied. We need, therefore, only to concern ourselves with the steric effect of the alkylthio group. In our work on alkoxy and alkylamino groups, we have demonstrated the validity of the equation

$$\upsilon_{Z'X} = \upsilon_{ZX} + d \quad (4)$$

where υ is the steric parameter we have defined elsewhere[5,6] and Z and Z′ refer to constant groups to which the variable fragment, X, and the rest of the molecule are attached. Thus, we have been able to successfully correlate rates of acid- and base-catalyzed hydrolysis of alkyl carboxylates and of *N*-alkyl amides with υ_{CH_2X} values by means of the modified Taft equation

$$\log k_{Z'X} = \psi\upsilon_{CH_2X} + h \quad (5)$$

In these cases, Z is the CH_2 group and Z′ is oxygen in the case of alkyl carboxylates or nitrogen in the case of *N*-alkyl amides. Using the υ_{CH_2X} values[5,6] we have attempted such correlations here. For the data and the results of the correlations with eq 5, see the paragraph at the end of this paper concerning supplementary material. The results obtained for the correlation of the three sets of base-catalyzed hydrolyses (sets 1–3) and four sets of acid-catalyzed hydrolyses (sets 4–7) of alkyl thiolacetates with eq 5 are not good enough to permit the definition of υ values for alkylthio groups. The data were therefore correlated with eq 5 using the υ_{OX} values. For the results, see Table II and the discussion of the supplementary material. The alkaline hydrolysis of alkyl thiolacetates in 40% aqueous dioxane at 35 °C (set 1B) gave results which are significant at the 99.9% confidence level (CL). We have therefore utilized this set of data to define υ_{SX} values. We have already shown that the ψ value obtained from correlation of a data set with the modified Taft equation (eq 5) by means of υ_{ZX} values is the same as that obtained from correlation by means of $\upsilon_{Z'X}$ values. Thus, the value of ψ obtained from correlation of set 1 with the υ_{OX} constants should be equal to the value of ψ which would result from the correlation of this data with υ_{SX} values.

We therefore used the data of set 1 together with the ψ value obtained for set 1B in defining υ_{SX} values. The only other requirement for the definition of υ_{SX} values is a value of υ_{SX} for some substituent. For this purpose, we again use our previous approach and take the difference between υ_{Me} and υ_{Et} to represent the effect of replacing a hydrogen in the methyl group by a methyl group. Then by the same type of argument as that previously used[1]

$$\upsilon_{SMe} = \upsilon_{SH} + \upsilon_{Et} - \upsilon_{Me} = 0.64 \quad (6)$$

In this manner we have obtained the relationship

$$\upsilon_{SX} = -1.14 \log k_{SX} + 2.06 \quad (7)$$

Values of υ_{SX} calculated from eq 7 and the data of set 1 are presented in Table I. Sets 2–7 were correlated with eq 5 by means of the υ_{SX} constants defined above (sets 2C–7C). The results obtained are very much better than those which were obtained by correlation with υ_{CH_2X} and υ_{OX} values. Whereas with the υ_{CH_2X} constants, all six sets did not give significant results, with the υ_{SR} values all six sets gave significant results. Had the sets contained more than four points each, the results would probably have been much better.

The υ_{SX} values were correlated with the υ_{OX} values by means of the equation

$$\upsilon_{SX} = m\upsilon_{OX} + d \quad (8)$$

The results obtained were: m, 0.998; d, 0.460; r, 0.944; F, 49.49 (CL = 99.9%); s_{est}, 0.100; s_m, 0.142 (CL = 99.9%); s_d, 0.103 (CL = 99.0%); n, 8. The value of m obtained is in excellent agreement with the value of 1.00 predicted by eq 4. The use of eq

Table II. Results of Correlations with Equations 5 and 9

Set[k]	ψ	h	r[a]	F[b]	s_{est}	n[d]
1B	−0.874	1.40	0.946	51.35[e]	0.0862	8
2C	−1.22	0.487	0.972	33.90[i]	0.143	4
3C	−1.07	1.10	0.990	101.2[g]	0.0722	4
4C	−0.455	0.789	0.919	10.88[j]	0.0940	4
5C	−0.394	1.17	0.935	14.01[j]	0.0717	4
6C	−0.392	0.509	0.963	25.46[i]	0.0530	4
7C	−0.276	0.843	0.979	46.67[h]	0.0276	4
8C	−2.03	2.45	0.978	88.97[e]	0.152	6
9D	−7.23	5.65	0.996	271.1[f]	0.251	4
10C	−1.07	2.25	0.857	13.88[h]	0.138	7
11C	0.510	−0.612	0.997	361.0[f]	0.0189	4
12C	0.488	−0.445	0.986	71.34[h]	0.0406	4
13C	0.533	−0.161	0.998	507.3[f]	0.0166	4
14C	0.555	−0.124	0.996	270.6[f]	0.0237	4
15D	0.977	−2.18	0.948	17.81[j]	0.133	4
16D	−6.67	5.86	0.996	260.1[f]	0.237	4
17D	−7.34	8.28	0.985	67.47[h]	0.511	4
18E	−4.72	2.80	0.951	37.74[f]	0.181	6
19E	−5.45	3.91	0.932	26.35[g]	0.250	6
20D	−1.03	1.66	0.975	116.9[e]	0.122	8
21D	−1.30	3.24	0.901	95.33[e]	0.207	24
22D	−5.36	14.4	0.808	9.422[i]	0.451	7
23D	−7.52	7.30	0.998	621.7[f]	0.173	4
24D	−4.50	3.52	0.981	50.94[h]	0.361	4

[a] Correlation coefficient. [b] F test for significance of regression. Superscript indicates confidence level (CL). [c] Standard errors of the estimate, ψ, and h. Superscript indicates CL of the "Student's t" test. [d] Number of points in the set. [e] 99.9% CL. [f] 99.5% CL. [g] 99.0% CL. [h] 97.5% CL. [i] 95.0% CL. [j] 90.0% CL. [k] The reactions studied are: (1) AcSR + OH^-, 40% aqueous dioxane, 35 °C; (2) AcSR + OH^-, 43% w/w aqueous MeOAc, 0 °C; (3) AcSR + OH^-, 62% aqueous MeOAc, 20 °C; (4,5) AcSR + H_3O^+, 43% w/w aqueous MeOAc, 30 °C, 40 °C; (6, 7) AcSR + H_3O^+, 62% w/w aqueous MeOAc, 30 °C, 40 °C; (8) AcSR + Ac_2O, $MeNO_2$, $AlCl_3$, 45 °C; (9) $RSSO_3^-$ + SO_3^{2-}, H_2O, pH 7.9, μ = 0.5, 25 °C; (10) RSCl + H_2O, $CHCl_3$, 25 °C; (11–14) RS^- + 4-$XC_6H_4C_2Br$, MeOH, 25.65 °C (X = Me, H, Cl, Br); (15) Cl_3CSR + MeOH, 60% MeOH–Et_2O, 20 °C; (16, 17) Cl_3CSR + Nu, 60% aqueous MeOH, 20 °C (Nu = OMe^- benzthiazole, 2-thiolate); (18, 19) RSCl + BuC_2H, EtOAc, Cl_3CH, 25 °C; (20) R^1SR^2 + O_2(g), V_2O_5, 200 °C; (21) R^1SR^2 + N_2O_4, CCl_4, 10 °C; (22) pK_a $(R^1R^2SCH_2SR^1R^2)^{2+}$, H_2O; (23) 4-$MeC_6H_4S(O)R$ + HCl, 2:1 v/v dioxane–12 M aqueous HCl, 25 °C; (24) PhS(O)R + I^-, aqueous 4.0 M $HClO_4$, 35 °C.

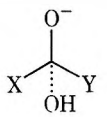
Table III. Values of ψ as a Function of Intermediate Structure, Solvent, and Temperature

Intermediate	X	Y	Solvent	T °C	ψ	Ref	Set in ref
I	SR	Me	40% v/v dioxane–H_2O	35	−0.874	*a*	1B
I	OR	Me	40% v/v dioxane–H_2O	35	−2.65	*b*	3
I	R	OMe	40% v/v dioxane–H_2O	35	−1.98	*c*	5
I	SR	Me	43% w/w MeOAc–H_2O	0	−1.22	*a*	2C
I	SR	Me	62% w/w MeOAc–H_2O	20	−1.07	*a*	3C
I	OR	Me	62% w/w MeOAc–H_2O	20	−2.92	*b*	6
I	R	OEt	70% v/v MeOAc–H_2O	24.8	−2.65	*c*	1
II	SR	Me	43% w/w MeOAc–H_2O	30	−0.455	*a*	4C
II	SR	Me	43% w/w MeOAc–H_2O	40	−0.394	*a*	5C
II	SR	Me	62% w/w MeOAc–H_2O	30	−0.392	*a*	6C
II	SR	Me	62% w/w MeOAc–H_2O	40	−0.276	*a*	7C
II	OR	Me	62% w/w MeOAc–H_2O	30.1	−0.967	*b*	7
II	OR	Me	62% w/w MeOAc–H_2O	40	−0.767	*b*	8
II	R	OEt	70% v/v MeOAc–H_2O	0	−1.80	*d*	12
II	R	OEt	70% v/v MeOAc–H_2O	40	−1.78	*d*	13

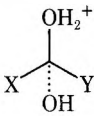
[a] This work. [b] Reference 1. [c] M. Charton, *J. Am. Chem. Soc.*, 97, 3691 (1975). [d] Reference 5

8 permits the estimation of many additional υ_{SX} values.

It is useful at this point to consider the variation of ψ with the structure of the intermediates I and II through which the



I



II

reaction proceeds. Values of ψ for acid-catalyzed and for base-catalyzed hydrolysis of various types of ester are given in Table III.

Inspection of the ψ values in Table III shows that the values obtained for base-catalyzed hydrolysis of alkyl acetates and methyl or ethyl carboxylates are two to three times greater than are the values for alkyl thiolacetates. There are two possible explanations for this observation: (1) the SR and OR groups exert different electrical effects on the reaction; (2) the transition states for the reaction of the alkyl acetates and methyl or ethyl carboxylates resemble the intermediate I to a much greater extent than the transition state for the reaction of the alkyl thiolacetates; as the degree of steric hindrance increases as the resemblance to I increases, this accounts for the magnitude of the ψ values.

From the structure of I, we expect X and Y to exert only a

Table IV. Results of Correlations with Equation 10

Set	$\psi_{(1)}$	$\psi_{(2)}$	h	R^a	F^b	r^c	$s_{est}{}^d$	$s\psi_{(1)}{}^d$	$s\psi_{(2)}{}^d$	$s_h{}^d$	n^e
20F	−0.783	−1.28	1.65	0.975	49.11[f]	0.985[f]	0.133	1.24[g]	1.20[h]	0.173[f]	8
21F	−1.69	−0.753	3.21	0.924	61.28[f]	0.419	0.187	0.200[f]	0.255[i]	0.182[f]	24
22F	−3.99	−21.4	22.1	0.945	16.77[j]	0.198	0.280	1.17[k]	5.45[l]	2.88[i]	7

[a] Multiple correlation coefficient. [b] F test for significance of correlation. Superscript indicates confidence level. [c] Partial correlation coefficient of $\upsilon_{(1)}$ on $\upsilon_{(2)}$. Superscript indicates CL if ≥90.0%. [d] Standard errors of the estimate, $\psi_{(1)}$, $\psi_{(2)}$, and h. Superscripts indicate CL of the "Student's t" test. [e] Number of points in the set. [f] 99.9% CL. [g] 20% CL. [h] 50.0% CL. [i] 99.0% CL. [j] 97.5% CL. [k] 95.0% CL. [l] 98.0% CL.

localized effect. The σ_I values for SR groups in Table I give an average value of 0.27. Thus, the localized electrical effect of the OR and SR groups is the same. We may therefore reject the first explanation of the difference in the sensitivity of the base-catalyzed hydrolysis reaction to steric effects.

In the acid-catalyzed hydrolysis of the above compounds, the alkyl acetates have ψ values two to three times greater and the ethyl carboxylates 4.5 to 6 times greater than those of the alkyl thiolacetates. We may account for this situation in terms of the extent to which the transition state resembles the intermediate II. We note that for all three types of substrate, the acid-catalyzed reaction is less susceptible to steric effects than is the base-catalyzed reaction.

The limited results available in Table IV suggest that the temperature effect on the susceptibility of acid-catalyzed hydrolysis to steric effects is generally small, but the solvent effect on the susceptibility of both acid- and base-catalyzed hydrolysis to steric effects is significant. Up to this point we have considered only reactions involving the attack of a nucleophile at the carbon atom of a carbonyl group. We now extend our investigations to a range of reaction types, including attack of thiolate ions on ArC_2Br, attack of nucleophiles on divalent sulfur, and oxidation of sulfides. The data for these and other reactions of sulfur compounds bearing alkyl groups are given in the Supplementary Material. Results of best correlations with the modified Taft equation are in Table II and the others are in Supplementary Material. Set 8 involves the exchange of acetyl groups between ^{14}C-labeled Ac_2O and alkyl thiolacetates, catalyzed by $AlCl_3$. The reaction is reported to occur at the S atom, with the acetyl groups of the Ac_2O being equivalent.[7] A possible mechanism is shown in Scheme I. Correlations were carried out with υ_{SX} and υ_X. Best results were obtained with υ_{SX}. This is in accord with a resemblance between the tetrahedral intermediates I and II and the transition state IV.

According to Fava and Iliceto,[8] the rates for the reactions

$$SO_3^{2-} + RSSO_3^- \rightarrow RSS^*O_3^- + SO_3^{2-}$$

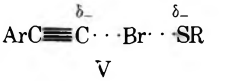
and

$$^*Br^- + RCH_2Br \rightarrow RCH_2Br^* + Br^-$$

show almost the same dependence on steric effects. They conclude that this means that the reaction of the Bunte salt with sulfite goes by the same mechanism as that of the alkylmethyl bromide with bromide ion, that is, by way of a species in which the entering and leaving groups occupy the apical positions of a trigonal bipyramid. Pryor and Smith[9] have observed, however, that for a number of reactions in which the alkyl group is varied, the rate constants give excellent correlations with each other even though the mechanisms are very different. This is not at all surprising, as the success of these correlations merely implies that the steric effect of the alkyl groups is comparable in these different reactions. What this means in terms of the interpretation of correlations with the υ parameters is that if two reactions are both well correlated by the same υ parameter, they may or may not occur by the same or similar mechanisms, while if the two reactions are best correlated by different υ parameters, they probably occur by different mechanisms. We find that the rates for the reaction of the Bunte salts with SO_3^{2-} give somewhat better correlation (set 9D) with the υ_X constants which were defined from rates of esterification of carboxylic acids[5] than with the υ_X' constants which were defined from rates of reaction of RCH_2Br with $^*Br^-$.[10] Thus, the conclusions of Fava and Iliceto seem unwarranted.

The reaction of alkylsulfenyl chlorides with water (set 10) should presumably by analogous to the reaction of Bunte salts with sulfite. In fact, however, correlation with the υ_X constants is not significant while correlation with the υ_X' constants is poor. Better results are obtained with the υ_{SX} values (set 10C). To obtain the correlation with the υ_{SR} values, it was necessary to calculate an υ_{SR} value for R = CH_2-t-Bu from eq 8. A value of 1.16 was obtained for $\upsilon_{SCH_2\text{-}t\text{-}Bu}$. The results obtained indicate that the hydrolysis of alkylsulfenyl chlorides proceeds by a different mechanism from that of the reaction of Bunte salts with sulfite.

The reaction of 4-substituted phenylethynyl bromides with alkylthiolate ions occurs by displacement on bromine.[11] Data were correlated with the υ_{SX}, υ_X, and υ_X' constants (sets 11–14C, 11–14D, and 11–14E, respectively). Best results were obtained with the υ_{SX} constants. These constants constitute a measure of the size of the alkyl thiolation. The fact that the correlations obtained with υ_{SX} were not only significant, but in three of the four sets excellent, indicates that steric effects definitely exist. In that case we may rule out a linear transition state such as V, for which steric effects should be negligible.

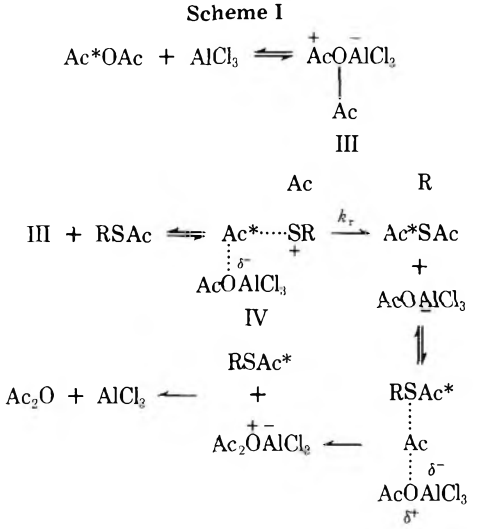


V

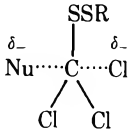
It might be noted that V is positive for sets 11–14, indicating steric acceleration of the reaction.

Set 15 is said to proceed by a near S_N1 mechanism involving a chlorine atom on the CCl_3 group of the CCl_3SSR.[12] In the absence of information on what type of steric effect, if any,

Scheme I



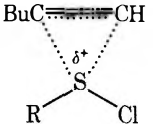
might be encountered here, we have correlated the data with the υ_{SX}, υ_X, and υ_X' constants. Best results were obtained with the υ_X constants, but were only significant at the 90.0% confidence level. Had more data been available, better correlation would probably have been obtained. Sets 16 and 17 are said to occur by a near S_N2 reaction. The leaving group is a Cl atom on the CCl_3 group. Thus, the transition state should be close to VI, where Nu^- is the nucleophile. What are really required



VI

then for optimum correlation are υ_{SSR}' constants, which are of course unavailable. We have carried out correlations with the υ_{SX}, υ_X, and υ_X' constants. the reaction with OMe^- gives best results with the υ_X constants (set 16D), an excellent correlation being obtained. The reaction with 2-thiolbenzothiazole anion also gives best results with the υ_X constants (set 17D), the correlation is good. The value of ψ is slightly greater for the reaction with 2-thiolbenzothiazole anion than for the reaction with methoxide ion. The small difference between the ψ values suggests that the Nu^- to C bond is less than half formed, thereby minimizing interaction between the attacking nucleophile and the SSR group.

The mechanism for the addition of alkylsulfenyl halides to 1-butyne is uncertain. Thus, DiNunno and Scorrano[13] have observed that the regioselectivity of the reaction is anti-Markownikoff and the stereoselectivity is trans. They further note a significant solvent effect on the reaction rate. The addition of arylsulfenyl chlorides to acetylenes has been shown to involve electrophilic attack by a sulfur atom bearing an increment of positive charge.[14] As VII does not resemble any



VII

of the transition states used to define υ parameters, the data were correlated with the υ_{SX}, υ_X, and υ_X' constants. The best results were obtained with the υ_X' constants, for which excellent and very good correlations were obtained (sets 18E and 19E).

The mechanism of the reaction of alkyl sulfides with oxygen in the vapor phase over V_2O_5 does not seem to be known. The data have been correlated with the equation

$$\log k_X = \psi\Sigma\upsilon_X + h \qquad (9)$$

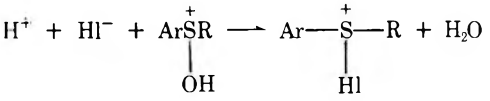
as this equation was previously found applicable to biomolecular nucleophilic substitutions at carbon.[10] The data have also been correlated with the equation

$$\log k_X = \psi_1 \upsilon_{X(1)} + \psi_2\upsilon_{X(2)} + h \qquad (10)$$

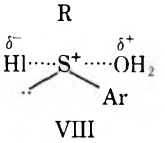
where $\upsilon_{X(1)}$ and $\upsilon_{X(2)}$ are the steric parameters for the larger and smaller substituents, respectively ($\upsilon_{X(1)} \geq \upsilon_{X(2)}$).

The results of the correlations with eq 10 (set 20F) are given in Table IV, and those with eq 9 (set 20D) are reported in Table II. Better results were obtained with eq 9, but no conclusion can be reached as to the validity of eq 10 as $\upsilon_{X(1)}$ and $\upsilon_{X(2)}$ are collinear. The reaction of the alkyl sulfides with N_2O_4 in CCl_4 was also correlated with eq 9 and 10 (sets 21D and F, respectively) with results which are about the same. Thus, both correlations were significant at the 99.9% CL, and whereas the correlation coefficient for 21F is greater than that for 21D, the F value for 21D is greater than that for 21F.

The pK_a values of the disulfoniomethanes were also correlated with eq 9 and 10 (sets 22D and 22F). In this set, best results were obtained with eq 10. We are in doubt as to the significance of this correlation, since υ_2 is more than five times greater than υ_1. We are unable to explain this observation, since it seems to us that the larger group should have the greater steric effect. Thus, at least for the sets we have studied involving multiple substitution (sets 20–22), eq 9 seems more useful than eq 10. With regard to sets 23 and 24, according to



Kice, the rate-determining step is the reaction given in eq 11, for which a possible transition state is VIII. This transition



VIII

state resembles an S_N2 transition state. Correlations have therefore been carried out with the υ_X and υ_x' constants. Both sets give somewhat better results with the υ_X constants. This suggests that steric effects in these reactions resemble those for the reaction of Bunte salts with sulfite.

In conclusion, data for a number of reactions involving alkyl groups attached to sulfur has been successfully correlated with the modified Taft equation using the υ_{SX} parameters defined here or the υ_X or υ_X' parameters previously defined. Of the 24 sets studied, 23 gave significant results. Thus, the effect of alkyl groups attached to sulfur upon reaction rates and equilibria is largely, if not wholly, steric.

Supplementary Material Available: Tables of the data used in the correlations and the results of all the correlations (6 pages). Ordering information is given on any current masthead page.

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Micellar Effects upon the Hydrogen Ion and General Acid Catalyzed Hydration of 1,4-Dihydropyridines[1]

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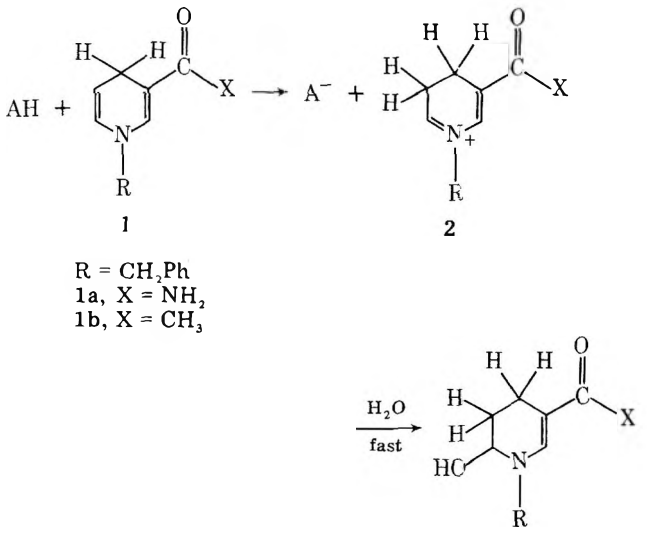
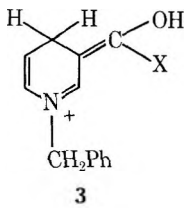
The rate-limiting step in the hydration of 1-benzyldihydronicotinamide (**1a**) and 1-benzyl-3-acetyl-1,4-dihydropyridine (**1b**) is a slow proton transfer, as shown by the kinetic deuterium solvent isotope effects and buffer catalysis. Reactions in dilute HCl are strongly inhibited by cationic micelles of cetyltrimethylammonium bromide (CTABr) and the inhibition can be related to the micellar binding of the substrates determined spectrophotometrically or by solubility. Anionic micelles of sodium lauryl sulfate (NaLS) only weakly catalyze hydration in dilute HCl, and rate constants go through maxima with increasing [NaLS]. The dependence of rate on [NaLS] can be explained quantitatively in terms of substrate and hydrogen ion incorporation in the micelle and formation of an unreactive conjugate acid in the micelle. The equilibrium constants for unproductive protonation in the micelle corrected for reagent distribution are similar to those in water but the rate constants are lower. Micelles of sodium *n*-dodecyl hydrogen phosphate are good catalysts, giving rate enhancements of $\sim 10^3$ relative to those in water.

The acid hydration of dihydropyridine derivatives (**1**) in aqueous solution is an enamine addition and involves proton transfer from HA followed by rapid attack of water upon the cation (**2**).[4] Because of the biological importance of dihydropyridine nucleotides catalysis of this reaction is of considerable interest and we examined micellar effects in a model system. To date much of the mechanistic work has been on nucleotide derivatives, which are too hydrophilic to be good substrates for use with aqueous micelles, and therefore we first examined hydration of our substrates **1a,b** in the absence of surfactants for purposes of comparison with the reactions in the presence of micellized surfactants. The protonations are irreversible in aqueous acid, but not in nonpolar solvents,[5] and the reactions in aqueous solution are general acid catalyzed.[6] The slow protonation is assisted by electron release by the ring nitrogen, which is reduced by conjugation with the carbonyl group. The charge in the transition state, or the cation **2**, is delocalized, but probably it is largely on the ring nitrogen as shown, and substrate protonation, probably on the carbonyl group, **3**, should inhibit reaction.



1

R = CH_2Ph
1a, X = NH_2
1b, X = CH_3



3

Micelles of anionic surfactants typically speed hydrogen ion catalyzed reactions,[7] and we were interested in micellar effects upon the hydration of dihydropyridines because to date specific hydrogen ion catalyzed reactions have generally been examined. In these reactions the proton is fully transferred in the transition state whose formation involves other bond making or breaking steps.

Cationic micelles of cetyltrimethylammonium bromide, CTABr, inhibit and anionic micelles of sodium lauryl sulfate, NaLS, weakly catalyze hydration of dihydronicotinamide derivatives.[12] These experiments were in phosphate buffer so that the micelles could affect the buffer equilibria and have different, and perhaps opposite, effects upon the hydrogen ion and the dihydrogen phosphate ion catalyzed reactions.[13] We therefore examined these reactions under conditions in which the only catalyst is the hydrogen ion, because there is information on the distribution of hydrogen ions between water and anionic micelles of NaLS.[15,16]

The apparent low catalysis by NaLS is unusual because an alkyl dihydropyridine should be sufficiently hydrophobic to be incorporated into the micelle, and one of our prime aims was to understand the significance of this small effect. In addition we planned to analyze the relation between rate and surfactant concentration in terms of the distribution of hydrogen ions between water and the micelle.[15,16] These relations have been interpreted in terms of the distribution of reagents for acetal hydrolysis[15] and for a number of nucleophilic substitutions and additions,[17] and a general theoretical model has been derived,[18] but this approach has not been used extensively for reactions of hydrophilic ions. In addition, the kinetic form of the micellar catalysis is complex because it depends not only upon the incorporation of reagents into the micelle but also upon increased formation of an unreactive conjugate acid. We also planned to use a micelle which was itself a buffer and we therefore also examined the buffer catalysis in water and the kinetic solvent isotope and electrolyte effects in the absence of micelles.

Results

Reactions in the Absence of Surfactant. Strong Acid. The first-order rate constants of hydration in aqueous acid are illustrated in Figure 1. In dilute HCl at 25.0 °C the second-order rate constants, k_H ($k_H = k_\psi/[H^+]$), are 16.0 and 0.44 M^{-1} s^{-1} for **1a** and **1b**, respectively. The small differences between these and other rate constants[6] are probably due to differences in the ionic strengths of the reaction solutions. The reaction is first order with respect to hydrogen ion concentration in dilute acid, but with increasing acid concentrations the rate constants for the acetyl derivative (**1b**) reach maxima

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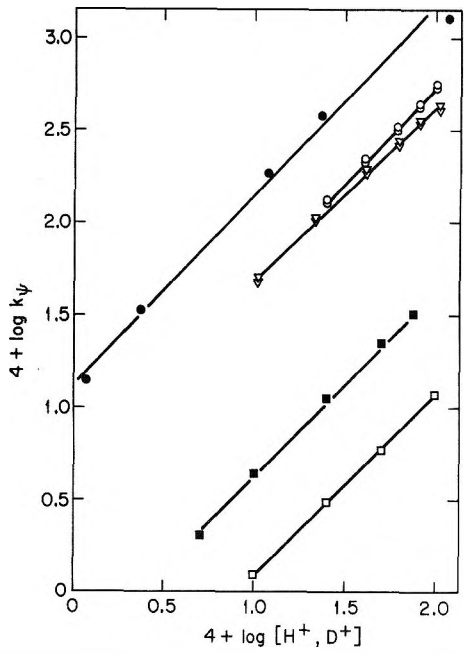


Figure 1. Hydration in dilute acid: **1a** HCl, ●; DCl, ○; D_2SO_4, ◇; **1b**, HCl, ■; DCl, □.

at ca. 1 M HCl and then fall slightly. The hydration of the acetamido derivative (**1a**) becomes too fast for us to observe a rate maximum (Figure 2).

The levelling of the rate constants with increasing acidity is general for these derivatives[6] and can be ascribed to buildup of unreactive cation (**3**, $HS^{+\prime}$). The structure of $HS^{+\prime}$ is probably **3**, and of HS^+, **2**.

Scheme I leads to eq 1, provided that protonation of the substrates to HS^+ or $HS^{+\prime}$ follows hydrogen ion concentration rather than any other function of acidity. Rearrangement of eq 1 gives eq 2 which fits the experimental data reasonably well (Figure 2) and gives for the acetamido derivative (**1a**) k_H = 15.6 M^{-1} s^{-1} and pK_a = 0.62, and for the acetyl derivative (**1b**) k_H = 0.47 M^{-1} s^{-1} and pK_a = 0.87. These equilibrium constants are in the expected range and the rate constants agree with those determined in dilute HCl even though the rate and equilibrium constants in Scheme I may follow some acidity function rather than hydrogen ion concentration, and protonation may not be wholly rate limiting when the water activity begins to decrease (cf. ref 5).

Scheme I

$$HS^{+\prime} \underset{K_a}{\overset{H^+}{\rightleftharpoons}} S \xrightarrow[H^+]{k_H} HS^+ \xrightarrow[\text{fast}]{H_2O} \text{products}$$

$$k_\psi = k_H K_a[H^+]/([H^+] + K_a) \quad (1)$$

$$1/k_\psi = 1/k_\psi K_a + 1/k_H[H^+] \quad (2)$$

Kinetic Salt Effects in Strong Acids. There are positive salt effects on the hydration of **1a** in dilute HCl (Table I). Salts typically increase acidity,[19-21] and our rate effects follow the expected form of eq 3:

$$\log k_s/k_0 = K_s[\text{salt}] \quad (3)$$

where k_s and k_0 are the rate constants in the presence and absence of added salt.

We see little dependence upon the nature of the salt, although salt effects are often highly specific, especially for Al reactions. In addition, the effects are smaller than those upon many Al reactions and acidity as measured by H_0' or H_R suggesting that the magnitude of the salt effects is related to the extent of proton transfer in the transition state.[21]

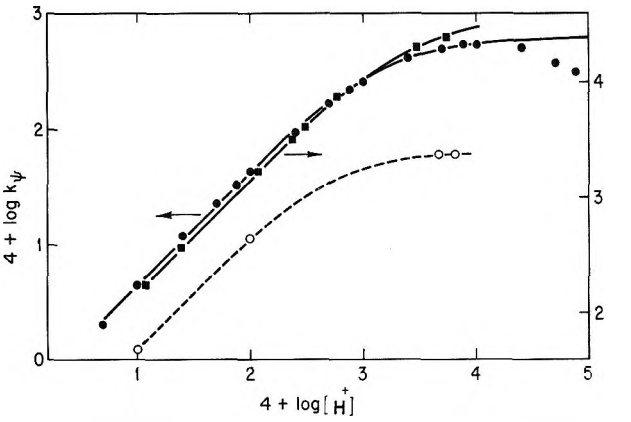


Figure 2. Hydration in moderately concentrated HCl (DCl broken line): **1a**, ■; 1b, ●, ○. The curves are calculated.

Table I. Salt Effects on Hydration in Dilute Acid[a]

Salt	K_s	Salt	K_s
LiCl	0.21	$NaClO_4$	0.23 (0.31)
LiBr	0.22	$NaNO_3$	0.23
$LiClO_4$	0.19	KCl	0.21
NaCl	0.31 (0.26)	KBr	0.31
NaBr	0.31	KNO_3	0.19

[a] At 25.0 °C with 5 × 10^{-3} M HCl, 0.5–2 M salt, and **1a**. The values in parentheses are for hydration of **1b**.

Table II. General Acid Catalysis[a]

Buffer	[HA]/[A]	$10^2 k_{cat}$, M^{-1} s^{-1} **1a**	**1b**
Acetic	2	5.07	0.13
	2[b]	5.50	
	1	4.80	0.12
Formic	2	24.2	0.73
Chloroacetic	1	101	2.44
Cyanoacetic	1	137	3.37
	0.5[c]	113	2.41
H_3O^+		1600[d]	44[d]

[a] At 25.0 °C and 0.1 ionic strength with NaCl unless specified. [b] Ionic strength 0.05. [c] Ionic strength 0.2. [d] Dilute HCl.

The situation is different for reactions of the acetyl derivative (**1b**) in 1 M HCl where added salts either have a very small positive effect or retard reaction; in the absence of salt $10^3 k_\psi$ = 52 s^{-1} and with added 2 M NaCl and 2 M $NaClO_4$ the respective values are 56.9 and 46.2 s^{-1}. These results are readily understandable because in the more acidic solutions protonation of the substrate generates unreactive conjugate acid. Added salts increase this protonation and this inhibitory effect offsets the normal positive kinetic salt effect. Apparently with sodium perchlorate, which decreases the first-order rate constant, k_ψ, the inhibitory effect is the more important.

Buffer Catalysis. These hydrations are general acid catalyzed, and the catalytic constants are in Table II. These constants depend slightly upon the reaction media, probably because of the specific electrolyte effects of chloride and carboxylate ions. The catalytic constants for the carboxylic acids follow the Bronsted catalysis law[22] although those for the hydrogen ion in dilute HCl are low as is often found. For catalysis by carboxylic acid α = 0.6 for both substrates, and is in the range found for other enamine protonations.

Kinetic Solvent Hydrogen Isotope Effects. Hydrations in dilute strong acid show normal hydrogen isotope effects[23]

Table III. Hydrogen Solvent Isotope Effects in Moderately Concentrated Acid[a]

	$10^4 k_\psi$, s^{-1}		
[HCl], [DCl], M	H_2O	D_2O	k_{H_2O}/k_{D_2O}
0.46	48	58.8	8.2
0.69	52	59.2	8.8
0.92	52	58.9	8.8
2.30	50	56.6	8.8

[a] At 25.0 °C with the acetyl derivative (**1b**) in HCl and DCl. The values of k_{H_2O} are interpolated where necessary.

(Figure 1) with k_{H_2O}/k_{D_2O} = 3.67 for the acetyl derivative (**1b**) and 3.2 for the acetamido derivative (**1a**) in the range HCl (DCl) of 0.001–0.01 M, but there are larger effects for the formic acid catalyzed reaction. In D_2O with sodium formate–formic acid 1:2, formic acid 0.02–0.1 M, and ionic strength 0.1 (NaCl), k_{cat} = 0.0457 and 0.00119 M^{-1} s^{-1}, for **1a** and **1b**, respectively, giving k_{H_2O}/k_{D_2O} = 5.3 and 6.2. These differences could be related both to differences in the extents of proton transfer in the transition state and to the secondary solvent isotope effects.

For lyonium ion transfer the normal primary isotope effect will be opposed by an inverse secondary isotope effect as the lyonium ion is converted into water with proton transfer.[24] The maximum inverse isotope effect has been estimated as k_{H_2O}/k_{D_2O} = 0.61,[24] on the assumption that the positive charge of the hydronium ion is largely lost in the transition state. The overall normal isotope effects of 3.2 and 3.67 for proton transfer to **1a** and **1b**, respectively, from lyonium ion suggest that there is a primary hydrogen isotope effect of ca. 6 which is partially offset by the inverse secondary effect. This secondary effect should be much less important in the formic acid catalyzed hydration (cf. ref 6).

These normal isotope effects upon the proton transfers are in the range expected for a reaction in which the zero point energy of the proton is lost in forming the transition state, and are consistent with the Bronsted α value of 0.6.

The kinetic solvent deuterium isotope effects on hydration of **1b** increase with increasing acid concentration (Figure 2 and Table III) where the unreactive conjugate acid (**3**) builds up in concentration because this conjugate acid is weaker in deuterium oxide than in water.[24] This additional secondary solvent isotope effect therefore augments the usual primary isotope effect in the hydrogen ion transfer, and the overall isotope effect reaches a maximum value of 8.8 when the bulk of the substrate is protonated.

In dilute hydrochloric or formic acid buffer where there is no substrate protonation the kinetic solvent deuterium isotope effect is smaller for the acetamido derivative (**1a**) than for the acetyl derivative (**1b**). The differences may depend on the extents of proton transfer, but there could also be a secondary effect due to isotopic exchange into the acetamido group, because this group is conjugated with the forming cationic center in the transition state.

Micellar Effects. As expected, anionic micelles catalyze and cationic micelles inhibit the hydrogen ion catalyzed hydration.[8–12] Although we see extensive inhibition the catalysis by NaLS is small, and in order to understand this behavior we need evidence on substrate incorporation in the micelles (see Experimental Section).

Substrate Incorporation. The extent of substrate binding to the micelles has been estimated spectrophotometrically[25] and by solubility,[17,26] and we write the binding constant K as:[27]

$$K_M = [S_M]/[S]([D] - cmc) \quad (4)$$

Table IV. Binding Constants[a]

	Surfactant				
Solute	CTABr			NaLS	
1a	453		460[c]	285	
1b	409	488[b]	370[c]	405	423[b]

[a] Values of K, M^{-1}, determined spectrophotometrically except where specified. [b] Determined by solubility. [c] Determined kinetically.

where S and S_M are the substrate in water and in the micelle, respectively, D is the surfactant (detergent), and cmc is the critical micelle concentration.

Determination of binding constants by the solubility method (Experimental Section) assumes that any increase in solubility is caused by incorporation of the substrate into the micelles, and that there is no material change in the micellar properties. In addition, the substrate should be only slightly soluble in water so that it does not change the nature of the bulk solvent. This method fails if the substrate is decomposed, and therefore we only used it with the less reactive **1b**. However, the spectrophotometric and solubility methods agree (Table IV), and they also agree with gel filtration results for incorporation of **1a** into CTABr.[28]

The binding constants of the acetyl derivative (**1b**) toward micellized CTABr and NaLS are very similar (Table IV), but the acetamido derivative (**1a**) binds more strongly to CTABr than to NaLS. Quaternary ammonium ions interact strongly with polarizable solutes, and cationic micelles readily incorporate aromatic solutes, especially those which have electron releasing and hydrophobic groups.[14,29] The acetyl group is more hydrophobic than the acetamido group, and therefore **1b** should be bound more strongly than **1a** to a micelle, as with anionic micelles of NaLS, but not with CTABr. The greater binding to CTABr of the acetamido derivative (**1a**) is therefore probably due to the greater electron withdrawing power of the acetyl group, which would reduce the interaction of the dihydropyridine group with the quaternary ammonium head groups of micellized CTABr.[29]

Inhibition by Cationic Micelles. The inhibition (Figure 3) can be treated quantitatively on the assumption that the substrate is partitioned between water and the micelles but that hydrogen ions are excluded from the micelle (Scheme II, where D_M is a micelle).[8–11,30]

The usual treatment of the inhibition follows eq 5:

$$k_\psi = \{k_W' + k_M' K_M([D] - cmc)\}/\{1 + K_M([D] - cmc)\} \quad (5)$$

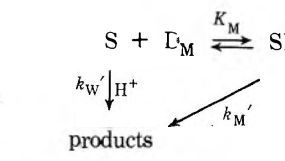
where k_W' and k_M' are first-order rate constants in water and the micelle, respectively. Although this equation works well in some systems it fails with hydrophobic substrates which decrease the cmc,[26] as is the case with these dihydropyridines. However, if we assume that k_M' = 0 we obtain eq 6:

$$(k_W'/k_\psi) - 1 = ([D] - cmc)K_M \quad (6)$$

Plots of $(k_W'/k_\psi) - 1$ against [D] are linear with slopes K_M given in Table IV, and the intercepts at ca. 4×10^{-4} M CTABr show that these substrates strongly decrease the cmc.

These kinetically derived association constants agree with the binding constants calculated physically, which supports

Scheme II



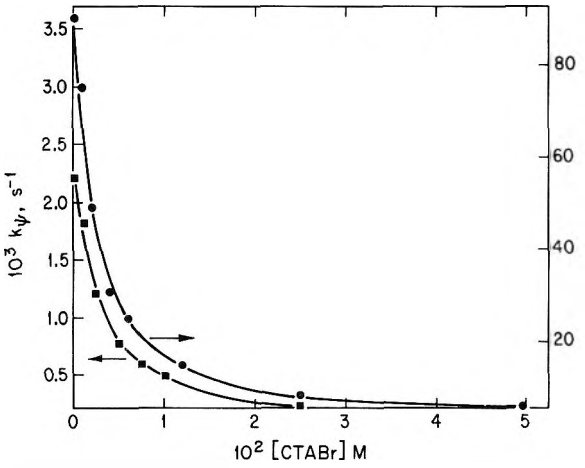


Figure 3. Micellar inhibition by CTABr: ●, **1a** in 0.0058 M HCl: □, **1b** in 0.005 M HCl. The curves are calculated.

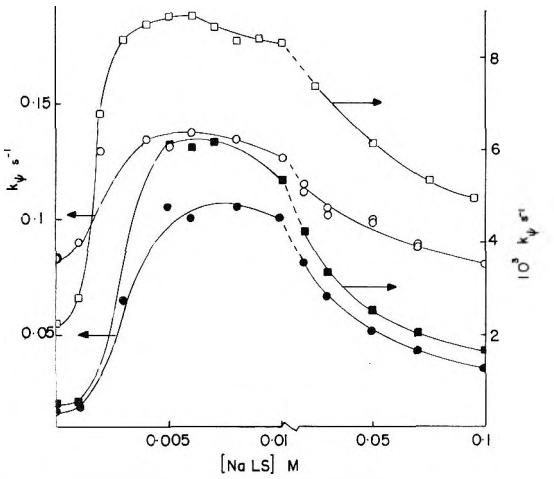


Figure 4. Micellar catalysis by NaLS. Solid points in 0.001 M HCl, open points in 0.005 M HCl: **1a**, ●, ○; **1b**, ■, □.

the validity of our kinetic treatment. Our kinetically estimated cmc for CTABr of ca. 4×10^{-4} M is lower than the values of 7×10^{-4} M estimated spectrophotometrically (Experimental Section) in part because of the effect of the added HCl. The curves in Figure 3 were calculated using these parameters and eq 6.

Catalysis by Micelles of Sodium Lauryl Sulfate. The rate enhancements by NaLS are unusually small (Figure 4 and Table V) and the rate maxima are reached at low surfactant concentrations below the cmc of NaLS in water.[31]

Micellar catalysis is generally discussed in terms of the maximum rate enhancement of the micelle, but this approach is clearly inadequate for these reactions. For example, although the hydrations are second order in dilute aqueous HCl (Figure 1) the maximum rate constants in NaLS are almost the same in 0.001 and 0.005 M HCl (Figure 4 and Table V). Bimolecular reactions in aqueous surfactant solutions are often less than first order with respect to an ionic reagent,[8-11,15,26] but this large effect is unusual.

Therefore a dissection of the effects which govern micellar catalysis of bimolecular reactions is needed. In principle, the relation between rate constant and surfactant concentration can be treated quantitatively if we can estimate the concentrations of both reactants in the micellar and aqueous pseudo phases. The reaction is too fast for us to estimate the substrate concentration on the micelles in acidic solution, and so we are forced to carry out this determination in neutral solution.

The distribution of hydrogen ions between water and micelles of NaLS has been estimated by pH,[15] conductivity, and indicator measurements on the ionization of maleic acid[16] for a range of acid and surfactant concentrations. These three methods agreed well and a plot of $m^s_{H^+}$ against $[H^+]/([H^+] + [Na^+])$ was linear with slope 0.82 ($m^s_{H^+}$ is the number of hydrogen ions per micellized sulfate head group). This relation gives $m^s_{H^+}$ in terms of the total concentrations of HCl and NaLS and its significance will be discussed elsewhere.

The first-order rate constants k_W' and k_M', Scheme II, will depend on the concentrations of hydrogen ion in the aqueous and micellar pseudo phase, which are $[H^+_W]$ and $m^s_{H^+}$, respectively. For convenience we write $[H^+_W]$ as a molarity, and assume that the volume of the micelles is much less than that of water, but we write $m^s_{H^+}$ as a ratio of bound hydrogen ions to head groups in the micelle. We could alternatively use a different measure of concentration; for example, we could estimate the hydrogen ion concentration in terms of micellar volume, and this approach is discussed later.

The second-order rate constants for reaction in water, k_H, and in the micelle, k_M, are given by:

$$k_W' = k_H[H^+_W]; k_M' = k_M m^s_{H^+} \quad (7)$$

Table V. Maximum First-Order Rate Constants in Anionic Micelles[a]

	[HCl], M	
Substrate	0.001	0.005
1a	10.6 (6.6)	13.3 (1.7)
1b	0.63 (14.3)	0.88 (4)

[a] Maximum values of $10^2 k_\psi$, s^{-1}; the values in parentheses are the enhancements over the rate constants in the absence of surfactants.

(The units of k_H are M^{-1} s^{-1} and those of k_M are s^{-1}.)

The total molarity of hydrogen ions $[H^+_T]$ is:

$$[H^+_T] = [H^+_W] + m^s_{H^+}([D] - cmc) \quad (8)$$

Equations 5 and 8 relate the first-order rate constant, k_ψ, to the constants K_M, k_{H^+}, and k_M, and the concentrations of hydrogen ions in water and the micelles.

Rearranging eq 5 and 8 gives:

$$\frac{k_\psi\{1 + K_M([D] - cmc)\} - k_H[H^+_T]}{([D] - cmc)} = m^s_{H^+}(k_M K_M - k_H) \quad (9)$$

Several assumptions are made in deriving eq 9. (i) The value of k_W is that determined in dilute aqueous acid; i.e., we identify k_W with the second-order rate constant k_H. (ii) The association constant K_M is not affected by dilute HCl. This assumption turns out to be reasonable at the higher surfactant concentrations, but it may not be so when [NaLS] → cmc. (iii) The value of $m^s_{H^+}$ is unaffected by added substrate. (iv) The cmc for the reaction solution can be estimated from the values in the presence of dilute HCl and substrate, and we used 10^{-3} and 2×10^{-3} M as the cmc for reaction in 5×10^{-3} and 10^{-3} M HCl, respectively (cf. ref 15). These assumptions are those often made in treating micellar catalysis and inhibition, but they complicate analysis of the rate constants near the rate maxima where the surfactant concentrations are not much greater than the cmc under the kinetic conditions.

The left-hand side of eq 9 can be calculated from the experimental data and the values of $m^s_{H^+}$ are known from independent physical measurement.[15,16]

An example of our method of estimating k_M is given in Table VI. These values are not constant but decrease with increasing concentration of hydrogen ions in the micelle, $m^s_{H^+}$. However, the important feature is that our values of k_M at a given $m^s_{H^+}$ are not directly related to the total hydrogen ion

Table VI. Analysis of Rate Constants for Reaction of the Acetyl Derivative (1b) in NaLS[a]

10^3[NaLS], M	$10^3 k_\psi$, s^{-1}	$10k_M$, s^{-1}	$m^s_{H^+}$	$10k_\psi/m^s_{H^+}$, s^{-1}
4	8.69	0.30	0.45	0.19
5	8.82	0.30	0.41	0.22
6	8.82	0.31	0.37	0.24
	(6.05)	(0.82)	(0.12)	(0.53)
7	8.62	0.32	0.34	0.25
8	8.38	0.32	0.32	0.27
8	(6.19)	(0.94)	(0.090)	(0.69)
9	8.43	0.34	0.29	0.29
10	8.32	0.36	0.27	0.31
10	(5.37)	(0.91)	(0.075)	(0.72)
20	(4.23)	(1.18)	(0.040)	(1.06)
25	7.37	0.57	0.14	0.54
30	(3.35)	(1.35)	(0.027)	(1.24)
50	6.12	0.84	0.074	0.83
50	(2.53)	(1.64)	(0.016)	(1.58)
70	(2.01)	(1.77)	(0.012)	(1.68)
75	5.32	1.05	0.051	1.04
95	4.93	1.21	0.041	1.20
100	(1.61)	(2.01)	(0.008)	(1.99)

[a] In 5×10^{-3} M HCl, except for values in parentheses which are for 10^{-3} M HCl.

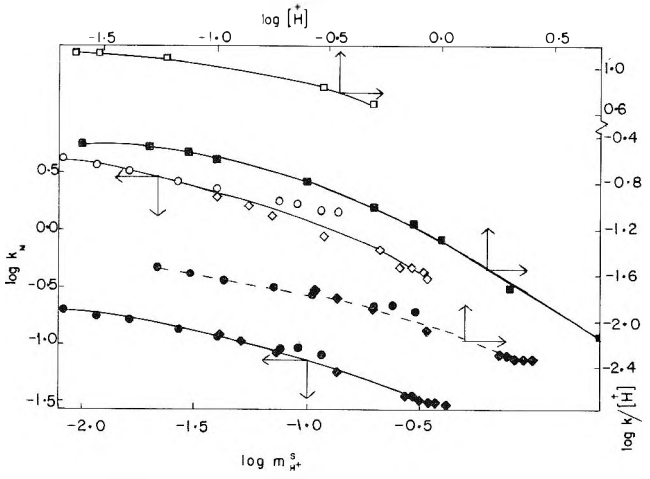


Figure 5. Variation of second-order rate constants for reactions in micelles of NaLS and in aqueous HCl. Open points are for reaction of **1a**, solid of **1b**. Reaction in aqueous HCl, □, ■; reaction in NaLS + 0.001 M HCl, ○, ●; reaction in NaLS + 0.005 M HCl.

concentration within the uncertainties of the method (Figure 5).

This behavior is similar to that shown in water where the second-order rate constant, $k_\psi/[H^+]$, decreases steadily with increasing hydrogen ion concentration (Figure 2) because of formation of the unreactive cation (**3**), and anionic micelles should increase the protonation of the substrates just as they assist attack of hydrogen ions upon them.

In both water and the Stern layer of a micelle, hydrogen ions act in two ways: (i) they add to the double bond of the enamine substrate giving the cation (**2**) which is rapidly hydrated, and (ii) they convert the substrate into the unreactive cation (**3**). The kinetic form is very similar in both systems as shown in Figure 5 where we plot log k_M against log $m^s_{H^+}$ for reaction in the Stern layer and log $k/[H^+]$ against log $[H^+]$ for reaction in water (k is the first-order rate constant). In water it is easy to follow the reactions in solutions which are sufficiently dilute for there to be almost no buildup of unreactive cation and where we observe second-order kinetics (Figures 1 and 2).

The anionic micelle concentrates hydrogen ions into the Stern layer so that there is extensive buildup of the unreactive cation (**3**) even when the total hydrogen ion concentration is only 10^{-3} M HCl.

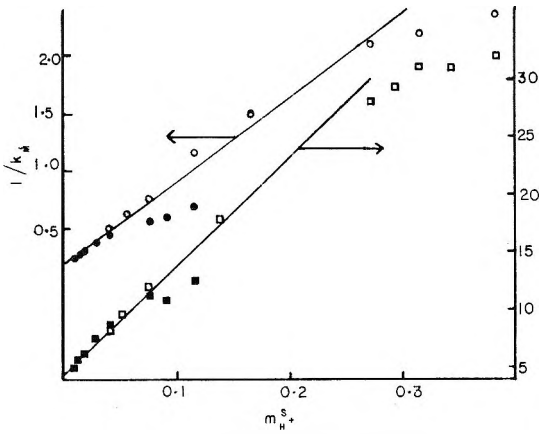


Figure 6. Estimation of rate and equilibrium constants for reactions in micelles of NaLS. Solid points in 0.001 M HCl, open in 0.005 M HCl: **1a**, ●, ○; **1b**, ■, □.

The unreactive cation (**3**) should bind more strongly than nonionic substrate to the anionic micelle, but our binding constant, k_M, is for the substrate. However, ca. 90% of the substrate should be micellar bound at surfactant concentrations above those corresponding to the rate maxima (Figure 4).

Under these conditions essentially all the reaction occurs in the micelle and eq 9 can be approximated by eq 10:

$$k_\psi = k_M m^s_{H^+} \tag{10}$$

The values of $k_\psi/m^s_{H^+}$ approach those of k_M as the surfactant concentration increases (Table VI), suggesting that our values of k_M are not particularly sensitive to the value of the binding constant, K_M. An additional problem which we have already noted is that our treatment is least satisfactory for low surfactant concentrations because eq 7–9 involve the term [D] − cmc which is most subject to error at low surfactant concentrations.

Two distinct effects must be considered in explaining the small micellar catalysis of these hydrations. The micelle concentrates hydrogen ions in the small volume of the Stern layer, which increases the rate of attack on the double bond, but also increases the concentration of unreactive cation. This situation is different from the typical situation for bimolecular reactions where the rate maxima arise because of a "dilution" of reagents in the micellar pseudophase[15,17,18,26] with increasing surfactant concentration. In the present situation we have to consider both "dilution" of the reagents and unproductive substrate protonation.

On this hypothesis we should be able to treat reactions in the micellar pseudophase in terms of Scheme I for reaction in aqueous acid, and write:

$$1/k_M = 1/k_H{}^M + m^s_{H^+}/k_H{}^M K_a{}^M \tag{11}$$

(where $k_H{}^M$ is the second-order rate constant in the micelle, corrected for substrate protonation, and $K_a{}^M$ is the acid dissociation constant in the micelle. Both constants are related to the concentration in terms of hydrogen ion per sulfate head group.)

This approach is shown in Figure 6. It fails for low concentrations of NaLS, because of the approximations of our treatment which underestimates the extent of substrate binding at low surfactant concentration. The points for this region deviate from the line, and these plots would be nearer to linearity had we used values of $k_\psi/m^s_{H^+}$ (Table VI) instead

of k_M, i.e., had we assumed total micellar incorporation of the substrate.

From the slopes and intercepts in Figure 6 we calculate for **1a** $k_H^M = 4.8\ s^{-1}$ and $K_a^M = 0.029$ and for **1b** $k_H^M = 0.22\ s^{-1}$ and $K_a^M = 0.048$. There is considerable uncertainty in these constants, but their magnitudes are not unreasonable, and their relation to the corresponding values in water will be discussed later. However, we note that these are true rather than apparent constants, which represent behavior in the micellar pseudophase.

All these observations suggest that the situation should be completely different for the micellar reactions followed at lower acidity. It is impracticable to do this by using very dilute strong acid and the usual approach of using buffers is unsatisfactory because micelles affect buffer equilibria. We therefore used *n*-dodecyl phosphate which micellizes and also forms its own buffer.

Reaction in Micellized Dodecyl Phosphate. Dodecylphosphoric acid is almost insoluble in water at 25 °C, and our aim was to use micelles of the monoanion. Unfortunately, the monosodium salt is also only sparingly soluble, but we were able to use a limited range of concentrations of the monopotassium salt (Table VII). We also tried to use large chain alkanecarboxylic acids in the same way, but although the alkali metal salts are soluble precipitation occurs when carboxylic acid is present. In both systems hydrogen bonding between acid and anion probably causes the low solubility.

The monopotassium salt is an effective catalyst for the hydrations when related to the measured pH of the solutions, which is ca. 7. (The low acidity in the water is understandable because most of the acidic species should be in the micelle.)

We cannot measure the binding constants of our substrate to micelles of potassium dodecyl phosphate, but comparison with binding to micellized NaLS (Table IV) suggests that the bulk of the substrate is bound at the higher surfactant concentrations.

The first-order rate constants decrease at relatively high surfactant concentration (Table VII), and added KCl inhibits the reaction. The rate constants also decrease as the monoanion is partially converted into the dianion, but the solubility increases so that we can follow a wider concentration range and observe a rate maximum.

Although the surfactant is largely monanionic we cannot assume that the head groups in the micelle are monoanionic. If we treat the micelle as a separate phase (i.e., as a pseudophase) we must also consider acid–base equilibria in that phase. Coulombic repulsions between head groups will be reduced if some of the hydrogen phosphate monoanions are converted into undissociated phosphoric acid, with release of an equivalent number of hydroxide ions to the water. This acid–base equilibrium on the micellar surface will be affected by added potassium ions which enter the Stern layer and reduce the coulombic repulsions between anionic head groups and so favor the acid dissociation of phosphate head groups in the micelle.

These qualitative considerations show how potassium ions can reduce the catalysis by promoting dissociation of acidic groups in the Stern layer, although it is difficult to account quantitatively for the effects, because added cations will change the micellar structure. It is also implicitly assumed that the micelles do not contain appreciable amounts of hydrogen ions, in view of the relatively high pH of the water. The solubility behavior of potassium hydrogen dodecyl phosphate in water makes it difficult to study the micellar structure by such physical methods as cmc measurement, but monomeric surfactant at pH 7 should be largely dianionic while that in the micelle will be monoanionic and undissociated acid.

The reactions are slow at pH 7 in the absence of added catalysts. For example, the reaction due to hydrogen ion catalysis would have first-order rate constants of ca. 1.6×10^{-6} and $4.4 \times 10^{-8}\ s^{-1}$ for **1a** and **1b**, respectively, and for reaction in 1 M KCl the first-order rate constants of the water-catalyzed reactions are ca. 8×10^{-7} and $2 \times 10^{-7}\ s^{-1}$ for **1a** and **1b**, respectively.[6] Therefore the reactions in the presence of micelles of potassium hydrogen *n*-dodecyl phosphate are faster than those in the aqueous pseudophase by factors of approximately 10^3. Our initial rate constants in unbuffered water at pH 5.7 and in low concentrations of the surfactant (Table VII) are consistent with this estimate.

Table VII. Catalysis by Potassium Dodecyl Phosphate[a]

10^3[surfactant], M	KCl, M	Substrate 1a	Substrate 1b
		~2	
0.5		~4	
1.0		~6	
7.0		(62.3)	
8.0		(66.1)	
9.0		(70.0)	
10.0		(72.4)	
20.0		(66.9)	
50.0		252.0 (49.9)	8.99
50.0	0.025	133.0	4.83
50.0	0.05	115.0	4.09
50.0	0.10	96.7	3.59
70.0		192.0	6.72
70.0	0.025	108.0	3.84
70.0	0.050	96.6	3.65
70.0	0.10	87.7	3.48
100		158.0	5.27
100	0.025	97.4	3.10
100	0.050	91.8	2.83
100	0.10	87.2	2.78

[a] Values of $10^5 k_\psi$, s^{-1} at 25.0 °C with n-$C_{12}H_{25}OPO_3HK$. The values in parentheses are for comicelles of 70% monoanion and 30% dianion.

Although we could not reach the optimum concentration of micellized monoanionic dodecyl phosphate (Table VII), the first-order rate constants in 0.05 M surfactant are approximately the same as those estimated for pH 3.5–4 in water. The pH of a solution of a monoanionic monoalkyl phosphate in water is ca. 4; e.g., for *n*-butyl phosphate $pK_1 = 1.8$ and $pK_2 = 6.84$,[33] so that the first-order rate constants in micellized dodecyl phosphate are, perhaps fortuitously, almost the same as those estimated for reaction in water at the pH of aqueous monoalkyl phosphate monoanion.

These results show that the micelle allows a marked difference in acidity to exist at its surface over that in bulk solvent. This situation is well understood in polyelectrolyte chemistry and is probably also important in catalysis by general acids at active sites of enzymes.

Kinetic Form of the Reaction in NaLS. The second-order rate constants in the micelle, k_M, s^{-1}, cannot be compared directly with those in water, k_{H^+} ($M^{-1}\ s^{-1}$). One approach is to express the concentration of hydrogen ions in water as a mole fraction and to compare k_M with $k_{H^+}/55.5$. Another is to express the second-order rate constants in the micelle in terms of the molarity of hydrogen ions in the micellar pseudophase. Reaction occurs in the Stern layer of the micelle and to follow this second approach we estimate the volume of this layer in 1 mol of micellized surfactant. Micelles have a density of approximately 1, and Romsted has estimated that the volume of the Stern layer of a micelle of NaLS is 51% of the total volume of the micelle.[18] These estimated values and the molecular weight of NaLS give a volume of Stern layer of 0.149 L mol^{-1}. Therefore the concentration of hydrogen ions in the Stern layer is $6.71 m^s_{H^+}$ M, and the corresponding second-order rate constant is $0.149\ k_M$, $M^{-1}\ s^{-1}$.

Table VIII. Comparison of Rate and Equilibrium Constants in the Micelle and in Water[a]

	H_2O		NaLS	
Substrate	k_H	K_a	k_H^M	K_a^M
1a	16.0	0.24	0.7 (4.8)	0.20 (0.029)
1b	0.44	0.13	0.033 (0.22)	0.32 (0.048)

[a] Calculated in terms of molarities; the values in parentheses are calculated in terms of mole fractions.

We have converted our values of k_M and $m^s_{H^+}$ for reaction in micelles of NaLS to a molar scale, and the results for **1b** are shown as the broken line in Figure 5. The pattern is similar for reaction of **1a**. The important point is that the second-order rate constants for reaction in the Stern layer are smaller than in water. They are also smaller in the Stern layer if comparison is based on values of $m^s_{H^+}$ and the mole fraction of hydrogen ions in water. Similar differences in rate constants were found for the hydrogen ion catalyzed hydrolysis of *p*-nitrobenzaldehyde diethyl acetal in micellized NaLS.[15]

The overall rate constants, k_M, depend upon the extent of unproductive substrate protonation, which gives **3**.

It is therefore necessary to compare the corrected rate, k_H^M, and equilibrium constant, K_A^M, for the reactions in the micelle, obtained using eq 11 and Figure 6, with those of k_H and K_a in water. This is done by correcting the constants for reactions in the micelle following Romsted's approach.[18] The comparisons are shown in Table VIII.

The acid dissociation constants are similar in the micelle and in water, and although it may not be realistic to compare concentrations in terms of these arbitrary volume elements the results suggest that micellar effects on protonation depend largely on the concentration of the bases **1a,b** and the hydrogen ions in the Stern layer. The corrected second-order rate constants, k_M^H, are considerably lower in the micelle than in water.

These decreases in rate constants probably arise in part from the Stern layer of the micelle having a lower polarity than water;[8,34] i.e., they can be ascribed to a microsolvent effect. Another possibility is that micellized laurylsulfuric acid is not strong and that it is a poorer catalyst than the solvated hydrogen ion, although this is not consistent with the effective catalysis by dodecyl hydrogen phosphate, or the evidence for substrate protonation. Addition of water to the first formed intermediate (**2**) may become slow in the Stern layer, but this too seems improbable because the micellar surface is hydrophilic and water addition is slow only in solvents of low water content.[5] Our results are not in accord with the plausible suggestion that the reactivity of hydrogen ions at a micellar surface is increased by partial or complete dehydration.

The decrease in the second-order rate constants in going from water to the micelle means that the micelle stabilizes the rectants more than the transition state relative to water. Extensive reactant incorporation in the micelles requires reactants to be more stable there than in the water, based on unit concentration, and this unfavorable initial state effect may overcome any favorable interactions between the micelle and the transition state.

Micellar Catalysis of Bimolecular Reactions. The high rates of many intramolecular reactions, relative to similar intermolecular reactions, are often explained in terms of favorable entropy effects.[35] Similar explanations are often applied to enzymic reactions, and they can be applied to micellar catalysis. However, the description which we use depends to some extent on our choice of standard state Bimolecular reactions in the Stern layer of micelles are often no faster and may even be slower than in water,[15-18] once allowance is made for reactant concentrations in the Stern layer, and this concentration can be considered as an entropy effect. These general principles also apply to protonation equilibria; for example, we require ca. 1 M HCl to convert these dihydropyridines into their unreactive conjugate acids (**3**), but there is extensive protonation in micelles of NaLS even when the total hydrogen ion concentration is only 10^{-3} M.

Although the micelle does not provide a favorable submicroscopic environment for these, and other, reactions of hydrogen ions there are many examples of favorable environmental micellar effects, as in unimolecular micellar catalyzed reactions.[11]

Experimental Section

Materials. The dihydropyridines were prepared by reduction of the pyridinium salts and were purified by crystallization from $EtOH-H_2O$[4a] or by dissolving the product in CH_2Cl_2, separating the impurities in the insoluble red layer, and then precipitating the product with petroleum ether (bp 30–60 °C). The melting points were: **1b**, 113.5–114.5 °C (lit.[4a] 110–114 °); **1b**, 63–67 °C (lit.[4a] 61–67 °C). The λ_{max}(EtOH) of 358 and 371 nm for **1a** and **1b**, respectively, agreed with literature values. The surfactants were prepared and purified by standard methods.[26,36]

Kinetics. The reactions at 25.0 °C were followed spectrophotometrically at 359 nm for **1a** and 377 nm for **1b**. The first-order rate constants, k_Ψ, are in s^{-1}. Solutions were made up using redistilled deionized water, and for the buffer-catalyzed reactions the ionic strength was maintained with NaCl. For reactions in NaLS and HCl freshly made up solutions were always used to avoid hydrolysis of the surfactant.[37] The substrate concentrations were 6.7×10^{-5} M.

Incorporation Experiments. Solubility Method. The solubilities were determined in deoxygenated water and in a range of surfactant solutions. The solutions were saturated and left at 25.0 °C, and the relative solubilities were determined spectrophotometrically.

From eq 4 we obtain:

$$\alpha = \frac{C_0K([D_T] - \text{cmc})}{1 + C_0K} \tag{12}$$

where α is the amount of substrate taken up by the micelles and C_0 is the solubility in water. The maximum total surfactant concentration $[D_T]$ was 0.1 M for NaLS and 0.02 M for CTABr, and the relative solubility of **1b** was determined from the absorbance at 377 nm, after sufficient dilution to break up the micelles.

Spectrophotometry. This method requires that the substrate has different absorbances in water and in the micelle, and that Beer's law is obeyed. For the equilibrium between substrate in water (S) and in the micelle (S_M) eq 4 gives:

$$K = f/\{(1 - f)([D] - \text{cmc}) - f(1 - f)[S_T]\} \tag{13}$$

where $f = [S_M]/[S_T]$. Under our conditions $[D] - \text{cmc} \gg f[S_T]$, so that

$$K = f/(1 - f)([D] - \text{cmc}) \tag{14}$$

and assuming that Beer's law is obeyed:

$$f = (A - A_{H_2O})/(A_M - A_{H_2O})$$

where A is the observed absorbance, A_{H_2O} is that in water, and A_M is that when all the substrate is incorporated into the micelle.

The wavelengths were: for **1a**, 358 nm in CTABr, 390 nm in NaLS; and for **1b**, 395 nm in CTABr, 395 and 405 nm in NaLS. Maximum [NaLS] was 0.3 M and the maximum [CTABr] was 0.09 M. A plot of $f/(1 - f)$ vs. [D] was linear and the intercept gave the cmc. The concentration of the dihydropyridines was 6.7×10^{-5} M.

The cmc calculated using eq 14 are: with **1a**, CTABr, 7×10^{-4} M, NaLS, 2×10^{-3} M; and with **1b**, CTABr, 7×10^{-4} M, NaLS, 3×10^{-3} M.

Registry No.—**1a**, 952-92-1; **1b**, 19350-64-2; NaLS, 151-21-3; potassium dodecyl phosphate, 65045-37-6; CTABr, 54-09-0.

References and Notes

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(3) On leave from the Faculty of Sciences, University of Chile, Santiago,

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Isoxazoles. 4. Hydrolysis of Sulfonamide Isoxazole Derivatives in Concentrated Sulfuric Acid Solutions. A New Treatment of the Medium Effects on Protonation Equilibria and Reaction Rates

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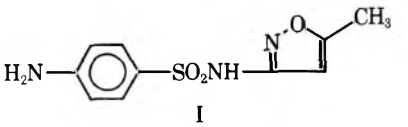
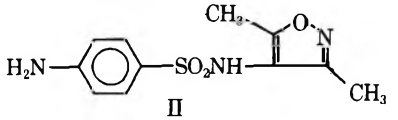
The acid hydrolysis of N^1-(5-methyl-3-isoxazolyl)sulfanilamide (I) and N^1-(3,5-dimethyl-4-isoxazolyl)sulfanilamide (II) to sulfanilic acid and their respective amino isoxazole derivatives in concentrated solutions of sulfuric acid was studied. An approach to correlate the medium effects on equilibria and reaction rates was made by introduction of a function, which represents the protonating ability of sulfuric acid solutions. The medium effects study has shown that I undergoes hydrolysis through protonation on the heterocyclic N atom, while II needs to be protonated on the sulfonamide group. The lower reactivity of II can be explained as mainly due to a more weakly basic site of protonation and a lower log (f_S/f_+) response toward changes in acidity.

We have previously reported[1–3] that the acid-catalyzed degradation of N^1-(3,4-dimethyl-5-isoxazolyl)sulfanilamide (III) in concentrated mineral acids occurs through two parallel pathways, one is the sulfonamide moiety hydrolysis and the other the isoxazole ring rupture. Both pathways can be associated with a preprotonation on the isoxazole N atom.

We here report a kinetic study of the hydrolysis of I and II in concentrated sulfuric acid solutions. Since Zuker and Hammett works[4] the study of medium effects on reaction rates in concentrated solutions of mineral acids has been focused by a method involving the correlation of rates with acidity functions[5,6] ($H_x = -\log (a_{H^+} f_X / f_{XH^+})$) or related magnitudes.[7] Such functions are built up from the measurements of the protonation equilibria of structurally related indicators and they involve the assumption that the ratio of activity coefficients of the acidic and basic forms of the indicators are the same within each set; however, this is not strictly true and few differences are found even within the set.



I



II

On the other hand, some efforts have been made in order to rationalize medium effects on reaction rates correlating them with representative magnitudes of some properties of the acid solutions, namely water activity[8] (a_{H_2O}) and more recently sulfuric acid activity[9,10] ($a_{H_2SO_4}$). However, there is no representative variable of some acid solution properties, with the exception of acidity functions, which can be applied in a wide concentration range. In this paper an alternative treatment is proposed.

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Scheme I

$$S + H^+ \rightleftarrows SH^+ \quad (a)$$

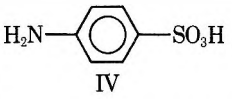
$$SH^+ \rightleftarrows \ddagger \rightarrow \text{products}$$

or

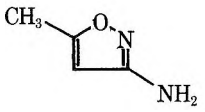
$$SH^+ + H_2O \rightleftarrows \ddagger \rightarrow \text{products} \quad (b)$$

Results and Discussion

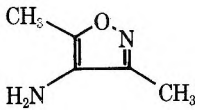
Under our reaction conditions I gives IV and V whereas II leads to IV and VI, both in quantitative yields. Both reactions



IV



V



VI

show first-order kinetics and are acid catalyzed. Consequently, the usual mechanism depicted in **Scheme I** can be used to explain the results.

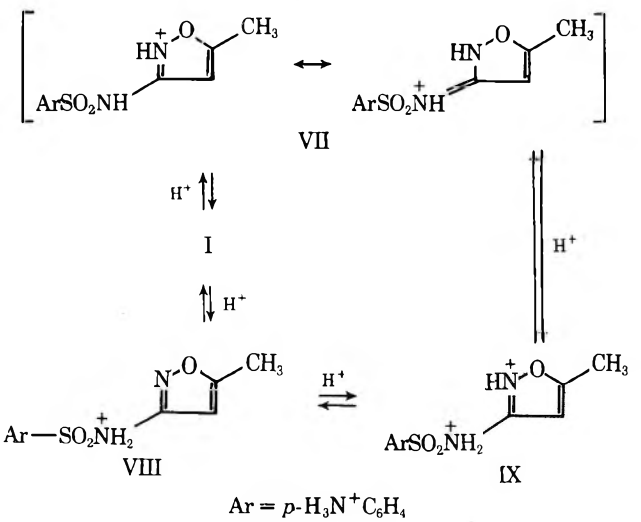
a. Protonation equilibria. The substrates under study carry three basic sites: one is the aromatic amine, which is almost completely protonated under our reaction conditions; the second is the nitrogen of the isoxazole ring, which in the case of I has a pK_a of −3.52 (l.f.e.r. method)[1] (the NMR study of II suggests an analogous behavior); and the third is the sulfonamide group which in the case of neutral alkyl[11] and aryl[12] sulfonamides have pK_a values around −5.5 and −6.6 and are protonated on nitrogen; however, its basicity in I and II is expected to be decreased by the electronic effects of the ammonium and the heterocyclic ring. In fact, UV and NMR analysis of II in sulfuric acid 96% shows no experimentally detectable changes.

The protonation equilibria involved can be described by Schemes II and III, I, VII, II, and X being the predominant species.

Species VII, VIII, and IX for I and X, XI, and XII for II can in principle be responsable for the acid catalysis observed. The following study of the medium influence on the reaction rates will permit the description of the major reaction pathways for each substrate.

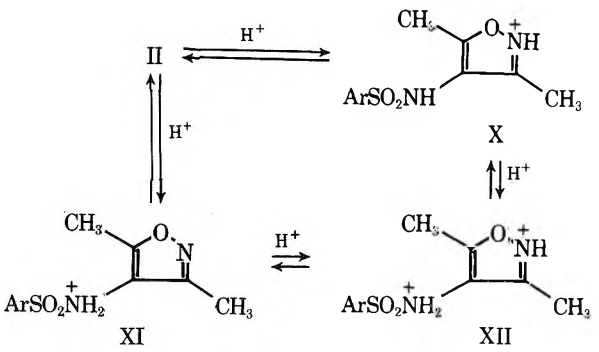
b. An Approach to Correlate the Medium Effects on Equilibria and Reaction Rates. The protonating ability toward different kinds of bases is the chief property of aqueous

Scheme II



Ar = p-$H_3N^+C_6H_4$

Scheme III



Ar = p-$H_3N^+C_6H_4$

solutions of sulfuric acid. This property is mainly due to hydrogen ions with different degrees of solvation. This mixture manifests changes in its protonating ability upon changing the acid concentrations which are much greater than what could be attributed merely to the changes in hydrogen ion concentration. The major species in moderately concentrated solutions are $H(H_2O)_n^+$, HSO_4^-, H_2O, and in a minor degree SO_4^{2-}, while at higher acid concentrations of H_2SO_4, $H_3SO_4^+$, and $H_2S_2O_7$ become important.[6,10]

Several theoretical approaches were made in order to understand the concentration dependence of the acidity of aqueous strong acids considering the chemical hydration of hydrogen ion.[13-17] Such approaches have been widely used to account for the fact that the increasing protonating ability of the medium is due largely to the decreasing water activity. However, an unambiguous definition of their acidity is not available owing to its complexity and because individual ion activities cannot be measured experimentally. Reaction 1 is considered the main one in moderately concentrated solutions

$$H_2SO_4 + nH_2O \rightleftarrows HSO_4^- + H(H_2O)_n^+ \quad (1)$$

$$a_{H(H_2O)_n^+} = Ka^n{}_{H_2O} a_{H_2SO_4}/a_{HSO_4^-} \quad (2)$$

According to eq 2, it can be seen that there is a direct contribution from $a_{H_2SO_4}$ to $a_{H(H_2O)_n^+}$, while a_{H_2O} raised to an adequate power affords a more complex functional relationship with $a_{H(H_2O)_n^+}$ since n is also a function of the medium composition; however, as it was mentioned above, it has been largely recognized that the acidity and water activity are inversely related in concentrated mineral acid solutions. Similar considerations can be applied to other equilibria where solvated hydrogen ions are generated.

Based on the following premises, (a) the acidity of aqueous sulfuric acid solutions lies essentially on solvated hydrogen ions, (b) due to the complexity of the system it is not possible to give an explicit definition of the acidity as a function of ionic specie activities, and (c) a_{H_2O} and $a_{H_2SO_4}$ are both a measure of the "free" specie concentrations in the solution[16] (a representative function of the protonating ability of the solution (a_S) is defined on the grounds of the "nonionic portion" of the system).

The "molar activity fractions" of sulfuric acid ($A_{H_2SO_4}$) and water (A_{H_2O}) can be calculated as in eq 3.

$$A_{H_2SO_4} = a_{H_2SO_4}/(a_{H_2SO_4} + a_{H_2O}) \text{ and } A_{H_2O} = a_{H_2O}/(a_{H_2SO_4} + a_{H_2O}) \quad (3)$$

The reference states used are $a_{H_2O} = 1$ for pure water ($N_{H_2O} = 1$) and $a_{H_2SO_4} = 1$ for pure sulfuric acid ($N_{H_2SO_4} = 1$), where N represents the respective stoichiometric molar fractions.

The protonating ability a_S is defined as directly proportional to $A_{H_2SO_4}$ and inversely proportional to A_{H_2O}, eq 4,

Table I. Reaction Rates at Various Sulfuric Acid Concentrations

H_2SO_4 (wt %)	log a_S[c]	I[a] log k_ψ	I[a] log ($[SH^+]^d/[S]$)	I[a] log ($k_\psi[S]_{st}/[SH^+]$)	II[b] log k_ψ
34.72	−8.505	−4.618	−1.627	−2.981	−4.971
46.52	−6.747	−3.745	−0.670	−2.990	−4.506
58.90	−4.598	−3.146	0.499	−3.026	−4.058
62.98	−3.777	−3.088	0.945	−3.041	
67.87	−2.698	−3.049	1.532	−3.036	
72.04	−1.689	−3.113	2.081	−3.107	−3.390
78.77	+0.0236	−3.142	3.013	−3.142	−2.917

[a] Reaction at 100 °C. [b] Reaction at 135 °C. [c] Log a_S values were obtained by interpolation of log a_S vs. (wt %).[2] [d] Calculated from log ($[SH^+]/[S]$) = 0.544 log a_S + 3.00.

Table II. Acidity Functions Against Log a_S in Aqueous Sulfuric Acid[a]

	$-H_0$[b]	$-H'''$[b]	$-H_i$[b]	$-H_R$[c]	$-H_A$[b]
Slope	0.595	0.738	0.784	1.175	0.328
Intercept	7.09	9.11	9.50	13.99	4.50
δ Points	0.057	0.113	0.040	0.122	0.045
δ Slope	0.003	0.006	0.004	0.012	0.003
r	0.9997	0.9994	0.9997	0.9993	0.9994
Range, wt %	10–90	10–90	10–70[d]	10–70[e]	20–90[d]
No. of points	17	17	13	13	15

[a] Values of log a_S were calculated from a_{H_2O} and $a_{H_2SO_4}$ data reported by M. Liler;[6] the latter were only available between 40 and 100 wt %; therefore, we have widened the data up to 10 wt % in the same way he described it (by Gibbs–Duhem equation). The log a_S values obtained are: −11.47, −10.88, −10.19, −9.745, −9.128, and −8.464 for 10, 15, 20, 25, 30, and 35 wt %, respectively. [b] Acidity function values were taken from ref 22. [c] Values from ref 6. [d] There are no data at concentrations higher than 70 wt % for H_i and lower than 16 wt % for H_A. [e] Deviations of linearity were observed at concentrations higher than 70 wt %.

$$a_S = A_{H_2SO_4}/A_{H_2O} \quad (4)$$

and taking logarithms

$$\log a_S = \log (A_{H_2SO_4}/A_{H_2O}) = \log (a_{H_2SO_4}/a_{H_2O}) \quad (5)$$

A plot (not shown) of log a_S against $N_{H_2SO_4}$ shows a steady increase with the acid concentration. Below $N_{H_2SO_4}$ = 0.35 the increase is mainly due to $A_{H_2SO_4}$, whereas above this point A_{H_2O} is the major contributor.

The fact that a_S gives a satisfactory account of the protonating ability of concentrated aqueous sulfuric acid is demonstrated by the linear relationships found between log a_S and acidity functions (Figure 1, Table II) or the logarithms of the ionization ratios of weak bases, within a wide range of acidity.[18] The definition of a_S (eq 4) implies that all hydrogen ions are supplied by sulfuric acid; therefore, in very diluted solutions where the autoprotolysis of water generates significant quantites of protons, eq 4 is no longer valid. However, in the concentration range used in the present paper hydrogen ions supplied by water are only a very small fraction of total hydrogen ions and consequently can be neglected. Therefore, log a_S will be used here as a variable to discuss the medium effects on protonation equilibria and reaction rates. The usual equations[5-7] for the phenomenological and theoretical interpretation of the equilibrium and kinetic processes described in Scheme I can be expressed as linear functions of log a_S (eq 6–9).

$$\log ([SH^-]/[S]) = pK_{SH^+} + \log (a_{H^+}f_S/f_{SH^+}) = G_e \log a_S + D_e \quad (6)$$

$$\log k_\psi - \log ([SH^+]/[S]_{st}) = \log k + \log (f_{SH^+}/f_\ddagger) = G_r \log a_S + D_r \quad (7)$$

$$\log k_\psi + \log ([SH^+]/[S]) - \log (SH^+/S_{st}) = \log (ka_{H^+}f_S/K_{SH^+}f_\ddagger) = (G_e + G_r) \log a_S + (D_e + D_r) \quad (8)$$

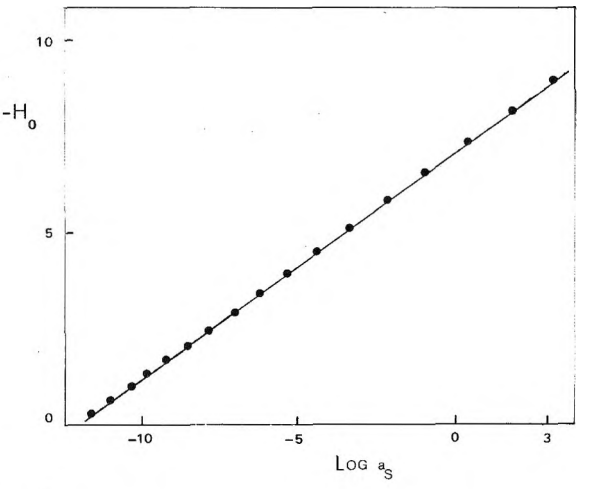


Figure 1.

When [S] ≫ [SH^+] the left member of eq 8 reduces to log k_ψ, then

$$\log k_\psi = \log (ka_{H^+}f_S/K_{SH^+}f_\ddagger) = G_t \log a_S + D_t \quad (9)$$

Equation 6 states that there is a linear relationship between log ($a_{H^+}f_S/f_{SH^+}$) and log a_S, with a proportionality constant G_e, which is a measure of the sensitivity of the activity coefficient ratio (f_S/f_{SH^+}) toward changes in protonating ability of the solution and allows the characterization of step a in Scheme I. In the same way, eq 7 describes the relationship between log ($f_{SH^+}/f_\ddagger$) and log a_S; therefore, the proportionality constant G_r is a measure of the sensitivity of this ratio to the changes in the medium giving information about step b (Scheme I). Finally, eq 9 can be applied when only a small fraction of the total substrate is protonated, thus $G_t = G_e + G_r$ measures the overall medium effects on steps a and b.

c. Medium Effect Correlations. For the protonation

Table III. Activation and Medium Effect Parameters

Compd	G_e	D_e	G_r	D_r	G_t	D_t	E_a, kcal/mol[a]	$\Delta S^{\ddagger}$, eu[b]
I	0.544	3.00	−0.019	−3.12	0.525	−0.12	29.6	4.6
II					0.236	−2.95	28.4	−6.9

[a] Calculated with values of Table IV by Arrhenius plots. [b] Calculated according to ref 23.

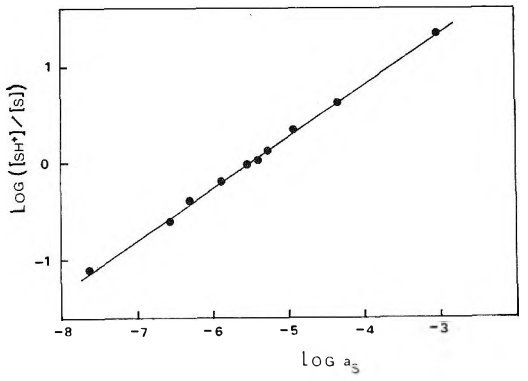


Figure 2.

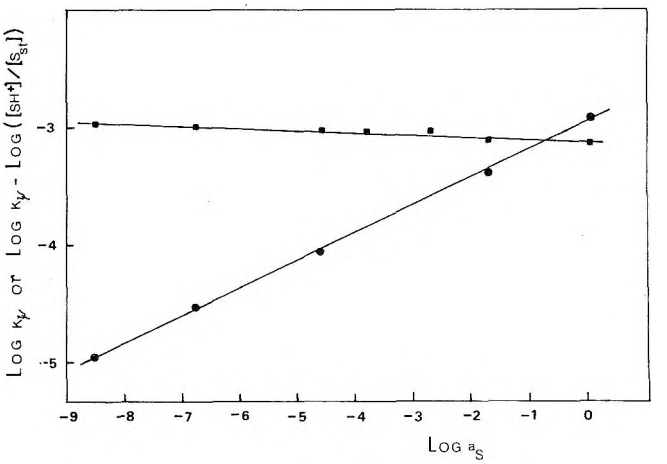


Figure 3.

equilibrium I ⇄ VII (Scheme II) the logarithms of the ionization ratios, from ref 1, were correlated by eq 6 (Figure 2). From the regression line, G_e and D_e parameters were calculated and are quoted in Table III.

The reaction rates of I increase up to ca. 68% sulfuric acid and then level off. The leveling off region coincides with the almost complete converaion of I into VII, thus, the data can be adequately correlated by eq 7. G_r obtained has a value near zero (−0.019) (Figure 3, Table III) indicating a similar response of f_{SH^+} and $f_{\pm}$ to medium changes; since f_{SH^+} pertains to compound VII, the transition state of the reaction must be very closely related to it and we can infer that the decomposition of VII is a monomolecular step. Besides, the dependence of the rate on acidity allows the elimination of VIII and IX as possible intermediates.

The rate of II increases with the acid concentration in the whole range studied (34.7–78.8%). Figure 3 shows that the data are nicely correlated with log a_S through eq 9 which indicates that the reactive specie is only a very small fraction of the total substrate, thus XI and XII appear the most likely intermediates. The linear relationship found also indicates that both species react at similar rates since XI prevails at low and XII at high acidity. Since G_t expresses the overall medium dependence of the reaction and equilibrium parameters for the protonation of II and X (Scheme III) are unknown, the mechanism of step b cannot be elucidated.

Table III also includes activation parameters for both reactions. By comparison of their activation energy values, it can be seen that they are quite similar, and this is also true for what has been reported for the hydrolysis of III in hydrochloric acid[19] (E_a = 25.4 kcal/mol).

It is clear now that the lower sensitivity to acid-catalyzed hydrolysis of II compared with I (and with III) can be explained as mainly due to differences in the mechanism of the reaction of I and II. The impossibility of resonance interaction between the protonated nitrogen of X and the amide nitrogen renders this specie inefficient to form the transition state for the hydrolysis of II, leaving XI and XII as alternatives. The high acidity of the latter two species and the weaker response of log ($f_S/f_{\pm}$) toward changes in acidity for II as compared with I (G_t of I > G_t of II) make compound II less reactive than I.

Values of $\Delta S^{\ddagger}$ for I and II are 4.3 and −6.9 eu, respectively, but at the acid concentration used in the activation parameter determinations, I is practically completely in its protonated form, then $k_\psi \simeq k$ and $\Delta S^{\ddagger}$ has a maximum value for this reaction, whereas II exists mainly in its unprotonated form, therefore $k_\psi < k$ and consequently the $\Delta S^{\ddagger}$ obtained must increase when reaction conditions reach those of I. These values are consistent with those typically reported for hydrolysis reactions that proceed by the A-1 mechanism,[20] whereas A-2 hydrolysis has considerable more negative values.[20]

Experimental Section

Materials and Apparatus. Sulfuric acid analytical reagent grade Carlo Erba G.R. was used; H_3PO_4, NaH_2PO_4, and NaOH were all analytical reagent grade; I was a commercial NF product purified according to ref 1; and II was prepared in the same way as it has been previously reported.[21]

Spectrophotometric readings and UV absorption spectra were taken in a Beckman DB-G spectrophotometer. NMR spectra were recorded on a Varian T-60, and chemical shifts are quoted in ppm downfield from tetramethylsilane.

Reactions. The hydrolysis reactions were carried out in sealed ampules of 5-mL capacity containing approximately 3 mL of solution which was prepared quantitatively by transferring 0.250 g of I or II to a volumetric flask of 100 mL capacity and adding the appropriate sulfuric acid solution until the volume was completed. The same procedure was followed with each acid solution.

The ampules were immersed in a constant temperature oil bath at 100.0 ± 0.2 °C for I and at 135.0 ± 0.2 °C for II; they were then withdrawn at appropriate intervals and quickly cooled in an ice bath for analysis at a later time.

Identification of Hydrolysis Products. Both I and II give a unique product with aromatic amino group, which was identified by TLC as IV using the procedure described earlier ref 2. V and VI, products from I and II, respectively, were both separated from reaction mixtures previously alkalinized with 20% NaOH by ether extractions. The ethereal extracts were dried (Na_2SO_4) and evaporation of the solvent yielded the respective amino derivatives, which were purified and identified by its mp and mixture mp with those of known pure samples.

Quantitative Determinations and Kinetic Study. One milliliter of each one of the reaction mixtures was put into volumetric flasks of 50-mL capacity and neutralized by addition of an adequate volume of 1 N NaOH solution, and the flask was filled to the mark with 0.1 M phosphate buffer of pH 2.3. Two milliliters of these solutions was again diluted to 10 mL with the same buffer solution.

The relative concentrations of the reactants and products were

Table IV. Reaction Rates at Several Temperatures in Sulfuric Acid (70 wt %)

I		II	
Temp, °C	$k_\psi \times 10^4$, s^{-1}	Temp, °C	$k_\psi \times 10^4$, s^{-1}
79.0	0.802	115.0	0.751
88.5	2.32	124.0	1.77
99.0	6.89	134.0	3.84
109.0	21.6	144.2	10.2

determined by UV spectrophotometric analysis using for both I and II reaction light of 268 nm as the analytical wavelength; this one corresponds to a maximum in the absorption spectra for both reactants. Each kinetic experience was carried out using 10 ampules, which were processed as described above, and their absorbances were regarded. From plots of ln $(A_t - A_\infty/A_0 - A_\infty)$ vs. time (sec) were obtained straight lines as habitually are found in first-order kinetics. The slopes obtained from regression lines were considered as pseudo-first-order constants k_ψ.

Medium and Temperature Effects on Reaction Rates. Tables I and IV report the results obtained when I and II hydrolyses were carried out at several different acid concentrations and at several temperatures, respectively.

NMR in Sulfuric Acid. For II, methyl signals change from 1.98 and 2.05 in H_2SO_4 at 32 wt % to 2.37 and 2.50 in H_2SO_4 at 70 wt %.

Registry No.—I, 723-46-6; II, 64682-95-7; sulfuric acid, 7664-93-9.

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Nitrogen-15 Magnetic Resonance Spectroscopy. Natural-Abundance Spectra of Secondary Amides[1]

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The ^{15}N chemical shifts of 17 *N*-alkyl- and *N*-arylethanamides have been determined at the natural-abundance level of ^{15}N using Fourier-transform methods. The shift effects produced by several substituent groups are compared with corresponding substituent effects in amino acids, amino acid derivatives, and dipeptides. The results show that *N*-alkylethanamides are not especially good models for predicting ^{15}N shifts in dipeptides. The sensitivity of the ^{15}N shift of *N*-arylethanamides to electronic effects, as reflected in the Hammett ρ constant, is less than that of the ^{15}N shift in para-substituted benzenamines.

Peptides contain many fewer nitrogen atoms than carbon or hydrogen atoms and it might be expected that ^{15}N NMR spectroscopy would be useful for structural studies of peptides in solution. The well-known difficulties in observing the NMR signals of ^{15}N, with its low natural abundance and often long relaxation times, have been partially overcome by the use of large samples, high magnetic-field strengths, quadrature detection, and Fourier-transform techniques.

Assignments of signals in the ^{15}N spectra of peptides have been aided by chemical shifts of model systems.[2-6] Further help may possibly be expected from secondary amides of the type $CH_3CONHC_\alpha H_2R$, which could provide a measure of the substituent effect of R on the chemical shift of peptide nitrogen. A number of ^{14}N shifts of secondary amides have been determined,[7-9] but the generally broad signals obtained with this nucleus can introduce shift uncertainties. The ^{15}N spectra of *N*-methylethanamide[10] and *N*-methylmethanamide[11] have been reported, but there appears to be no other systematic study of substituent effects in secondary amides. As a result, we have determined the ^{15}N chemical shifts at the natural-abundance level of a series of secondary amides with R groups generally chosen to correspond structurally to peptide groupings of naturally occurring amino acids.

The sensitivity of ^{15}N NMR shifts to electronic factors, as reflected in Hammett ρ constants, has been determined for several para-substituted *N*-phenylethanamides and the results have been compared with similar studies on para-substituted benzenamines.[12]

Experimental Section

Primary aliphatic and aromatic amines were obtained commercially and acetylated by standard procedures. The physical properties of the products were consistent with reported values.[13]

Proton-noise decoupled ^{15}N spectra were recorded at the natural-abundance level with a Bruker WH-180 NMR spectrometer operating at 18.25 MHz. Measurements were made with 15–22-mL samples in 25-mm o.d. tubes, using quadrature detection and Fourier-transform

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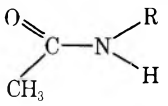
Table I. ^{15}N Chemical Shifts in *N*-Alkyl- and *N*-Arylethanamides[a]



R	Registry no.	$\delta_{^{15}N}$, ppm
H	60-35-5	270.6[b]
CH_3	79-16-3	268.2
CH_3CH_2	625-50-3	249.2
$(CH_3)_2CH$	1118-69-0	237.9
$(CH_3)_3C$	762-84-5	235.6
$CH_3CH_2CH_2$	5331-48-6	254.2
$(CH_3)_2CHCH_2$	1540-94-9	256.2
$CH_3CH_2CH_2CH_2$	1119-49-9	254.3
$CH_3CH_2CH_2CH_2CH_2$	2524-60-9	254.0
$CH_3CH_2(CH_3)CH$	1189-05-5	240.3
$CH_3CH_2(CH_3)_2C$	15501-38-9	239.3
$C_6H_5CH_2CH_2$	877-95-2	256.1
p-$CH_3OC_6H_4$	51-66-1	242.9[c]
p-$CH_3C_6H_4$	103-89-9	241.6[c]
C_6H_5	103-84-4	240.8[c]
p-ClC_6H_4	539-03-7	242.0[c]
p-$NO_2C_6H_4$		

[a] Upfield from external $D^{15}NO_3$. Chemical shifts measured with 36–44 mol % solutions in chloroform. [b] 4 mol % solution in chloroform. [c] 10–16 mol % solutions in dimethyl sulfoxide.

mode operation. Each spectrum was obtained using a repetition rate of 4.5 s, an acquisition time of 0.819 s, and a total accumulation of 2000 transients. The pulse angle was 20° (20-μs pulse width), and 4 W of proton decoupling power was used. The chemical shifts are reported in parts per million upfield from external 1.0 M $H^{15}NO_3$ in D_2O contained in a coaxial 5-mm o.d. tube.

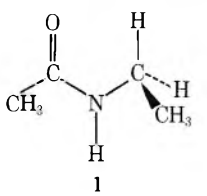
Results and Discussion

The ^{15}N chemical shifts for *N*-alkylethanamides are given in Table I. The shift for ethanamide, also included here, was measured at a lower concentration than the secondary amides. The ^{14}N chemical shift of ethanamide has already been reported, but with respect to a different reference.[7]

The results in Table I show that ^{15}N shift differences for secondary amides are quite large and are susceptible to the same kinds of electronic and steric influences as ^{13}C shifts[14] and ^{15}N shifts in aliphatic amines.[15] Thus, there are deshielding α and β effects, as well as a shielding, presumably sterically induced, γ effect. The δ and ε effects appear to be almost negligible.

The shifts for secondary amides in Table I are downfield of the shift for ethanamides. As noted previously,[7] N-methylation of ethanamides causes only a slight downfield shift in the nitrogen chemical shift (2.4 ppm). However, a much larger shift of 19.0 ppm is observed in going from the *N*-methyl to the *N*-ethyl derivative. The β effect of a methyl substituent on the ^{15}N shift of a primary amine is approximately the same magnitude (18.2 ppm).[15]

In contrast to the results for primary amines, the β effects in secondary amides diminish substantially as the degree of substitution of the *N*-methyl group increases. In the change from *N*-ethyl to *N*-isopropyl, a downfield shift for the ^{15}N nucleus of 11.3 ppm is observed. Substitution of a third methyl group on the *N*-methyl carbon moves the ^{15}N shift downfield



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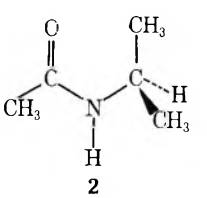

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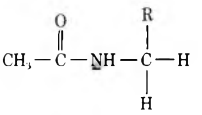
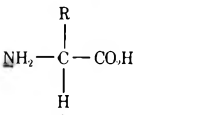
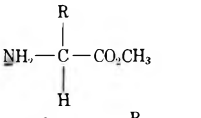
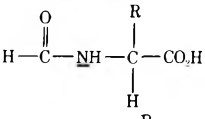
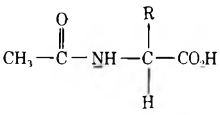
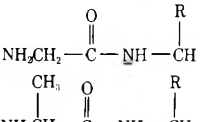
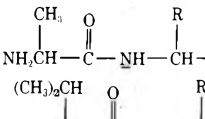
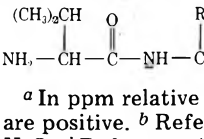
Table II. Substituent Effects on the ^{15}N Shifts of Secondary Amides, Amino Acids and their Derivatives, and Dipeptides[a]

Substituent group (R)	CH_3	$(CH_3)_2CH$	$C_6H_5CH_2$
	19.0	12.0	12.1
	13.0[b]	6.1[b]	9.1[c]
	13.2[d]	8.3[d]	10.4[d]
	15.0[f]	8.0[f]	10.7[f]
	15.0[g]	8.6[g]	11.5[g]
	14.5[e]	8.2[e]	
	14.3[e]	8.2[e]	
	13.2[e]	8.0[e]	

[a] In ppm relative to R = H in all series. Downfield shifts are positive. [b] Reference 3c, in 6 N HCl. [c] Reference 3c, in H_2O. [d] Reference 4, 5–9 M aqueous solution with pH values in the range 0.5–2.0. [e] Reference 5, 0.2 M aqueous solutions in pH range 5.0–6.2. [f] Reference 2, 3–4 M in dimethyl sulfoxide. [g] Reference 2; 1 M in dimethyl sulfoxide.

a further 2.3 ppm. Corresponding β effects derived from comparison of the ^{15}N shifts for *N*-propyl-, *N*-(1-methylpropyl)-, and *N*-(1,1-dimethylpropyl)ethanamides show β effects of 13.9 and 1.0 ppm, in fair agreement with the values above. The dependence of the β effect on the extent of substitution at the *N*-methyl carbon may be the result of steric effects. Thus, for *N*-ethylethanamide, the α-methyl group can avoid steric interactions with the carbonyl group by assuming conformation **1**. As the α hydrogens in **1** are replaced by methyl groups, the contribution of conformers like **2**, where a methyl group is eclipsed by the carbonyl group, are expected to increase and the resulting steric interactions could significantly affect the ^{15}N shifts.

While the signs of the alkyl-substituent shift parameters parallel those observed for ^{13}C spectra, the magnitudes differ considerably; α_N is somewhat smaller than α_C (−9.1 ppm) while β_N is almost twice as large as β_C (−9.40 ppm).[14]

Contrary to reports from earlier ^{14}N studies,[7] the γ effects of methyl groups are upfield (Table I) in accord with ^{13}C spectra.[14] Changing from *N*-ethyl to *N*-propyl makes an upfield shift for the ^{15}N nucleus of 5.0 ppm. The γ effect of a second methyl substituent on the ^{15}N shift (i.e., *N*-(2-methylpropyl)ethanamide) is 2.0-ppm upfield.

The sequence of ^{15}N shifts observed for *N*-propyl-, *N*-butyl-, and *N*-pentylethanamides indicates that the δ and ε effects of methyl substituents on ^{15}N shifts in secondary amides are not experimentally significant (−0.1 and 0.3 ppm, respectively). The effect of substituting a phenyl group on the β carbon of *N*-ethylethanamide is a 6.9-ppm upfield ^{15}N shift.

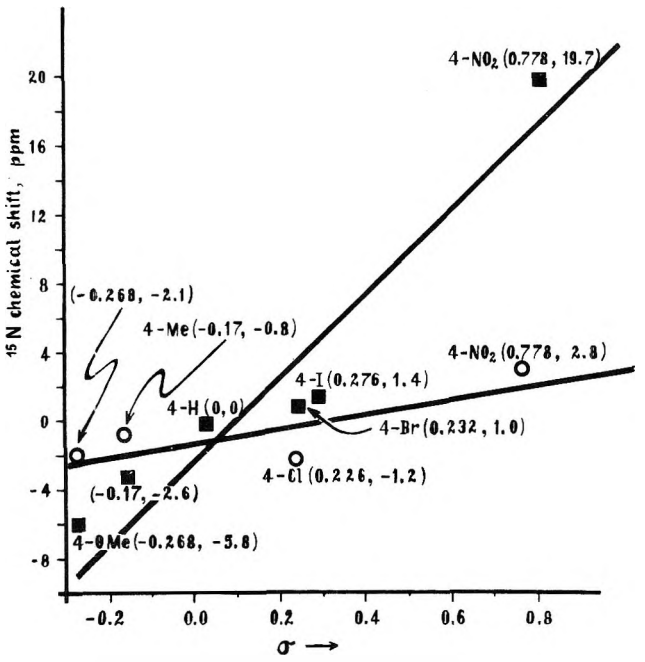


Figure 1. Correlation of ^{15}N chemical shifts for para-substituted benzenamines (■) and para-substituted *N*-phenylethanamides (○) with Hammett substituent constants (σ).

A number of β effects for N-substituted ethanamides are given in the top line of Table II. Only those N-substituted ethanamides of Table I which have R groups corresponding structurally to naturally occurring amino acid residues are included in Table II. Lines 2–8 of Table II are β effects for various R groups in amino acids as well as dipeptides. The numbers in Table II provide a test of the suitability of the secondary amides (line 1) as models for peptide linkages. It will be seen that the available data indicate that the β effects in line 1 are rather consistently larger than the corresponding effects for the same substituents in amino acids, dipeptides, etc. A possible explanation is that the shifts in line 1 of Table II were obtained in different solvents at different concentrations and different pH values than for the other substances. However, it is more likely that a systematic error is introduced by making comparisons on the basis of R = H as the standard substance for secondary amides, because the smaller the shifts are, the higher the degree of substitution at the α carbon. About all one can say is that there is a degree of parallelism between the ^{15}N shifts of various kinds of substances with a given change in the R group.

To determine the sensitivity of ^{15}N resonances in secondary amides to electronic effects, the ^{15}N shifts of *N*-phenylethanamide and several of its para-substituted derivatives were measured for 10–16 mol % solutions in dimethyl sulfoxide (Table I). Substitution of a directly bound phenyl group on nitrogen changes the shift of ethanamide 26.6 ppm downfield. Electron-donating groups in the para position of the phenyl ring cause upfield shifts, while electron-withdrawing para substituents produce the opposite effect. The range of chemical shifts between the *p*-nitro and *p*-methoxy substituents is only 4.9 ppm compared with the 25.5-ppm difference between the same substituents for benzenamines.[12] The ^{15}N shift of amide nitrogens are thus much less sensitive to electron withdrawal and donation than the ^{15}N shifts of amines, although both give reasonable trends with the Hammett substituent constants (Figure 1). The smaller change in shift for para-substituted amides compared with benzenamines is expected because of the strong conjugation of the amide nitrogen lone-pair electrons with the carbonyl groups, which compete for conjugation with the π system of the benzene ring. The downfield shift produced by electronegative para substituents in *N*-phenylethanamide (acetanilide) can be attributed to p–π interaction between the amide nitrogen lone pair and the aromatic ring, thus causing decreased π-electron density at the nitrogen with concomitant deshielding.

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Spatial Proximity by Electrophilic Addition to the Tricyclo[4.2.2.0^{2,5}]deca-3,7-diene System. Structures and Some Comments on the Feature of π Participation

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Reactions of tricyclo[4.2.2.0^{2,5}]deca-3,7-diene derivatives with halogens and sulfur-containing electrophiles have been examined. The transannular halo lactone products were fully identified by x-ray crystallographic techniques. Mechanisms for their addition reactions are also discussed.

Rigid molecules containing two isolated double bonds in spatial proximity are known to undergo facile chemical reaction involving π participation between these two double bonds.[2] The transannular reaction of these molecules has provided a simple synthetic route to new highly strained polycyclic hydrocarbons and information about the participation between these two double bonds.

In the first part of this series,[3] it was reported that the reaction of tricyclo[4.2.2.0^{2,5}]deca-3,7-diene derivatives with electrophiles such as bromine and iodine chloride proceeds by transannular cross bonding of the proximal π bonds. In contrast with our results, Farnum et al.[4] reported that 1,2-addition of bromine to the cyclobutene moiety of this system occurred in addition to the transannular reaction. On the other hand, the preferential cross bridging was explained based on the orbital mixing of the HOMO and LUMO of the double bond system with the LUMO of the electrophiles by Inagaki et al.[5]

To provide some additional data for understanding these reaction modes, we have reexamined the reactions of dimethyl tricyclo[4.2.2.0^{2,5}]deca-3,7-diene-9,10-dicarboxylate (**1**) with bromine and iodine. Moreover, the structure of the products has been determined by x-ray crystallographic techniques. We have also investigated the reaction of **1** with sulfur-containing electrophiles.

Results

Addition of Halogen. Reaction of **1** with bromine in acetic acid at room temperature gave transannular bromo lactone compound **2.** Similar bromination at 80 °C gave not only **2a** (63%) but also **3a** (38%). In the case of **1** with bromine in chloroform at room temperature, **2a** was obtained. In contrast, a similar reaction at refluxing temperature gave **2a** (28%) and **3a** (68%). In addition, reaction of **1** with bromine in carbon tetrachloride at room temperature gave **2a** (84%) and **3a** (14%). Similar reaction at refluxing temperature gave only **3a** (93%). These results of the bromination of **1** under various conditions are summarized in Table I and Scheme I.

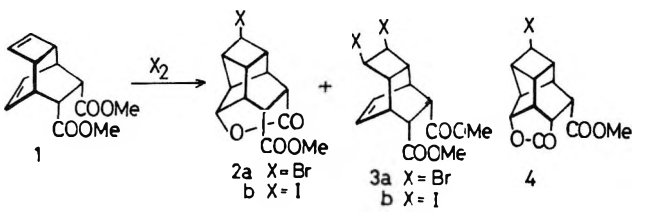
Previously, structure elucidation of the halogenated compounds was accomplished by their spectral analyses and chemical transformations. Compound **2a** was assigned as a cross-type compound with the five-membered lactone moiety **4,** since **2a** shows carbonyl absorption at 1770 and 1735 cm^{-1}. In spite of the characteristic carbonyl absorption of the five-membered lactone moiety,[6] it was proved that **2a** has a six-membered ring lactone moiety by an x-ray crystallographic technique as described below.

Compound **3a** shows carbonyl absorption at 1740 cm^{-1}. Elemental analysis shows the product to be $C_{14}H_{16}O_4Br_2$. The NMR spectrum of **3a** exhibits equivalent hydrogens α to the bromine at δ 4.22 and two equivalent vinyl hydrogens as a clean triplet centered at δ 6.48.[5] On the basis of the above data, the structure of **3a** was established as a cis dibromide as shown in Scheme I. Another support for the assignment has been furnished by x-ray studies as described below.

Owing to the difficulty of iodination of **1** with iodine and potassium iodide in aqueous solvent, iodine chloride and iodine azide were used for these compounds.[3,7] For comparison with the bromination of **1,** reaction of **1** with iodine in organic solvents was investigated. Reaction of **1** with iodine in benzene at room temperature gave **2b** (94%). Treatment of **2b** with n-Bu_3SnH gave deiodinated compound **5,** which was also given both by reduction of **2a** with n-Bu_3SnH and by acetolysis of tricyclo[4.2.2.0^{2,5}]deca-7-enyl-3-tosylate (**6**).[8] These results indicate that the structures of **2b** and **5** have the same skeleton as **2a,** a transannular cross-bonding compound with the six-membered lactone moiety. Reaction of **1** with iodine in refluxing cyclohexane gave **3b.** Compound **3b** was easily assigned as a cis diiodide on the basis of its IR spectrum, NMR spectrum, and elemental analysis.

In connection with the halogenation of **1,** we have previously reported that acid-catalyzed epoxide cleavage of 3,4-epoxytricyclo[4.2.2.0^{2,5}]deca-7-ene (**7**) gave **8a.**[9] Although compound **8a** had been assigned as a five-membered lactone on the basis of its IR spectrum, compound **8a** was proved to be a six-membered lactone by its correlation with the bromo lactone compound **2a;** acetolysis of **8b** gave **9** and **10** in a 1:1 ratio.[10] The reaction of **2a** with equimolar silver acetate in acetic acid at reflux temperature gave **9** and **10.** Furthermore, from the reaction of **2b** with silver acetate, chemical transformations

Scheme I



Scheme II

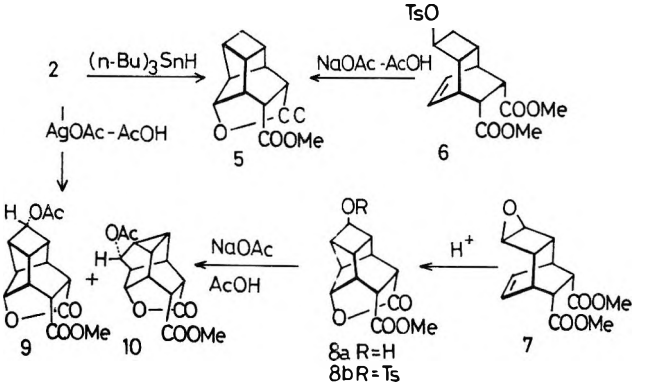


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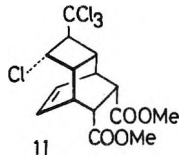
Table I. Reaction of 1 to Halogen under Various Conditions

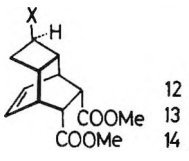
Reagents	Solvent	Temp, °C	Reaction products (yield, %)
Br_2	AcOH	20	**2a** (quant); **3a**
Br_2	AcOH	80	**2a** (63); **3a** (37)
Br_2	$CHCl_3$	20	**2a** (quant); **3a**
Br_2	$CHCl_3$	61	**2a** (28); **3a** (68)
Br_2	CCl_4	20	**2a** (84); **3a** (14)
Br_2	CCl_4	77	**2a; 3a** (93)
I_2	Benzene	20	**2b**; (94); **3b**
I_2	Cyclohexane	81	**2b; 3b** (44)

as previously reported[10] confirmed that **8a,b, 9,** and **10** have exactly a six-membered lactone moiety. These results are summarized in Scheme II.

Addition of Free Radicals. Fray et al.[11] reported that the free-radical addition of bromotrichloromethane and carbon tetrachloride to the 1:1 adduct of cyclooctatetraene and maleic anhydride results in trans addition to the cyclobutene double bond. In accordance with these results, reaction of **1** with carbon tetrachloride in the presence of AIBN gave **11,** a trans



11



12 X=Br
13 X= -S-⟨⟩-Cl
14 X= -SO-⟨⟩-Cl

adduct to the cyclobutene double bond. Reaction of **1** with hydrogen bromide in the presence of AIBN at 80 °C gave **12.** The configuration of the bromine moiety in **12** was determined to be exo on the basis of a chemical shift of a proton adjacent to bromine (multiple centered at δ 4.0). Similar reaction in the absence of a radical initiator resulted in the recovery of **1.** In order to compare these results with a reaction under milder conditions, we carried out the addition of *p*-chlorobenzenethiol to **1** in a cyclohexane solution with an access of oxygen at room temperature, which afforded **13** and **14,** and none of the transannular products by free-radical addition were detected.[12]

Additions of Methanesulfenyl Chloride and Thiocyanogen. Reaction of methanesulfenyl chloride with a methylene chloride solution of the diester **1** at −30 °C gave the trans adduct **15** in 85% yield. The NMR spectrum of **15** exhibits a hydrogen adjacent to the chlorine as a double doublet centered at δ 4.35. This chemical shift corresponded to that of the trans adduct of benzenesulfenyl chloride to the diester **1** (δ 4.42).[13] Similar treatment of **1** with thiocyanogen in acetic acid at room temperature in the presence of a radical inhibitor gave **16** (44%) and **17** (27%). The IR spectrum of **16** shows thiocyanate absorption at 2160 cm^{-1} together with carbonyl absorptions at 1780 and 1755 cm^{-1}. The NMR spectrum of **16** exhibits a methine proton signal adjacent to a lactone moiety at δ 4.85 (dd), one methyl group at δ 3.72, and a methine proton signal adjacent to a thiocyanate at δ 3.60 (s), but no olefinic proton signals were observed. The final structural determination of the compound was accomplished by chemical transformation. Reduction of **16** with sodium borohydride and nickel chloride[14] gave **5.** The IR spectrum of **17** shows thiocyanate absorption at 2160 cm^{-1}. The NMR spectrum of **17** exhibits two olefinic proton signals as a multiplet centered at δ 6.50, two methine proton signals adjacent to thiocyanate at δ 4.25 and 3.60, and two methyl groups at δ 3.60. The presence of nonequivalent vinyl hydrogens and methine proton signals adjacent to the thiocyanate suggested **17** to be trans dithiocyanate. These results are summarized in Scheme III.

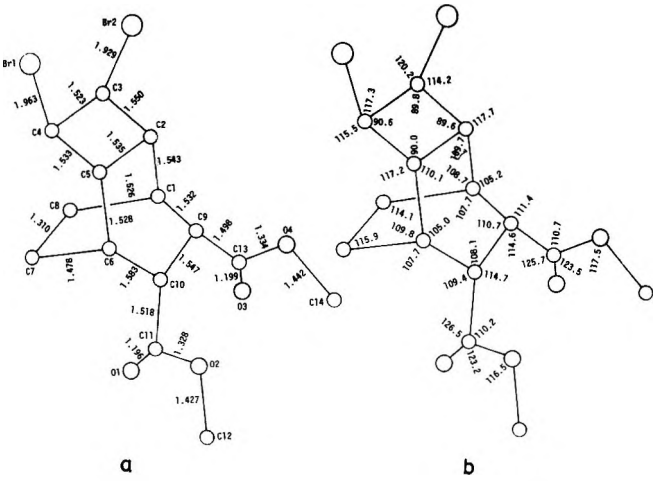
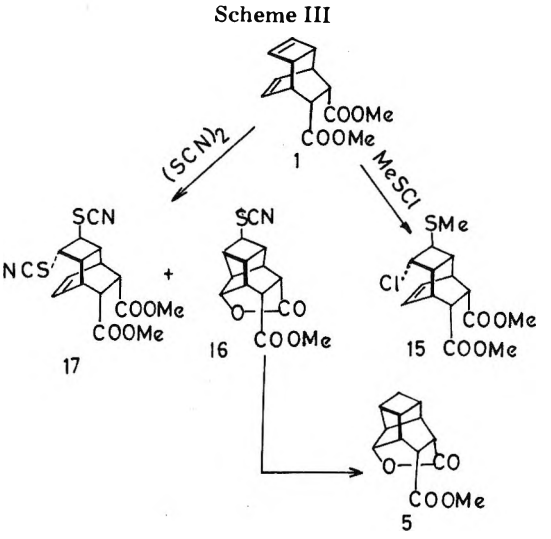


Figure 1. (a) Bond Lengths (Å) of **3a.** (b) Bond angles (deg) of **3a.**

Scheme III



Description of Structures. Compound 3a. The atomic parameters are given in Tables II and III. The bond lengths and angles are shown in Figure 1, together with the atom numbering system. The estimated standard deviations of the bond lengths are 0.011–0.016 Å, while those of the bond angles are 0.7–1.0°. The stereoscopic view obtained by the program ORTEP[15] is shown in Figure 2. The four-membered ring is planar. All four bond lengths and angles in the ring are nearly equivalent. The C(7)–C(8) double bond length is slightly shorter than the usual value. The distance of the nonbonded contact between C(1) and C(6) is 2.580 Å. The molecule consists of six planar fragments. They are a four-membered ring, three four-atom systems each containing both C(1) and C(6), and two ester groups. The planarity is excellent in each group. The equations of the least-squares planes are listed in Table IV. The framework of tricyclo[4.2.2.0^{2,5}]deca-3,7-diene has a pseudomirror plane bisecting the bonds of C(3)–C(4), C(2)–C(5), C(7)–C(8), and C(9)–C(10). The view of the molecule projected along the C(1) to C(6) direction on the dihedral angles between the three planes of the four-atom systems. Among the three dihedral angles, both the ones between the planes C(1) and C(2) and between C(2) and C(3) are enlarged to decrease the steric repulsions between the C(7)–C(8) group and the four-membered ring and those between the C(7)–C(8) and the two C=O groups in the ester groups. The distances of the nonbonded C(7)···C(4) and C(8)···C(3) contacts are 2.950 and 2.976 Å, respectively. Taking this molecular skeleton into consideration, it is clear that only an exo–cis adduct of halo-

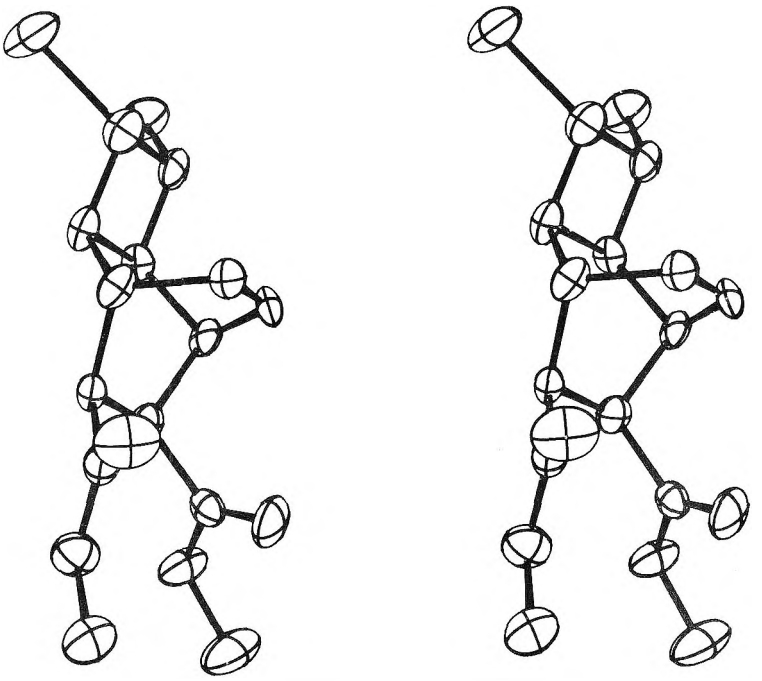


Figure 2. Stereodrawing of **3a** with thermal ellipsoids drawn to enclose 50% probability.

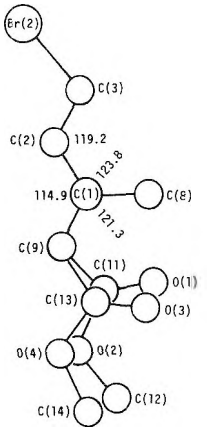


Figure 3. A view of **3a** projected along the C(1) to C(6) direction.

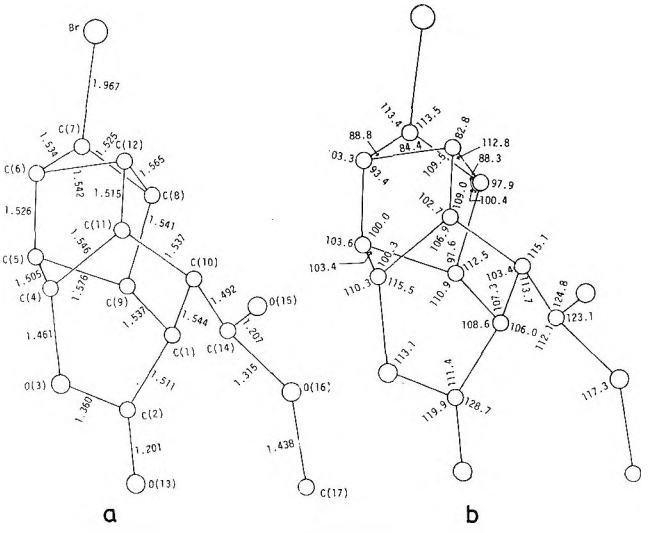


Figure 4. (a) Bond lengths (Å) of **2a**. (b) Bond angles (deg) of **2a**.

gens can be obtained to avoid the steric repulsion between halogens and the C(7)–C(8) bond. The torsion angle Br(1)–C(4)–C(3)–Br(2) is 0.3°. The carbonyl oxygen atoms of the ester groups are the nearest atoms to the C(7)–C(8) double bond, and the disposition is in favor with the lactone ring formation. The distances of the nonbonded contacts are: C(7)···O(1), 3.028; C(7)···O(3), 3.955; C(8)···O(1), 3.480; and C(8)···O(3), 3.117 Å. The dihedral angles between the plane C(3) and the ester groups are 88.7° between C(3) and C(6), and 50.6° between C(3) and C(5).

Compound 2a. The atomic parameters are given in Tables V and VI. The bond lengths and angles are shown in Figure 4, together with the atom numbering system. The estimated standard deviations of the bond lengths are 0.009–0.014 Å, while those of the bond angles are 0.6–0.9°. The stereoscopic view is shown in Figure 5. This molecule is expected to have large strains imposed by a cage formation. The strains are mainly found on the distortions of the bond angles from the ideal tetrahedral value. Each atom in the fused ring system has one or two small bond angles, while most of the bond lengths are normal. The puckering of the four-membered ring is severe; the dihedral angles in the ring are 138.8° between the C(6)C(7)C(8) plane and the C(6)C(8)C(12) plane and 136.6° between C(6)C(7)C(12) and C(7)C(8)C(12). The values in this ring are close to the value of 135° found in photooxidized dimer of plastoquinone-1.[16] Both of the two five-membered rings are in the so-called "envelope" form; C(7) is puckered out in the C(5)C(6)C(7)C(8)C(9) ring, and C(5) is puckered out in the C(4)C(5)C(6)C(11)C(12) ring. Most of the bond angles in the six-membered lactone rings are normal. Each of the four-atom systems, C(1)C(2)O(3)C(4), C(1)-C(9)C(5)C(4), and C(1)C(10)C(11)C(4), is nearly planar. Fairly short nonbonded contacts are found between C(2) and C(14), 2.800 Å, and between C(11) and O(15), 2.878 Å.

Discussion

With respect to halogenation, it is very interesting that 1,2-addition occurs only in the sterically unhindered olefins on the cyclobutene moiety by a cis fashion. It is apparent that the reaction of **1** with halogen is dependent on reaction temperatures and solvents. At elevated reaction temperature, 1,2-addition was superior to transannular reaction, although the effect of temperature was small in a protic solvent such as acetic acid. A convenient explanation of these facts and that of the regiospecific reaction, predominant cis addition, and

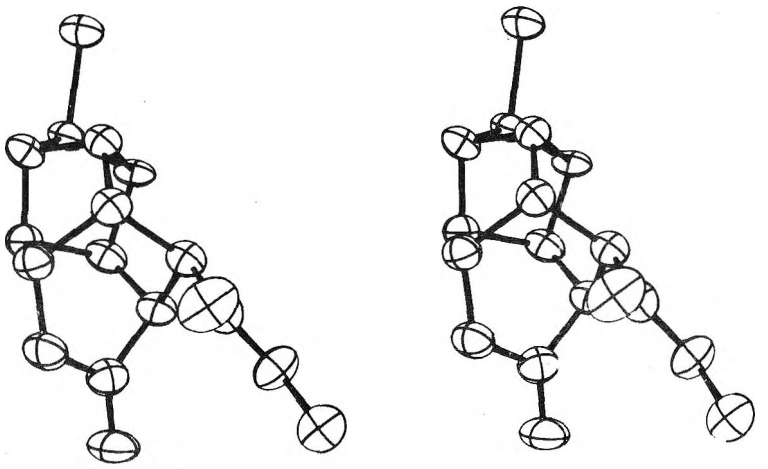


Figure 5. Stereodrawing of 2a with thermal ellipsoids drawn to enclose 50% probability.

cross-bonding at transannular reaction is provided by the following hypothesis. It seems that the reaction pathway in the halogenation of 1 might involve the initial attack of the reagent at the cyclobutene double bond and participation by cyclohexene double bond as shown in Scheme IV.

When X^+ approached the cyclobutene HOMO from the direction perpendicular to the plane of the molecule, the resulting LUMO of the cyclobutyl cation extended to the opposite direction of the location of X. As a result of this perturbation of orbital, the participation of the HOMO of the cyclohexene double bond to the LUMO of the developing cation became effective. At the first stage of this interaction, an overlap with the p lobe which is located close to the cation center might be predominant. However, on account of the difference of the total strain energy of the resulting polycyclic cation and the relief of van der Waals repulsion among the methine protons in the cyclobutane moiety, the interaction with the p lobe on a remote carbon atom increased its significance with progress of the reaction.

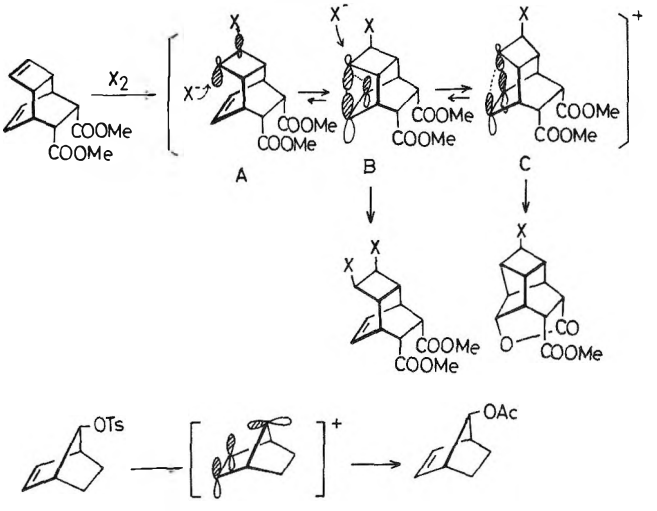
If the reaction was carried out under conditions that stabilized the cation intermediate, electrophilic attack of the reagent at the cyclobutane double bond gave the cation C followed by lactonization affording the cage compound. This explains why the yield of transannular product is high at room temperature or in acetic acid. At elevated temperature, cation B might be trapped by X^- before the formation of cation C. In this connection, solvolysis of 7-norbornadienyl tosylate is reported to give a retention product.[17] This retention of configuration has been rationalized in terms of π participation (Scheme IV).

It seems reasonable to assume that the attack of bromine at an intermediacy of cation B occurs from the less-hindered and electronically favored side to give an exo–cis 1,2-adduct. If the 1,2-adduct was derived from cation A, the product should be a trans dihalide via attack to the most extended site of LUMO.[18]

We have previously reported that cis addition of mercuric acetate and iodine azide on the cyclobutene moiety can be explained by examination on the transition state according to the twist strain theory.[19] Because of the highly strained anti coplanar transition state, the cis addition occurs preferentially via the syn transition state. However, this explanation proved to be in conflict with the results of free-radical addition to this system. As described above, the addition occurred on the cyclobutene double bond by trans fashion.

It was explained that the trans addition was due to the steric hindrance of the exo-trichloromethyl group.[11] However the steric effect is not adequate to explain the result. Reaction of 1 with mercuric acetate resulted in the formation of the exo–

Scheme IV



cis adduct in spite of the bulkiness of the reagents.[20,21]

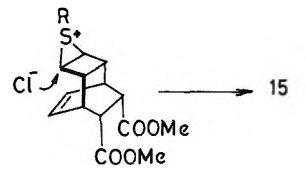
It is probable that the difference between the free-radical addition and the reaction of electrophiles is attributed to the mode of orbital interactions. The orbital interactions between the singly occupied molecular orbital (SOMO) and the lowest unoccupied molecular orbital (LUMO) of the closed-shell molecule were reported to be of importance. In the case of an addition of methyl radical to ethylene,[22] the configuration in which an electron is transferred from the SOMO of methyl to the LUMO of ethylene is calculated to be the most dominant, and the one from the HOMO of ethylene to the SOMO of methyl is the next dominant.

Although we can not ascertain the feature of the interactions between 1 and the radicals, they must differ from that of an electrophilic reaction which is controlled by the HOMO of the cyclobutene double bond. On account of the interaction controlled mainly by LUMO of the cyclobutene double bond, the participation between the resulting cyclobutyl radical and cyclohexene double bond might be uneffective.

As a result, it is to be noted that the free-radical addition to 1 resulted in trans addition to the cyclobutene double bond instead of cis addition and transannular cyclization. On the other hand, the observed trans stereospecific addition of methanesulfenyl chloride to the cyclobutene moiety is consistent with a bridged episulfonium ion with little charge on the carbon atom (Scheme V).

Reaction of thiocyanogen with 1 is also trans stereospecific for the cyclobutene double bond. A two-step heterolytic addition reaction involving initial electrophilic attack on the

Scheme V



alkene by an electron-deficient sulfur atom of the thiocyanogen molecule with the formation of a cyanosulfonium ion followed by a trans-diaxial opening of the sulfonium ring by a thiocyanate anion or a cyclohexene double bond accounts for the observed trans stereospecificity. The electron withdrawing group might enhance the cationic character of the carbon and make an overlap between the back lobe of sulfonium ion and the p lobe of the cyclohexene double bond effective.

Experimental Section

The melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer. The NMR spectra were taken with a Jeol C-60-XL spectrometer with tetramethylsilane as an internal standard and the chemical shifts are expressed in δ values. The IR spectra were taken with a Jasco Model IRA-1 grating infrared spectrophotometer.

General Procedure for the Bromination of 1. An excess of bromine was added to a solution of 1 in various solvents. The mixture was stirred for 10 h under these conditions. Evaporation of the solvent followed by silica gel chromatography and recrystallization gave products.

(a) A solution of 1 (500 mg) and bromine (600 mg) in acetic acid (20 mL) was stirred at 20 °C. Workup gave **2a** (540 mg).

(b) Bromine (960 mg) was added to a solution of 1 (800 mg) in acetic acid (20 mL) at 80 °C. The mixture was stirred for 10 h at 80 °C. Workup gave **2a** (680 mg) and **3a** (462 mg).

3a: mp 237–238 °C; IR (KBr) 1740 cm^{-1}; NMR ($CDCl_3$) 6.48 (2 H, t, J = 4.5 Hz), 4.22 (2 H, d, J = 3.25 Hz), 3.58 (6 H, s, COOMe 2), 2.8–3.3 (6 H, m). Anal. Calcd for $C_{14}H_{16}O_4Br_2$: C, 41.21 H, 3.95. Found: C, 41.22; H, 3.86.

(c) A solution of 1 (250 mg) and bromine (300 mg) in chloroform was stirred at 20 °C. Workup gave **2a** (270 mg).

(d) To a solution of 1 (500 mg) in refluxing chloroform (20 mL), bromine (600 mg) was added. Workup gave **2a** (170 mg) and **3a** (520 mg).

(e) A solution of 1 (200 mg) and bromine (250 mg) in carbon tetrachloride was stirred at 20 °C. Workup gave **2a** (110 mg) and **3a** (50 mg).

(f) Bromine (300 mg) was added to a solution of 1 (250 mg) in refluxing carbon tetrachloride. Workup gave **2a** (28 mg) and **3a** (380 mg).

Iodination of 1. (a) A solution of 1 (250 mg) and iodine (260 mg) in benzene (20 ml) was stirred at 20 °C. Workup gave **2b** (350 mg).

(b) To a solution of 1 (500 mg) in refluxing cyclohexane, iodine (510 mg) was added. The mixture was refluxed for 8 h. Workup gave **3b** (432 mg).

3b: mp 220–222 °C; IR (KBr) 1740 cm^{-1}; NMR ($CDCl_3$) 6.52 (2 H, t, J = 4.5 Hz), 4.50 (2 H, d, J = 3.75 Hz), 3.59 (6 H, s, COOMe 2), 3.3–3.0 (4 H, m) 2.78 (2 H, s).

Anal. Calcd for $C_{14}H_{16}O_3I_2$: C, 33.49; H, 3.21. Found: C, 33.63; H, 3.30.

Reduction of 2a. A solution of **2a** (800 mg) and n-Bu_3SnH (1 g) in toluene (30 mL) was stirred for 8 h at 80 °C. Evaporation of the solvent followed by silica gel chromatography gave **2a** (560 mg) and **5** (160 mg).

5: mp 87–88 °C; IR (KBr) 1760, 1740 cm^{-1}; NMR ($CDCl_3$) 4.78 (1 H, dd, J = 3.0 and 6.75 Hz), 3.68 (3 H, s, COOMe), 3.22 (1 H, t, J = 5.25 Hz), 2.8–2.6 (7 H, m), 1.95 (1 H, m), 1.95 (1 H, m), 1.40 (1 H, d, J = 8.25 Hz).

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.40; H, 6.11.

Reduction of 2b. A solution of **2b** (1.1 g) and n-Bu_3SnH (1.5 g) in toluene (30 mL) was stirred for 8 h at 40 °C. Workup gave **5** (450 mg).

Reaction of 2a with Silver Acetate. A mixture of **2a** (380 mg) and silver acetate (380 mg) in acetic acid (30 mL) was refluxed for 15 h. The reaction mixture was filtered for precipitated silver salts, and the solvent was evaporated by reduced pressure. The residue was subjected to silica gel chromatography using chloroform–benzene to give a mixture of **9** and **10** (60 mg) and **2a** (290 mg).

Reaction of 1 with Carbon Tetrachloride. A solution of 1 (1,0 g) and azobis(isobutyronitrile) (100 mg) in carbon tetrachloride (30 mL) was refluxed for 8 h. Evaporation of the solvent followed by silica gel chromatography gave **11**[11] (1.0 g) and 1 (280 mg).

Reaction of 1 with Hydrogen Bromide. To a solution of 1 (700 mg) and azobis(isobutyronitrile) (100 mg) in refluxing benzene (30 mL), hydrogen bromide was bubbled. Evaporation of the solvent followed by chromatography gave **12** (800 mg).

12: mp 98–100 °C; IR (KBr) 1750 cm^{-1}; NMR ($CDCl_3$) 6.45 (2 H, t, J = 3.75 Hz), 3.95 (1 H, m), 3.57 (6 H, s, COOMe 2), 3.2–2.2 (8 H, m).

Anal. Calcd for $C_{14}H_{17}O_4Br$: C, 51.08; H, 5.20. Found: C, 51.08; H, 5.22.

Reaction of 1 with *p*-Chlorobenzenethiol. A solution of 1 (500 mg) and p-chlorobenzenethiol (290 mg) in cyclohexane (20 mg) was stirred for 24 h. After evaporation of the solvent, the residue was dissolved in chloroform. The solution was washed with 4% aqueous sodium hydroxide and then water. Evaporation of the solvent followed by chromatography gave **13** (400 mg) and **14** (44 mg).

13: mp 123–124 °C; IR (KBr) 1740 cm^{-1}; NMR ($CDCl_3$) 7.4–7.0 (4 H, m), 6.50 (2 H, t, J = 3.75 Hz), 3.59 (7 H, s, COOMe 2 and 1 H), 3.40 (1 H, m), 3.1–2.8 (4 H, m), 2.55 (2 H, m), 2.04 (2 H, m).

Anal. Calcd for $C_{20}H_{21}O_4SCl$; C, 61.14; H, 5.39. Found: C, 61.23; H, 5.42.

14: mp 197–199 °C; IR (KBr) 1740 cm^{-1}; NMR ($CDCl_3$) 7.50 (4 H, s), 6.40 (2, H, m), 3.58 (6 H, s), 3.2–1.8 (9 H, m).

Anal. Calcd for $C_{20}H_{21}O_5SCl$: C, 58.75; H, 5.18. Found: C, 58.80; H, 5.18.

Reaction of 1 with Methanesulfenyl Chloride. To a solution of 1 (2.5 g) in dichloromethane (10 mL), methanesulfenyl chloride (1.0 g) was added at −30 °C. The solution was stirred for 4 h. After evaporation of the solvent, the residue was subjected to silica gel chromatography using benzene–chloroform to give **15** (2.72 g): mp 99–100 °C: IR (KBr) 1740 cm^{-1}; NMR ($CDCl_3$) 6.56 (1 H, t, J = 7.5 Hz), 6.38 (1 H, t, J = 7.50 Hz), 4.35 (1 H, dd, J = 6.0, 7.50 Hz), 3.60 (3 H, s, COOMe), 3.4–2.8 (7 H, m), and 2.10 (3 H, s, SMe).

Anal. Calcd for $C_{15}H_{19}O_4SCl$: C, 54.45; H, 5.79. Found: C, 54.51; H, 5.66.

Reaction of 1 with Thiocyanogen. To a solution of thiocyanogen in acetic acid (80 mL) generated in situ from thiocyanate (6.1 g) and bromine (1 mL), 2,6-*tert*-butyl-*p*-cresol (0.1 g) as a radical inhibitor and 1 (2.0 g) were added. The reaction mixture was stirred for 8 h at room temperature. The reaction mixture was filtered to remove polymeric thiocyanogen, and the product was isolated by dilution of the solution with water followed by extraction with chloroform and removal of solvent under reduced pressure. The resulting residue was subjected to silica gel chromatography (using benzene–chloroform) to give **16** (220 mg) and **17** (450 mg).

16: mp 175–176 °C; IR (KBr) 2160, 1780 and 1755 cm^{-1}; NMR ($CDCl_3$) 4.85 (1 H, J = 3.25, 7.50), 3.75 (3 H, s, COOMe), 3.60 (1 H, s), 3.5–2.5 (8 H, m).

Anal. Calcd for $C_{14}H_{13}O_4SN$: C, 57.72; H, 4.50; N, 4.81. Found: C, 57.50; H, 4.69; N, 4.86.

17: mp 117–118 °C; IR (KBr) 2160, 1740 cm^{-1}; NMR ($CDCl_3$) 6.50 (2 H, m), 4.25 (1 H, m), 3.60 (7 H, s, COOMe 2 and 1 H), 3.5–2.8 (6 H, m).

Anal. Calcd for $C_{16}H_{16}O_4S_2N_2$: C, 52.73; H, 4.43; N, 7.69. Found: C, 52.52; H, 4.41; N, 7.90.

Reduction of 16. To a solution of **3** (200 mg) and $NiCl_2 \cdot 6H_2O$ (2.0 g) in ethanol (20 mL), a solution of sodium borohydride (580 mg) in water (5 mL) was added. The mixture was refluxed under reduced pressure followed by silica gel chromatography to give **5** (100 mg).

Structure Determination. Crystal data are as follows. Compound **3a:** $P2_1/a$, a = 19.097 (3), b = 6.859 (2), c = 12.701 (3) Å, β = 119.15 (3)°, Z = 4, d_{obsd} = 1.77, d_{calcd} = 1.875 g·cm^{-3}, μ = 59.2 cm^{-1} (for Mo Kα).

Compound **2a:** $P\bar{1}$, a = 7.359 (1), b = 12.268 (1), c = 7.240 (1) Å, α = 81.90 (1), β = 108.76 (1), γ = 77.75 (1)°, Z = 2, d_{obsd} = 1.77, d_{calcd} = 1.764 g·cm^{-3}, μ = 34.6 cm^{-1} (for Mo Kα).

The data collections were carried out on a Rigaku four circle diffractometer, using Zr-filtered Mo Kα radiation. The crystals used for data collection had the dimensions of 0.1 × 0.4 × 0.1 mm (elongated in the b direction) for **3a** and 0.40 × 0.35 × 0.05 mm (elongated in the a direction) for **2a**. Integrated intensities were measured by the $\omega - 2\theta$ scan method, with a speed of 2° (ω) min^{-1} and range of (1.40 ± 0.35 tan θ)° (ω). For **3a**, 2928 independent reflections with $2\theta \leq 52.5°$ were obtained, of which nonzero reflections were 2068; for **2a**, 2244 reflections with $2\theta \leq 50°$ were obtained, of which 1854 were nonzero.

The intensity data were corrected for Lorentz and polarization effects, but no absorption correction was made. The data set of **2a** was corrected for crystal deterioration.

The structures were solved by the heavy-atom method, and the refinement was carried out by the block-diagonal least-squares procedure.[23,24] Temperature factors were anisotropic for the nonhydrogen atoms and isotropic for the hydrogen atoms. In the refinement, the function minimized was $\Sigma\omega(|F_o| - |F_c|)^2$. For **3a** only nonzero reflections were included, and the temperature factors of the hydrogen atoms were held constant ($B = 3.8$ Å^2) in the refinement; the weight was $1/(\sigma^2|F_o| + a|F_o| + b|F_o|^2)$, and the final refinement ($a = -0.1297$, $b = 0.0140$) gave the $R(\Sigma||F_o| - |F_c||/\Sigma|F_o|)$ of 0.104. For **2a** the weighting scheme was $\omega = 1/2$ for $F_o = \theta$, $\omega = 1$ for $\theta < |F_o| < 2\theta$, and $\omega = (2\theta/|F_o|)^2$ for $|F_o| \geq 2\theta$, and the final R is 0.080 for 1854 nonzero reflections. The atomic scattering factors were taken from ref 24. All the calculations were carried out on FACOM 230-60 and 230-75 computers of Nagoya University.

Acknowledgment. The diffractometer intensity measurements were kindly made possible by Professor M. Kakudo of Osaka University, to whom our thanks are due. We thank Tomomitsu Ito, Yasuyuki Yamada, Hiromi Ito, and Tsuneo Yamamoto of the Faculty of Engineering, Nagoya University, for technical assistance.

Registry No.—**1**, 35211-83-7; **2a**, 64682-19-5; **2b**, 51425-75-3; **3a**, 64682-20-8; **3b**, 64682-21-9; **5**, 64682-22-0; **12**, 64682-23-1; **13**, 64682-24-2; **14**, 64682-25-3; **15**, 64682-26-4; **16**, 64728-31-0; **17**, 64682-27-5; bromine, 7726-95-6; iodine, 7553-56-2; Bu_3SnH, 688-73-3; azobis(isobutyronitrile), 764-28-3; *p*-chlorobenzenethiol, 106-54-7; methanesulfenyl chloride, 5813-48-8; thiocyanogen, 505-14-6.

Supplementary Material Available: Tables II–VI, positional and thermal parameters for the structures **2a** and **32** (7 pages). Ordering information is given on any current masthead page.

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(21) A referee pointed out that cis oxymercuration products most likely arise by concerted cycloadditions, as discussed by Professor Cristol in 1976, and thus have nothing to do with the radical additions. However, they discussed the dependence of the reaction mechanisms (mercurinium ion, carbenium ion, and concerted reactions) on the reaction conditions and concluded that a cis concerted addition process intervenes when neither the process via mercurinium ion nor that via carbenium ion occurs readily. In this case, the cis oxymercurations can not explained by the molecular addition as discussed previously.
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Ring Expansion by [2,3]Sigmatropic Shift: Conversion of Five-Membered into Eight-Membered Heterocycles

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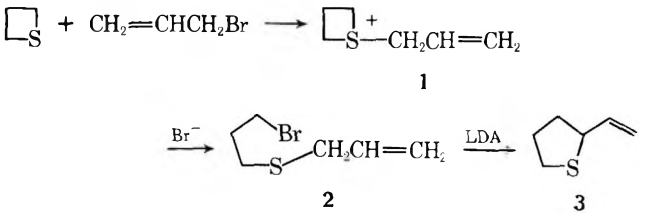
Syntheses of α-vinyltetrahydrothiophene and 2-vinyl-*N*-benzylpyrrolidine are described. Conversion of these heterocycles into ylides by an alkylation–deprotonation sequence results in rearrangement to eight-membered heterocycles. In the sulfur series, *cis*-thiacyclooctenes are formed preferentially, but a trans alkene has been isolated in one case. In the nitrogen series, comparable amounts of cis and trans alkenes are formed. The origin of olefin geometry is considered as a function of ylide geometry. In both the sulfur and the nitrogen series, the stereochemistry of ylides is subject to interconversion of diastereomers. Reversible deprotonation α to the vinyl group is a sufficient explanation for diastereomer interconversion in both heterocyclic series, but other mechanisms are not ruled out.

Synthetic approaches to macrocyclic natural products under way in our laboratory require the development of methodology for easily repeatable multicarbon ring expansion ("ring growing reactions"). A solution to this problem has been devised using the [2,3]sigmatropic rearrangement of ylides obtained from α-vinyl heterocycles, as described in a preliminary communication.[1] Assuming that techniques for heteroatom extrusion can be developed, these rearrangements provide rapid access to large rings with varying functionality. In this report we shall describe fundamental aspects of the most difficult ring expansion in terms of ring size, the conversion of five- to eight-membered heterocycles.

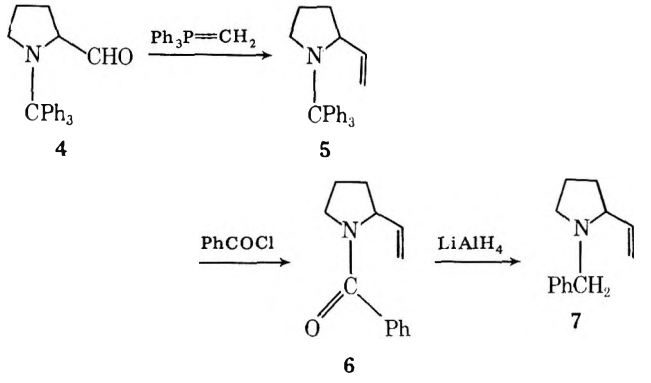
Preparation of α-Vinyl Heterocycles. Our synthesis of α-vinyltetrahydrothiophene (**3**) begins with the conversion of thietane into the allylic sulfide **2** via fragmentation of an unstable thietanium bromide (**1**, Scheme I). Similar frag-

0022-3263/78/1943-1185$01.00/0

Scheme I



Scheme II



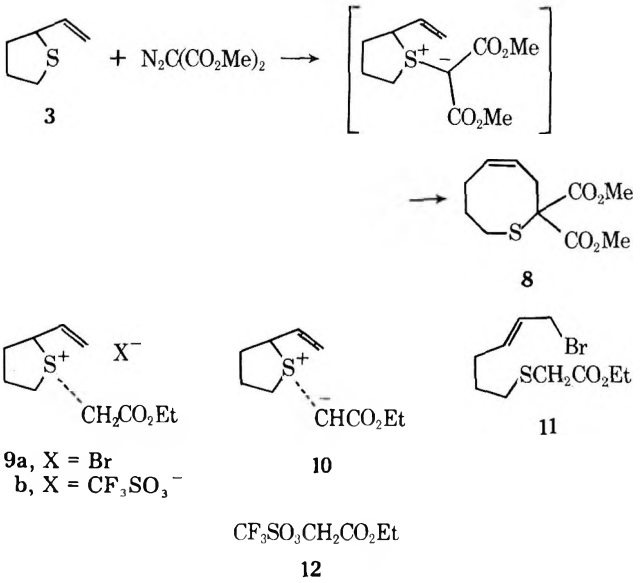
mentation of thietanium salts is well-known.[2] Cyclization to **3** can then be achieved by treatment of **2** with lithium diisopropylamide at −78 °C. An 85% isolated yield of **3** results if **2** is added slowly to the solution of LDA. An alternative route to **3** by Grignard displacement of α-chlorotetrahydrothiophene has also been examined, but it appears less suitable for preparation of reasonable amounts of material.[3]

The analogous nitrogen heterocycle **7** is available from the known *N*-tritylpyrrolidinecarboxaldehyde **4**[4] (Scheme II). The Wittig reaction can be used to convert **4** into the α-vinyl compound **5**, and heating the latter with benzoyl chloride results in **6**. Finally, lithium aluminum hydride reduction affords 2-vinyl-*N*-benzylpyrrolidine (**7**). Attempts to use 2-vinyl-*N*-tritylpyrrolidine (**5**) in ring expansion reactions failed because we were unable to isolate the corresponding *N*-tritylammonium precursors of ammonium ylides.

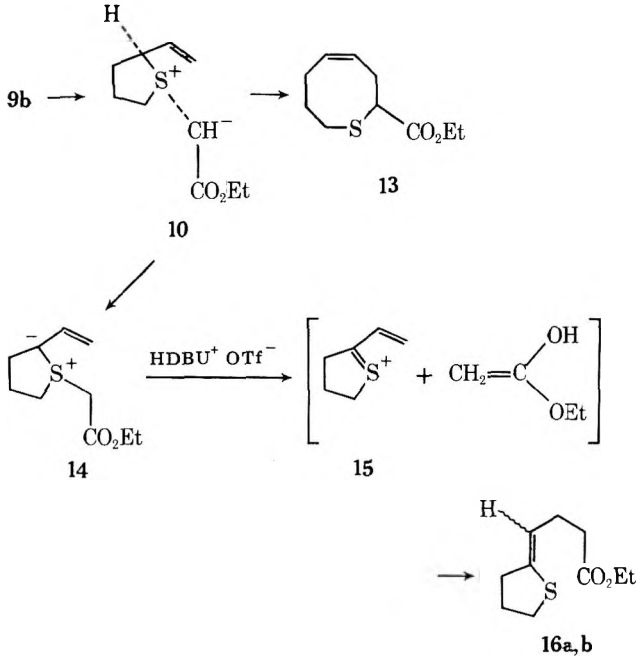
Ring Expansions in the Sulfur Series. A well-precedented approach to generation of sulfur ylides which might undergo ring expansion is to combine the sulfide with a diazocarbonyl compound under conditions of carbenoid generation.[5] Thus, treatment of **3** with dimethyl diazomalonate and copper bronze in toluene at 100 °C results in a single major product (53% isolated) which has all of the spectral characteristics expected for the *cis*-thiacyclooctene **8** (Scheme III). No other isomers can be isolated in significant quantity. Attempts to employ a similar carbenoid decomposition of ethyl diazoacetate for generation of ylide **10** proved unsatisfactory. At best, 15% of a ring expansion product, **13** (Scheme IV), was formed according to GLPC analysis, and numerous polar side products were also present.

An alternative approach to **10** was considered. Alkylation of **3** with ethyl bromoacetate should give the sulfonium bromide **9a**, and subsequent deprotonation would lead to **10**. However, it proved necessary to heat **3** in neat ethyl bromoacetate to achieve conversion of the starting material. Under these conditions no salts could be isolated at all. Instead, a neutral substance, **11**, was obtained; **11** is obviously derived from **9a** by nucleophilic attack of bromide ion at the vinyl terminus. In order to avoid this side reaction, an alkylating agent having a nonnucleophilic anion as the leaving group was necessary. The trifluoromethanesulfonate **12**[6] derived from ethyl glycolate proved ideal for the problem at hand. Thus, **3** affords crystalline triflate salt **9b** (86%) after

Scheme III



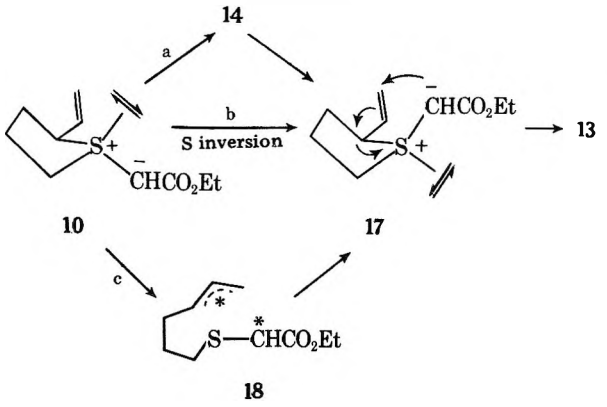
Scheme IV



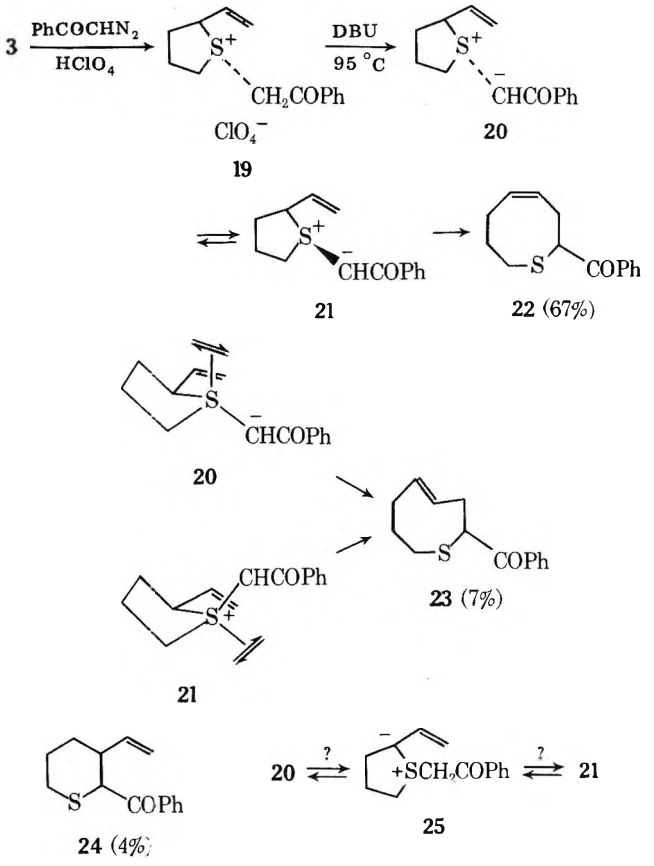
treatment with **12** at 0 °C. The crystalline salt is obviously homogeneous by NMR spectroscopy and is assigned the trans stereochemistry based on the assumption that least hindered approach by alkylating agent **12** occurs under the conditions used. On treatment with sodium bromide in a two-phase system of water–chloroform, **9b** is converted into **11** (77% isolated) after 2.5 h at room temperature. Thus, nucleophilic agents must be avoided in subsequent reactions of salts related to **9**.

Ring expansion of **9b** can be achieved with a variety of bases, including K_2CO_3, LDA, and DBU (1,5-diazabicyclo[5.4.0]undec-5-ene), but the highest yield (80%) of thiacyclooctene **13** (Scheme IV) is obtained using potassium *tert*-butoxide in acetonitrile (20 °C, 2 h). No other isomers can be found in sufficient quantity for characterization using this procedure. In contrast, DBU-induced rearrangement of **9b** gives comparable amounts of **13** and a mixture of isomeric vinyl sulfides **16a,b**. The isomers are extremely difficult to purify, and repeated preparative thin-layer chromatography is required for partial separation of one isomer (**16a**). By

Scheme V



Scheme VI



270-MHz spectroscopy it was found that **16a** contains no asymmetric carbons and retains one vinyl proton. All of the necessary coupling interactions were present as required for structure **16a.** An NMR spectrum of the enriched **16a,b** mixture after partial removal of **16a** can be interpreted to show that a second closely analogous set of signals is present which can only be due to the other geometrical isomer of the vinyl sulfide. It is obviously necessary to remove the allylic proton α to vinyl at some stage to account for the appearance of **16a,b.** We suggest that ylide **10** equilibrates with isomer **14.** In the presence of an acid catalyst such as protonated DBU ($HDBU^+ \cdot CF_3SO_3^-$), **14** might undergo cleavage to sulfonium ion **15** and the enol form of ethyl acetate. Recombination of these fragments by Michael addition would then lead to **16a,b.** The alternative of simple Stevens rearrangement by **14** would also give **16a,b.** However, this rationale fails to explain why **16a,b** is formed only in the DBU-induced rearrangement.

If the stereochemistry assigned to **9b** is correct, then formation of **13** requires interconversion of ylide diastereomers **10** and **17.** Only the cis diastereomer (**17**) can attain a reasonable geometry for a [2,3] shift via a cisoid vinyl rotamer, which would result in cis olefin **13** (Scheme V). Three reasonable mechanisms for this interconversion can be considered: (a) reversible deprotonation–reprotonation α to the vinyl group via ylide isomer **14;** (b) pyramidal inversion at sulfur in the ylide **10;**[7-9] (c) fragmentation of the allylic C–S bond and reclosure of an intermediate diradical or dipole (**18**).

Indirect evidence for the formation of **14** has already been presented, so path a would be a sufficient mechanism to account for the formation of **17.** Path b has some analogy in the facile inversion of a nonstabilized ylide,[9] but acyclic stabilized ylides invert slowly at 25 °C.[7] Furthermore, Fava et al. have pointed out that pyramidal inversion in a cyclic system should be slower for steric reasons.[8] Additional kinetic studies are required before the pyramidal inversion process can be proved or disproved in our system.[10] Path c appears less likely. The intermediate **18** should be capable of Stevens rearrangement[11] to form a six-membered ring, but no such product has been obtained from **9b.**

One additional example of tetrahydrothiophene ring expansion was examined. Treatment of **3** with diazoacetophenone and perchloric acid according to the method of Flower, Holt, and Hope[12] gives the phenacylsulfonium salt **19** in good yield (Scheme VI). In the presence of DBU at 20 °C, a slow rearrangement to thiacyclooctenes results (23% of cis alkene **22** and 2% of trans alkene **23** after 1.25 h). For efficient conversion and good product recovery it is necessary to heat the solution of salt and base. Thus, reaction of **19** and DBU at 95 °C in toluene (10 min) affords three products (ca. 80% recovery) consisting of **22** (67%), the trans isomer **23** (7%), and the Stevens product **24** (4%).

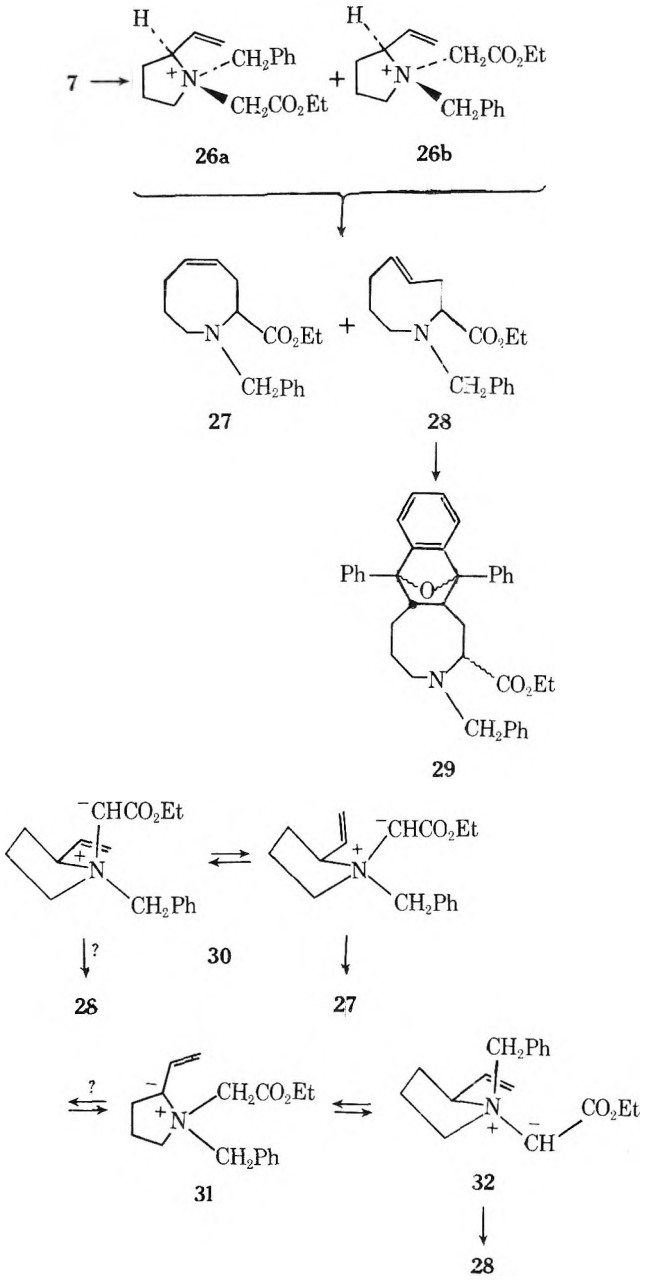
As before, sulfonium salt formation gives a homogeneous crystalline isomer which is assumed to be the trans diastereomer. Therefore, it again is necessary to postulate interconversion of diastereomers to explain the appearance of cis alkene **22.** However, the thermal barrier for ring expansion shows that the process which interconverts ester-stabilized ylides **10** and **17** is considerably less effective for the phenacyl ylides **20** and **21.** It is reasonable to argue that interconversion of the highly stabilized phenacyl ylide **20** with **25** would be more difficult than the analogous process **10** ⇌ **14** in the ester series and might not in fact take place. Although we cannot prove that **25** is not formed, we note that products analogous to **16a,b** are not observed in the phenacyl series whether or not DBU is used as the base. In any event, pyramidal inversion at sulfur must be regarded as a realistic alternative for diastereomer interconversion at 95 °C, pending kinetic studies in more closely related ylide systems. Also, the S–C fragmentation–recombination process might be considered since a Stevens product **24** is formed to a significant extent.

In contrast to the ester-stabilized system, the phenacyl ylide is capable of rearrangement to a trans double-bond isomer **23.** As shown in Scheme VI, either ylide diastereomer **20** or **21** can attain the necessary transoid geometry with reasonable five-center overlap for a [2,3] shift. Since the trans olefin constitutes an asymmetric center in an eight-membered ring, two geometric isomers of **23** are possible.[13] However, we have observed only one diastereomer in the product mixture.

Nitrogen Ring Expansions. Alkylation of 2-vinyl-*N*-benzyl-pyrrolidine (**7**) with the triflate reagent **12** affords a mixture of diastereomers **26** (Scheme VII). One of the two ammonium salts can be crystallized efficiently as the bromide. The other isomer has not been obtained pure, but NMR analysis indicates less that 10% residual crystalline isomer in the oily salt.

Treatment of either diasteromer **26a** or **26b** with potassium *tert*-butoxide at 20 °C gives a mixture of two ring expansion products (ca. 2-h reaction time). One of the products can be

Scheme VII



isolated by chromatography and is clearly the cis olefin according to the NMR spectrum. The second product decomposes on silica gel and has not been purified or fully characterized. However, a 270-MHz NMR spectrum of the crude mixture of ring expansion products shows, in addition to signals from **27**, a highly characteristic doublet of doublets of doublets at δ 5.45 (J = 15.5, 11.8, and 3.7 Hz) identical in appearance with the upfield olefin signal of **23** and other trans cyclooctene derivatives. The infrared spectrum of the mixture contains a typical *trans*-cyclooctene absorption at 971 cm^{-1} which disappears on attempted chromatography, acid treatment, or prolonged manipulation at ambient temperatures.

Based on this evidence, structure **28** can be assigned to the unstable product. In confirmation of the *trans*-azacyclooctene structure, the mixture of **27** and **28** reacts with diphenylisobenzofuran at 20 °C to give adduct **29** (mixture of at least three diastereomers) together with unreacted cis olefin **27**. Adduct **29** is characterized by the correct molecular ion and the absence of vinylic hydrogens in the NMR spectrum.

The ratio of **27**/**28** is 3:2 starting from the crystalline salt, while a slight preference for trans olefin **28** is observed from the oily salt. We suggest therefore that **26b** is the oily salt and that rearrangement to **28** occurs competitively with interconversion of ylides **32** and **30**. Due to the geometrical requirements for cis olefin formation as discussed in the sulfur series, ylide **32** cannot give **27** without prior stereochemical change. The most reasonable mechanism for interconversion of **32** and **30** involves the ylide **31**. According to molecular models, ylide **30** could conceivably rearrange to either **27** or **28**. Thus, it is clear that **32** must lose stereochemistry competitively with ring expansion, but there is not sufficient evidence to show whether **30** likewise equilibrates with **31** under the conditions employed.

Conclusion

Ring expansion of five-membered sulfur or nitrogen heterocycles by a [2,3]sigmatropic shift is a viable method for synthesis of eight-membered heterocycles. Interconversion of ylide diastereomers is necessary for rearrangement in the sulfur series and also plays a role in the nitrogen series. In several of the examples studied diastereomer interconversion is probably the slowest step in the overall reaction and accounts for the relatively slow rates for 2,3 shifts. In subsequent publications we will show that rearrangement of ylides derived from larger, more flexible rings is much more facile and does not require interconversion of diastereomers.

Experimental Section

Allyl 3-Bromopropyl Sulfide(2). To thietane[1] (7.9 g, 0.107 mol) in acetonitrile (40 mL, Aldrich, used without further purification) was added allyl bromide (12.84 g, 0.107 mol) at room temperature. The mixture was stirred overnight. The solvent was removed at reduced pressure, and the residue was distillad to give **2** (17.4 g, 0.0393 mol, 85%): bp 43–44 °C (0.5 Torr); IR (neat) 1635 m cm^{-1}; NMR ($CDCl_3$) δ 5.8 (1 H, ddt, J = 17, 10, 7 Hz), 5.15 (2 H, m), 3.5 (2 H, t, J = 8 Hz), 3.18 (2 H, d, J = 7 Hz), 2.64 (2 H, t, J = 8 Hz), 2.1 (2 H, quintet, J = 8 Hz); m/e 196 (M + 2), 194 (M), 154, 152, 74, 63; exact mass, 193.97675; calcd for $C_6H_{11}SBr$, 193.97654.

α-Vinyltetrahydrothiophene (3). To diisopropylamine (Aldrich, 5.76 mL, 41.30 mmol, distilled from BaO) was added dropwise a hexane solution of n-butyllithium (25 mL, 41.30 mmol) at −70 °C. A nitrogen stream was maintained throughout the experiment. Dry tetrahydrofuran (50 mL, distilled from sodium benzophenone) was added. To this rapidly stirred solution allyl 3-bromopropyl sulfide (4.6 mL, 31 mmol) was then added dropwise over a 0.5-h period. Stirring was continued at −70 °C for 1 h, and then the mixture was quenched with water. After the mixture had warmed to room temperature it was washed with 10% HCl and then 10% $NaHCO_3$ solution, dried over Na_2SO_4, and filtered. The solvent was removed at atmospheric pressure using a fractionating column. The residue was distilled under reduced pressure to give **3** (2.99 g, 85%): bp 55–56 °C (16 Torr); IR (neat) 1630 m cm^{-1}; NMR ($CDCl_3$) δ 5.8 (1 H, ddd, J = 15, 10, 8 Hz), 5.08 (1 H, dd, J = 15, 2 Hz), 4.9 (1 H, dd, J = 10, 2 Hz), 3.9 (1 H, m), 2.85 (2 H, m), 1.4–2.3 (4 H, m); m/e 114 (M), 87, 85, 81, 71; exact mass, 114.05026; calcd for $C_6H_{10}S$, 114.05032.

***N*-Trityl-2-vinylpyrrolidine (5).** Methyltriphenylphosphonium bromide (0.564 g, 1.59 mmol) in dry THF (15 mL) was stirred at −78 °C under nitrogen. A solution of n-butyllithium in hexane (2.38 mmol) was added dropwise with stirring over 2 min and the mixture stirred for 2.5 h at −78 °C. A solution of *N*-trityl-2-formylpyrrolidine[4] (0.27 g, 0.793 mmol) in THF (4 mL) was added dropwise by syringe at −78 °C. After 40 min the mixture was warmed to 0 °C (0.5 h), quenched with water, and partitioned between ether–water. After extracting with 3 × 15 mL of ether, the combined organic layers were dried ($MgSO_4$) and evaporated (aspirator). The brown oil was separated by preparative layer chromatography (PLC) over silica gel (ether–hexane, 1:4) to give a major band, R_f 0.56. Extraction with ether and crystallization from hexane gave **5** as a white solid (73%), mp 94.5–95 °C, sufficiently pure for the next step; NMR ($CDCl_3$) δ 6.9–7.7 (15 H, m), 5.8 (1 H, ddd, J = 4.8, 8.9, 15.6 Hz), 5.29 (1 H, dd, J = 1.9, 15.6 Hz), 5.05 (1 H, dd, J = 1.9, 8.9 Hz), 3.77 (1 H, m), 3.25 (1 H, m), 2.35 (1 H, m), 0.7–1.7 (4 H, m).

***N*-Benzoyl-2-vinylpyrrolidine (6).** Benzoyl chloride (27 uL, 0.23 mmol) was refluxed with *N*-trityl-2-vinylpyrrolidine (71 mg, 0.21 mmol) in methylene chloride (5 mL) for 3.5 h. Evaporation of solvent gave an orange residue, and separation by PLC (silica gel, 10% ether–hexane) gave two major bands. The less polar (R_f 0.66) was

trityl chloride, while the more polar (R_f 0.32) was the desired *N*-benzoyl derivative **6** (35 mg, 82%). The oily product was used in the next step without further purification.

***N*-Benzyl-2-vinylpyrrolidine (7).** A solution of *N*-benzoyl-2-vinylpyrrolidine (33 mg, 0.165 mmol) in dry ether (2 mL) was added to a stirred mixture of $LiAlH_4$ (9 mg, 0.25 mmol) and ether (3 mL) at 20 °C. The mixture was then refluxed for 3 h and cooled to 0 °C, and solid $Na_2SO_4 \cdot 10H_2O$ was added slowly until frothing ceased. After extraction of ether-soluble products from the salts and evaporation of ether, a yellow oil was obtained (32 mg). Separation by PLC (silica gel, 1:1 ether–hexane) gave a major zone at R_f 0.5, and extraction with ether gave **7** as an oil, 21.4 mg (69%); NMR ($CDCl_3$) δ 7.32 (5 H, br s), 5.82 (1 H, ddd, J = 8, 9.5, 17.5 Hz), 5.12 (1 H, dd, J = 2, 17.5 Hz), 5.07 (1 H, dd, J = 2, 9.5 Hz), 4.03 and 3.09 (2 H, AB q, J = 13 Hz), 2.9 (2 H, m), 1.6–2.3 (5 H, m); exact mass, 187.13610; calcd for $C_{13}H_{17}N$, 187.13597.

Ring Expansion of 3 with Dimethyl Diazomalonate: Preparation of 8. In a 5-mL flask were mixed dimethyl diazomalonate (250 μL, 2.1 mmol), toluene (1 mL, distilled from $LiAlH_4$), copper bronze (161 mg, U.S. Bronze Powder Works), and α-vinyltetrahydrothiophene (**3**) (0.114 g, 1 mmol). The flask was fitted with a condenser and heated at 100 °C without stirring for 5 h under a slight positive pressure of nitrogen. The mixture was filtered and subjected to separation by LC (silica gel, 35% ether in hexane) to give **8** (0.13 g, 53%; oil): IR (neat) 1635 w, 1740 s cm^{-1}; NMR ($CDCl_3$) δ 5.9 (1 H, td, J = 8, 7 Hz), 5.45 (1 H, td, J = 8, 7 Hz), 3.8 (6 H, s), 2.9 (4 H, m), 2.25 (2 H, m), 1.8 (2 H, m); *m/e* 244 (M), 203, 185, 180, 157, 153, 144, 132, 125, 113, 100, 87; exact mass, 244.07905; calcd for $C_{11}H_{16}O_4S$, 244.07693.

Alkylation of 3 with Triflate 12: Isolation of 9b. Neat α-vinyltetrahydrothiophene (**3**, 0.52 g, 4.56 mmol) was added dropwise via syringe to a solution of triflate **12**[6] (1.19 g, 5.07 mmol) in acetonitrile (8 mL, distilled from P_2O_5) at 0 °C under nitrogen flow. The mixture was allowed to stir for 2 h and then warmed to room temperature. The acetonitrile was removed (aspirator, there is a tendency for bumping) to give a slightly red solid. Recrystallization in ethyl acetate gave needles of **9b** (1.47 g, 86%): mp 99–101 °C; IR (KBr) 1025 s, 1155 broad, 1250 broad, 1632 w, 1730 s cm^{-1}; NMR (CD_3CN) δ 5.88–6.24 (1 H, ddd, J = 18, 10, 8 Hz), 5.48 (1 H, d, J = 18 Hz), 5.40 (1 H, d, J = 10 Hz), 4.54–4.76 (1 H, m), 4.30 (2 H, s), 4.20 (2 H, q, J = 7 Hz), 3.40–3.80 (2 H, m), 2.0–2.6 (4 H, m), 1.24 (3 H, t, J = 7 Hz).

Conversion of Sulfonium Triflate 9b into Sulfide 11 by Bromide Ion. A solution of **9b** (0.1 g, 0.286 mol) in $CHCl_3$ (3 mL) was stirred with saturated aqueous NaBr (5 mL) at 20 °C for 2.5 h. After separation of layers, the aqueous phase was diluted 5-fold with water and extracted with $CHCl_3$ (3 × 10 mL). The combined organic phase was dried (Na_2SO_4) and evaporated (aspirator) to yield **11** (0.063 g, 77%) as a colorless oil, homogeneous by TLC (10% ether–hexane); NMR ($CDCl_3$) δ 5.72 (2 H, m), 4.18 (2 H, br q, J = 7 Hz), 3.94 (2 H, m), 3.20 (2 H, s), 2.64 (2 H, t, J = 8 Hz), 2.18 (2 H, br q, J = 7 Hz), 1.72 (2 H, br q, J = 7 Hz), 1.30 (3 H, t, J = 7 Hz); IR ($CHCl_3$) 1725 cm^{-1}; exact mass, 282.01188; calcd for $C_{10}H_{17}O_2SBr$, 282.01134.

Ring Expansion of 9b to 2-Carboethoxythiacyclooct-4-ene (13). Sulfonium salt **9b** (37 mg, 0.106 mmol) was dissolved in acetonitrile (0.5 mL, distilled from P_2O_5) under nitrogen flow at room temperature. To this solution was added solid potassium *tert*-butoxide (12.5 mg, 0.111 mmol), and it was allowed to stir for 2 h. Hexane was added to the mixture, and the reaction was quenched with 1 N HCl (1 mL) and washed twice with water (1 mL). The water washes were combined and back-extracted with ether. The organic layers were combined, and the solvents were removed (aspirator). Preparative layer chromatography (3 elutions in 10% ether–90% hexane) gave pure **13** (17.5 mg, 80%; oil), R_f = 0.6; IR (neat) 1650 w, 1710 s cm^{-1}; NMR ($CDCl_3$) δ 5.7 (2 H, m), 4.2 (2 H, q, J = 6 Hz), 3.35 (1 H, dd, J = 10, 4 Hz), 2.2–3.1 (6 H, m), 1.7 (2 H, m), 1.3 (3 H, t, J = 6 Hz); *m/e* = 200 (M), 159, 127, 125, 100, 93, 87; exact mass, 200.08748; calcd for $C_{10}H_{16}O_2S$, 200.08709.

Ring Expansion of 9b Using DBU as Base. A solution of **9b** (160 mg, 0.46 mmol) in acetonitrile (1.5 mL, distilled from P_2O_5) was treated with DBU (142 mg, 0.93 mmol) at 20 °C for 2 h. Partitioning between pentane and water gave an organic layer which was dried (Na_2SO_4), evaporated (aspirator), and separated by PLC (silica gel, 10% ether–hexane). A lead zone, R_f 0.6, was isolated to give **13** (30 mg, 33%). A slightly more polar zone, R_f 0.5, gave a mixture containing **16a, 16b,** and traces of a third, unidentified contaminant (43 mg, 47%). The more polar zone was chromatographed a second time (6% ether–hexane, 4 developments) and was partially resolved into a lead zone and a trailing zone. The upper half of the lead zone was carefully separated and recovered to give **16a,** containing ca. 10% **16b** and ca. 5% of the contaminant. An NMR study at 270 MHz with spin decoupling established the following characteristics of **16a:** ($CDCl_3$) δ 5.28 (1 H, br t, J = 6 Hz), 4.13 (2 H, q, J = 7 Hz), 3.01 (2 H, t, J = 6.4 Hz), 2.54 (2 H, br t, J = 6.8 Hz), 2.36 (4 H, m), 2.06 (2 H, m), 1.26 (3 H, t, J = 7 Hz). Decoupling at δ 5.28 caused simplification at δ 2.36 and sharpening of the triplet at δ 2.54. Decoupling at δ 3.01 collapsed the δ 2.06 signal to a triplet, J = 6.8 Hz, and decoupling at δ 2.54 sharpened the olefinic triplet and collapsed the δ 2.06 signal to a triplet with some off-resonance interference by the decoupler frequency. Irradiation at δ 2.36 collapsed the vinyl proton to a broad singlet.

An NMR spectrum of the remaining PLC zone enriched in **16b** revealed additional signals at δ 5.39 (1 H, t, J = 6.6 Hz), 3.23 (2 H, t, J = 8.5 Hz), 2.73 (2 H, br t, J = 8.4 Hz), 2.4 (overlapping signals with **18a**), 1.84 (2 H, m), and 1.3 (partially resolved methyl triplet overlapping **16a** signal).

Further characterization of **16a:** IR (CCl_4) 1730 s, 1637 m cm^{-1}; exact mass, 200.08700; calcd for $C_{10}H_{16}O_2S$, 200.08709.

Rearrangement of **9b** was performed in the same way using toluene as the solvent. After the usual workup, 39% of **13** and 33% of the zone containing **16a,b** resulted.

Phenacylsulfonium Salt 19. This material was made by analogy to a published procedure.[12] In a 50-mL flask were placed acetonitrile (6 mL, Aldrich, distilled from CaH_2), perchloric acid (61%, 1.84 g, 10.5 mmol), sulfide **3** (0.598 g, 0.725 mL, 5.25 mmol), and a magnetic stirring bar. To this rapidly stirred solution was added dropwise over a 25-min period diazoacetophenone (1.177 g, 8.06 mmol) in dry acetonitrile (8 mL). After addition was complete, the solvent was evaporated in vacuo at room temperature. The residue was recrystallized from 100% ethanol; yield 71%. The salt melts with decomposition at 158–159 °C; IR (CH_3CN) 1595 m, 1630 w, 1680 s cm^{-1}; NMR (CD_3CN) δ 7.95 (2 H, m), 7.6 (3 H, m), 6.05 (1 H, ddd, J = 17, 10, 8 Hz), 5.55 (1 H, d, J = 17 Hz), overlapping with 5.45 (1 H, d, J = 10 Hz), 4.2 (2 H, s), 4.65 (1 H, m), 3.6 (2 H, m), 2.0–2.6 (4 H, m).

Ring Expansion of 19. To the sulfonium salt **19** (253 mg, 0.762 mmol) was added toluene (20 mL, Mallinckrodt, distilled from LAH), and the flask was fitted with a condenser and a nitrogen stream was introduced. At 95 °C DBU (118.5 mg, 0.778 mmol) was added dropwise. The mixture was stirred rapidly during the addition. After 10 min at 95 °C the flask was allowed to cool to room temperature. After 1-h total elapsed time the reaction was quenched with 60% $HClO_4$. The toluene layer was washed with 10% K_2CO_3 solution, and the carbonate layer was back-extracted with pentane. The combined pentane–toluene layer was dried (Na_2SO_4) and filtered, and the solvent was evaporated to give a crude weight of 172 mg. Thin-layer silica gel chromatography (10% ether in hexane) yielded a major band (R_f 0.4, 119 mg) of cis alkene **22,** yield 67%; IR (neat) 690 m, 760 m, 1450 m, 1585 w, 1680 s cm^{-1}; NMR ($CDCl_3$) δ 7.96 (2 h, dd, J = 8, 2 Hz), 7.3–7.5 (3 H, m), 5.8 (2 H, m), 4.25 (1 H, dd, J = 10, 4 Hz), 2.1–3.1 (6 H, m), 1.75–2.1 (2 H, m); *m/e* 232 (M), 127, 105, 87, 85, 84; exact mass, 232. 09216; calcd for $C_{14}H_{16}OS$, 232.09219.

A minor zone at R_f 0.35 (12 mg, 7%) proved to be trans alkene **23:** IR (neat) 685 m, 715 m, 750 m, 840 w, 880 w, 970 m, 1450 s, 1575 m, 1590 m, 1670 s cm^{-1}; NMR ($CDCl_3$) δ 8.0 (2 H, dd, J = 8, 2 Hz), 7.4–7.7 (3 H, m), 6.1 (1 H, m), 5.35 (1 H, ddd, J = 16, 12, 4 Hz), 4.42 (1 H, dd, J = 12, 4 Hz), 1.8–3.3 (8 H, m); *m/e* 232 (M), 157, 145, 127, 105, 77; exact mass, 232.09219; calcd for $C_{14}H_{16}OS$, 232.09218.

A third band was the Stevens product, 2-benzoyl-3-vinylthiacyclohexane (**24,** 7 mg, 4%), R_f 0.25; IR ($CHCl_3$) 910 m, 990 m, 1000 m, 1250 m, 1448 m, 1580 w, 1595 w, 1635 w, 1670 s cm^{-1}; NMR ($CDCl_3$) δ 7.96 (2 H, dd, J = 8, 2 Hz), 7.3–7.7 (3 H, m), 5.9 (1 H, ddd, J = 17, 10, 7.5 Hz), 5.05 (2 H, m), 4.35 (1 H, d, J = 4 Hz), 1.5–3.0 (7 H, m); *m/e* 232 (M), 127, 105, 77; exact mass, 232.09219; calcd for $C_{14}H_{16}OS$, 232.09218.

***N*-Benzyl-*N*-carboethoxymethyl-2-vinylpyrrolidinium Bromide (26a and 26b).** Carboethoxymethyl trifluoromethanesulfonate (**12**,[6] 0.791 g, 2.89 mmol) was dissolved in acetonitrile (4 mL) and added dropwise to a stirred solution of *N*-benzyl-2-vinylpyrrolidine (**7,** 0.512 g, 2.73 mmol) in acetonitrile (10 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated (aspirator), and the residue was washed with ether. Decantation of the ether left a yellow oil (1.362 g) which could not be crystallized. This crude product was stirred for 5 min in a methanolic solution of sodium bromide (12 g). The solvent was evaporated, and the residue was taken up in water (30 mL) and extracted with chloroform (3 × 25 mL). The combined organic layers were dried over sodium sulfate, filtered, and evaporated to a yellow oil. Crystallization from tetrahydrofuran left a white solid (0.518 g) with a melting point of 143.5–144 °C and a yellow oil (0.457 g). The two fractions proved to be the expected diastereomers **26a** and **26b;** yield of the solid isomer 53%, yield of impure liquid isomer 47%. Solid isomer (**26a**): NMR ($CDCl_3$) δ 7.4 (5 H, m), 5.95–6.35 (1 H, m), 5.3–5.7 (2 H, m), 4.75–5.2 (3 H, m), 3.8–4.5 (6 H, m), 2.1–2.8 (4 H, m),

1.28 (3 H, t, J = 6.3 Hz); IR ($CHCl_3$) 2940 s, 2450 m, 1749 s cm^{-1}. Anal. Calcd for $C_{17}H_{24}NO_2Br$: C, 57.63; H, 6.82; N, 3.95. Found: C, 57.47; H, 6.74; N, 3.92.

Liquid isomer (**26b**): NMR ($CDCl_3$) δ 7.5 (5 H, pseudo s), 5.75–6.4 (1 H, m), 5.4–5.7 (2 H, m), 4.6–5.1 (3 H, m), 4.28 (2 H, q, J = 7 Hz), 4.0 (4 H, pseudo s), 2.0–2.28 (4 H, m), 1.35 (3 H, t, J = 7 Hz); IR ($CHCl_3$) 3020 s, 2397 m, 1749 w cm^{-1}.

N-Benzyl-2-carboethoxyazacyclooct-4-ene (27 and 28). *N*-Benzyl-*N*-carboethoxymethyl-2-vinylpyrrolidinium bromide (**26a**, solid isomer; 62.3 mg, 0.175 mmol) was dissolved in acetonitrile (2 mL). Solid, finely ground potassium carbonate (27.7 mg, 0.200 mmol) was quickly added, and the resulting heterogeneous mixture was stirred at room temperature for 3.5 h. The solvent was evaporated by a stream of nitrogen, and the residue was taken up in water (2 mL) and extracted with hexane (4 × 7 mL). The combined organic layers were dried over sodium sulfate, filtered, and evaporated to give a colorless oil (44.5 mg). Preparative layer chromatography on silica gel (EM Reagents, 60P-254) using a 1:1 ether–hexane mixture as the eluent left a colorless oil (22.9 mg) at an R_f of 0.65, which proved to be the cis isomer **27**, yield 48%; IR ($CHCl_3$) 2942 s, 1725 s, 701 m cm^{-1}; NMR ($CDCl_3$) δ 7.32 (5 H, m), 5.84 (1 H, ddd, J = 10.5, 9, 8 Hz), 5.69 (1 H, ddd, J = 9, 8, 8 Hz), 4.20 (2 H, q, J = 7 Hz), 3.94 (2 H, AB, J = 14 Hz), 3.41 (1 H, dd, J = 8.6, 5 Hz), 2.0–3.3 (6 H, m), 1.2–1.7 (2 H, m), 1.30 (3 H, t, J = 7 Hz); *m/e* 273, (base 200; exact mass, 273.17271; calcd for $C_{17}H_{23}NO_2$, 273.17288.

Analysis (NMR and IR) of the crude product after hexane extraction but prior to chromatography showed the presence of the unstable trans isomer **28**, which decomposed on silica gel. Additional absorbtions in the mixture were as follows: IR ($CHCl_3$) 1732 s, 971 m cm^{-1}; NMR ($CDCl_3$) δ 5.90 (1 H, m), 5.45 (1 H, ddd, J = 15.5, 11.8, 3.7 Hz), 4.22 (2 H, q), 1.33 (3 H, t), and additional unresolved signals overlapping those of **27**. Comparison of the peak heights of the methyl triplets at δ 1.33 and 1.30 in the NMR indicates the ratio of cis to trans isomers from the solid isomer **26a** is approximately 3:2.

The above procedure is somewhat modified for rearrangement of the liquid isomer **26b**. Potassium *tert*-butoxide (30.4 mg, 0.261 mmol) in dry tetrahydrofuran (1 mL, distilled from sodium benzophenone) was added dropwise to a stirred solution of *N*-benzyl-*N*-carboethoxymethyl-2-vinylpyrrolidinium bromide (liquid isomer **26b**; 87.5 mg, 0.247 mmol) in dry THF (3 mL). The resulting solution was stirred at room temperature for 2 h. Workup as before left a colorless oil (19.2 mg) after preparative layer chromatography which proved to be identical with the product **27** obtained from the solid isomer **26a**, 28% yield. In addition, the crude material from the hexane extraction contained both **27** and **28** in a ratio varying from 45:55 to 40:60, depending on the experiment.

An aliquot containing both the cis and trans isomers **27** and **28** was stirred with excess 1,8-diphenylisobenzofuran in methylene chloride for 3 h. Isolation of the products by preparative layer chromatography on silica gel (EM Reagents, 60P-254) using a 1:1 ether–hexane mixture as eluent gave recovered **27** (R_f 0.67) as well as a noncrystalline mixture of several diastereomers of the Diels–Alder adduct **29** (R_f 0.57), in which no olefinic protons were observed; NMR (CCl_4) δ 7.0–7.8 (19 H, m), 3.2–4.3 (5 H, m), 2.5–3.0 (1 H, m), 1.0–2.4 (11 H, m); *m/e* 543, 91 (base); exact mass, 543.27619; calcd for $C_{37}H_{37}NO_3$, 543.27734.

Acknowledgment. This work was supported by grants from the National Institutes of Health (CA17918-02) and the National Science Foundation (GD43891 X).

Registry No.—**2**, 64871-50-7; **3**, 57565-42-1; **4**, 64871-54-1; **5**, 64871-51-8; **6**, 64871-52-9; **7**, 64871-53-0; **8**, 64871-35-8; **9b**, 64871-37-0; **11**, 64871-38-1; **12**, 61836-02-0; **13**, 64871-39-2; (*Z*)-**16**, 64871-40-5; (*E*)-**16**, 64871-41-6; **19**, 64871-43-8; **22**, 57565-37-4; **23**, 57565-38-5; **24**, 64871-45-0; **26a**, 64871-46-1; **26b**, 64871-47-2; **27**, 64871-48-3; **28**, 64871-49-4; **29**, 64900-49-8; thietane, 287-27-4; allyl bromide, 106-95-6; benzoyl chloride, 98-88-4; dimethyl diazomalonate, 6773-29-1; diazoacetophenone, 3282-32-4.

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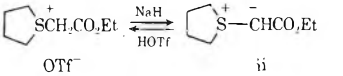

i ii

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Nucleophilic Substitution of Dihalopyridazines by Pyridazinethiones

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The reaction of 1 equiv of 3,6-dihalopyridazine (**1**) with 2 equiv of 6-halo-3(2*H*)-pyridazinethione (**2**) in slightly acidic, refluxing methanol yields the double-substitution product 3,6-bis(6-halo-3-pyridazinethio)pyridazine (**3**). The mechanism of the reaction is viewed as successive nucleophilic displacements upon protonated **1** by the thione tautomer of **2**.

The pyridazine ring system is highly resistant to electrophilic substitution, but for pyridazines substituted with appropriate leaving groups nucleophilic substitution is a facile process.[1] The conversion of **1a** to **2a** is a rather typical example.[2]

It was during the synthesis of **2a** from **1a**, inadvertently run under acidic rather than basic conditions, that we noted the formation of a new product (**3a**). This product was found to be the result of further reaction of **1a** with **2a**. In general, we have found that 3,6-dihalopyridazines (**1**) react in slightly

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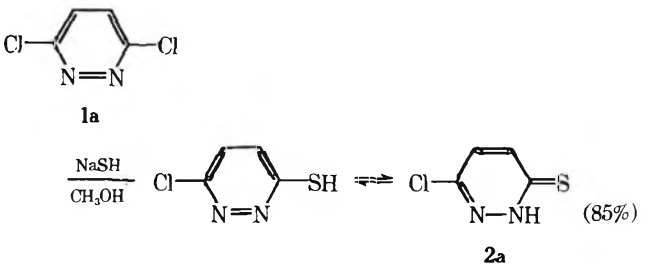
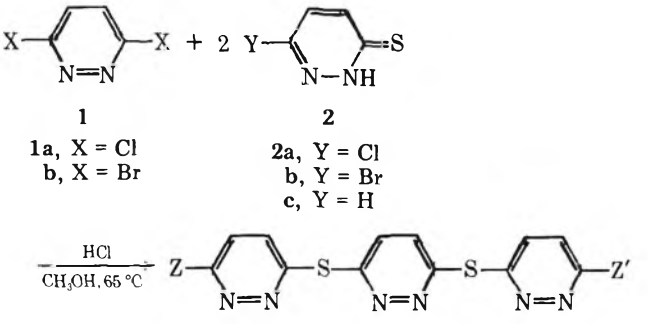


1a

2a

acidic, refluxing methanol with 6-halo-3(2*H*)-pyridazinethiones (**2**) to yield the double-substitution product 3,6-bis(6-halo-3-pyridazinethio)pyridazine (**3**).



1 **2**

1a, X = Cl
b, X = Br

2a, Y = Cl
b, Y = Br
c, Y = H

3

3a, Z,Z′ = Cl
b, Z,Z′ = Br
c, Z,Z′ = H
d, Z = Cl; Z′ = Br

Depending upon the substitution patterns of **1** and **2**, either **3a, b, c,** or **d** may be formed as the major product.

1a + 2 **2a** → **3a**

1b + 2 **2a** → **3a**

1b + 2 **2b** → **3b**

1a + 2 **2c** → **3c**

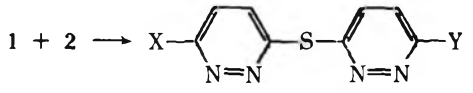
1b + 2 **2c** → **3c**

1a + 2 **2b** → **3d**

The release of halide ion as a product of the reaction was detected by potentiometric titration; yields were always 95–100% of theoretical.

Results and Discussion

We consider that the mechanism involves two successive displacements of halide ion by the nucleophilic sulfur of **2**.

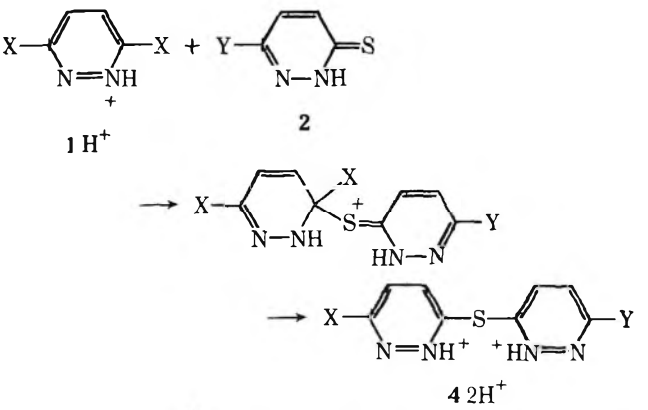


4

4 + 2 → **3**

Since the reaction does not take place under basic conditions (e.g., the conditions for synthesis of **2a** from **1a**) and since a slightly acidic medium is required, we expect that the nucleophilic attack occurs upon protonated **1**. However, the reaction cannot be run under strongly acidic conditions because **2** precipitates. The attacking nucleophile is probably the thione, rather than the thiol, tautomer of **2**, since the parent compound, 3(2*H*)-pyridazinethione,[3] and other derivatives[4,5] have been shown to exist predominantly in the thione form. The two-step mechanism shown below is typical for acid-catalyzed heterocyclic nucleophilic substitution.[6]

At least two alternative mechanisms involving neutral substrates may be envisioned.[7] One possibility is a preequilibrium between the slightly acidic **2** and the slightly basic **1**,



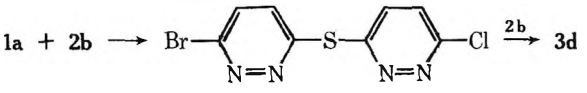
1 H^+ **2**

4 $2H^+$

followed by a rapid reaction of the resulting ion pair, as has been observed for arylthiol reactions with chloroquinoline.[8] Alternatively, **2** may act as a bifunctional nucleophile, involving H bonding to the ring N of **1** to enhance reactivity.[9] In the absence of any specific kinetic data, we cannot rule out these mechanistic possibilities.

We have never been able to isolate the expected intermediate **4**. Apparently, the initial substitution greatly increases the reactivity toward further nucleophilic substitution. Thus, **4** must be much more reactive toward **2** than **1** is and goes on to product **3** rapidly. Reactions run to partial completion and reactions with up to a tenfold excess of **1** over **2** gave only **3** and no evidence for **4**. A possible explanation is that the intermediate **4** is doubly protonated, which would be expected to enhance its reaction toward nucleophiles. In fact, the initial reaction between 1 H^+ and **2**, followed by halide ion loss, leads directly to doubly protonated **4**. Still further substitutions, after the second rapid substitution, are not observed, simply because the product **3** precipitates from solution. If the reaction is run in hot DMF, in which **3** is soluble, the only product observed is intractable polymeric material, suggesting that further substitution apparently can occur while **3** remains in solution.

The formation of a bromochloro derivative **3d** from **1a** plus **2b** is taken as evidence that the reaction must go through a bromochloro intermediate **4a** from which Br is a better leaving group than Cl. The nucleophile can only displace Cl from **1a**,



4a

but from **4a** displacement of Br is apparently preferred over displacement of Cl. The release of 1 equiv of Cl^-, followed by 1 equiv of Br^-, was monitored by potentiometric titration. This reactivity order is relatively unusual for activated aromatic or heterocyclic nucleophilic substitution, where the normal order of halogen reactivity is F ≫ Cl ≈ Br ≳ I.[10] In some cases, however, Br has been found to be a better leaving group than Cl in activated aromatic nucleophilic substitution[11] and in heterocyclic nucleophilic substitution.[12] The reversal of order of leaving-group activity indicates that carbon–halogen bond cleavage is significant in the rate-determining step.[10] Thus, the addition of **2** to **4** must involve a rapid initial attack followed by a rate-determining loss of halide ion.

Experimental Section

3,6-Dichloropyridazine (1a) and 3,6-dibromopyridazine (1b) were prepared from maleic hydrazide and $POCl_3$ or PBr_5.[13]

6-Chloro-3(2*H*)pyridazinethione (2a) and 6-bromo-3(2*H*)-pyridazinethione (2b) were prepared from **1a** or **1b** by refluxing with NaSH in methanol.[2]

3(2*H*)-Pyridazinethione (2c) was prepared from 3(2*H*)-pyridazinone by treatment with P_2S_5 in pyridine.[14] The pyridazinone was

prepared from **1a** by treatment with hot 3 N NaOH,[15] followed by hydrogenolysis.[16]

3,6-Bis(6-chloro-3-pyridazinethio)pyridazine (3a) was prepared by the reaction of either **1a** or **1b** with 2 equiv of **2a** in refluxing methanol. Inclusion of two drops of concentrated HCl improved the yields somewhat. During 3 h at reflux, a green solid precipitated. The reaction mixture was reduced to about half-volume by distillation at atmospheric pressure, cooled, and filtered. The solid residue was washed with hot methanol and recrystallized from DMF, mp 205–207 °C. The yield of purified product was 68% from **1a** and 75% from **1b**. The identity of the products from the two precursors was verified by the identity of the infrared spectra (see below) and the absence of a mixture melting point depression.

The structure of **3a** was deduced from the common method of synthesis (from **1a** or **1b**); from sodium fusion tests which indicated N, S, and Cl, but no Br; and from infrared, mass spectral, and elemental analyses: IR (KBr pellet): 3000, 1650, 1550, 1380, 1280, 1210, 1130, 1030, 1000, 840, and 770 cm^{-1}; mass spectrum[17] parent peaks at 368, 370, and 372 in the expected 9:6:1 ratio; M − Cl peaks at 333 and 335; other major fragments were at 223 and 225. Molecular weight was determined by the Rast method: 391 (calculated: 369). Anal.[18] Calcd for $C_{12}H_6Cl_2N_6S_2$: C, 39.0; H, 1.6; N, 22.8. Found: C, 39.20; H, 1.9; N, 22.0.

3,6-Bis(6-bromo-3-pyridazinethio)pyridazine (3b) was prepared similarly to **3a**, using 2 equiv of **2b** and 1 equiv of **1b**. Yields of the green product were typically 50%, after recrystallization from DMF: mp 216–217 °C (dec); IR (KBr pellet) 3000, 1630, 1510, 1440, 1370, 1260, 1120, 1030, 1000, 840, and 710 cm^{-1}; mass spectrum parent peaks at about 456, 458, 460 (very low intensities made accurate mass counting difficult; however, the expected 1:2:1 ratio was evident); M − Br peaks at 377 and 379; other major fragments were at 267 and 269. Anal.[19] Calcd for $C_{12}H_6Br_2N_6S_2$: C, 31.5; H, 1.3; N, 18.3. Found: C, 29.7; H, 2.0; N, 17.5.

3,6-Bis(3-pyridazinethio)pyridazine (3c) was prepared similarly, by the reaction of 2 equiv of **2c** with 1 equiv of either **1a** or **1b**. The dark-blue product was recrystallized from DMF, washed with acetone until the filtrate was clear, and dried in vacuo. The yield was 53%: mp 250 °C; IR (KBr pellet) 3060, 1533, 1400, 1340, 1280, 1240, 1110, 975 cm^{-1}. Anal.[19] Calcd for $C_{12}H_8N_6S_2$: C, 48.0; H, 2.7; N, 28.0. Found: C, 41.4; H, 2.6; N, 23.8.

3-(6-Bromo-3-pyridazinethio)-6-(6′-chloro-3′-pyridazinethio)pyridazine (3d) was prepared similarly to **3a** or **3b** using 1 equiv of **1a** and 2 equiv of **2b**. Recrystallization from DMF gave 41% of the green product: mp 194–196 °C (dec); IR (nujol mull) 1690, 1560, 1520, 1300, 1130, 1030, 840, 775, 765, 710 cm^{-1}; mass spectrum parent peaks at 412, 414, 416 (very weak; the expected 3:4:1 ratio was unconfirmed); peaks common to the spectrum of **3a** were observed at 333 and 335 (M − Br) and at 223 and 225; peaks common to the spectrum of **3b** were observed at 377 and 379 (M − Cl) and at 267 and 269. Anal.[18] Calcd for $C_{12}H_6BrClN_6S_2$: C, 34.8; H, 1.5; N, 20.3. Found: C, 38.3; H, 2.0; N, 19.5

Potentiometric Titrations. The release of halide ion was monitored by potentiometric titrations with standardized $AgNO_3$ solution. Standardizations were performed against KCl and KBr, including mixtures, such that both Cl^- and Br^- could be determined independently. Since the reactions were run in refluxing acidic methanol, the HX was trapped as a gas, entrained in a stream of nitrogen, and bubbled through an aqueous solution. An aliquot of this solution was then titrated with $AgNO_3$. Yields of halide were 2.0 equiv (±5%) based upon starting **1**.

Acknowledgments. We are pleased to acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Research Corporation, and the CSUF Departmental Associations Council for financial support of this work. We are also indebted to Mr. C. M. Reeske of Anaheim High School for his encouragement and contributions to the early phases of this work.

Registry No.—**1a**, 141-30-0; **1b**, 17973-86-3; **2a**, 3916-78-7; **2b**, 65027-58-9; **2c**, 28544-77-6; **3a**, 65027-59-0; **3b**, 65027-60-3; **3c**, 65027-48-7; **3d**, 65027-49-8; maleic hydrazide, 123-33-1; $POCl_3$, 10025-87-3; PBr_5, 7789-69-7; NaSH, 16721-80-5; 3(2*H*)-pyridazinone, 504-30-3; P_2S_5, 1314-80-3.

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(19) Elemental analyses performed by Caltech Analytical Facility, Pasadena, Calif.

Pyrimidines. 14. Novel Pyrimidine to Pyrimidine Transformation Reactions and Their Application to *C*-Nucleoside Conversion. A Facile Synthesis of Pseudoisocytidine[1,2]

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Novel pyrimidine to pyrimidine transformations by nucleophilic displacement of the N_1–C_2–N_3 portion of 1,3-dialkyluracils (I) by the N–C–N fragment of several 1,3-ambident nucleophiles have been investigated. Treatment of 1,3-dimethyluracil (Ia) with guanidine in refluxing ethanol afforded isocytosine (IIa). The ease with which the reaction occurs depends on the electronic nature of the substituent at C-5 and C-6 as well as the steric environment at C-6. Treatment of Ia with methylguanidine gave 2-*N*-methylisocytosine (III) (59%) and 1-methylisocytosine (IV) (19%). Compound Ia was also converted into uracil (V) and 2-thiouracil (VI) by treatment with urea and thiourea, respectively, in ethanol in the presence of sodium ethoxide. 1-Alkylated 2-thiouracils (VIb and VIc) were obtained as the major products when Ia was treated with 1-methylthiourea or 1-*n*-butylthiourea. Treatment of Ia with excess 1,3-dimethylthiourea afforded 1,3-dimethyl-2-thiouracil (VId). A plausible mechanism for the transformation of I to VI is offered. When Ia was treated with *S*-ethylthiuronium bromide, 2-*N*-cyanoisocytosine (VII) was obtained. Treatment of Ia with formamidine, acetamidine, benzamidine, or 1,1-dimethylurea in base caused decomposition of the nucleophilic reagents and unchanged Ia was recovered. Uracil, 1-methyluracil, or 3-methyluracil could not be converted into isocytosine by treatment with guanidine under various conditions. Application of this transformation reaction to 1,3-dimethylpseudouridine (VIII) gave the antileukemic agent pseudoisocytidine (IXa) in good yield when treated with guanidine. 2-*N*-Methylpseudoisocytidine (IXb) and 2-thiopseudouridine (X) were also prepared by treatment of VIII with *N*-methylguanidine and thiourea, respectively.

Certain uracil derivatives exhibit high reactivity toward nucleophilic reagents, such as NaSH,[3] Na_2SO_3,[4] $NaHSO_3$,[4,5] RSH,[4-6] ROH,[7] RNH_2,[8] NaCN,[9] and NaN_3,[10] bringing about addition, addition–elimination, cine substitution, or ring formation reactions. These reactions are known to occur via initial attack of a nucleophile on the pyrimidine C-6 position, giving rise to a 5,6-dihydropyrimidine intermediate from which the respective product is formed. In these transformations, the arrangement of the atoms in the pyrimidine ring is unchanged *throughout* the reaction.

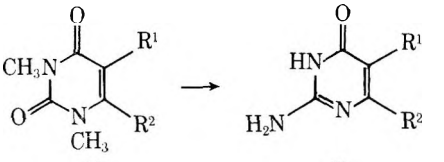
Pyrimidine to pyrimidine ring transformation by replacement of one ring nitrogen with another nitrogen atom has long been known (viz., the Dimroth rearrangement and its related reactions).[11] Replacement of a pyrimidine ring carbon by an exocyclic carbon atom by the Dimroth type mechanism has also been reported.[12]

Pyrimidine to pyrimidine transformation by replacement of the N_1–C_2 or N_1–C_2–N_3 portion of the pyrimidine with 1,2- or 1,3-ambident nucleophiles, however, has not been known until very recently.[13,14] Oostveen et al.[13] reported the formation of 2-amino-4-phenylpyrimidine and 2-amino-5-phenylpyrimidine by treatment of 1-methyl-4-phenylpyrimidinium iodide and 1-methyl-5-phenylpyrimidinium iodide with cyanamide, *O*-methylisourea, or *S*-methylisothiourea in basic media. In these reactions the two-atom fragment (N_1–C_2) of the pyrimidine ring is replaced by an N–C fragment of the reagent. They[13] also reported the conversion of 1-methylpyrimidinium iodide into 2-phenylpyrimidine and 2-*tert*-butylpyrimidine by treatment with benzamidine or pivalamidine in base. In these reactions the N_1–C_2–N_3 fragment of the pyrimidine is replaced by the N–C–N fragment of the amidine. During the course of our investigations into methods for simple pyrimidine to pyrimidine transformations that would be applicable to *C*-nucleoside conversions, we developed a novel ring transformation reaction which should have wide usage in the pyrimidine area in general and in the *C*-nucleoside area in particular. Preliminary communications on this subject have appeared.[2,14]

Uracil and cytosine derivatives undergo ring transformation with hydrazine or hydroxylamine to give the corresponding pyrazoles and isoxazoles. These nucleophiles selectively attack the pyrimidines in nucleic acid chains; thus these reagents have been used extensively in the chemical modification of nucleic acids.[15] In these transformations, the 1,2-ambident nucleophiles attack the pyrimidine C-6 position and then replace the N_1–C_2–N_3 portion of the pyrimidine by two atoms leading to five-membered ring heterocycles.

However, when uracil was treated with 1,3-ambident nucleophile, such as guanidine or thiourea, under various conditions, no reaction occurred; i.e., the N_1–C_2–N_3 portion of uracil was not replaced by the N–C–N fragment of the nucleophiles. The inability of 1,3-ambident nucleophiles to attack uracil may be due to anion formation in basic media which renders attack by nucleophiles more difficult. Consequently, 1,3-dialkylated uracils, such as 1,3-dimethyluracil (Ia) which lacks dissociable protons, should be more susceptible to nucleophilic attack. Indeed, Shugar and Fox[16] observed the instability of 1,3-dimethyluracil (Ia) in 1 N base, and later a mechanism which accounts for this instability was proposed by Santi et al.[17] Whatever the detailed mechanism is, Ia is attacked by hydroxyl ion nucleophiles at the C-4 and C-6 positions with the liberation eventually of 1,3-dimethylurea and formylacetic acid and products therefrom.[18] The susceptibility of 1,3-dialkyl uracils to 1,3-ambident nucleophiles was, therefore, investigated.

Treatment of 1,3-dimethyluracil (Ia) with ~7 molar excess of guanidine in refluxing ethanol for 18 h afforded 2-amino-4-hydroxypyrimidine (IIa, isocytosine) in good yield. The ease



I II

a, $R^1 = R^2 = H$
b, $R^1 = CH_3$; $R^2 = H$
c, $R^1 = H$; $R^2 = CH_3$
d, $R^1 = F$; $R^2 = H$
e, $R^1 = Br$; $R^2 = CH_3$

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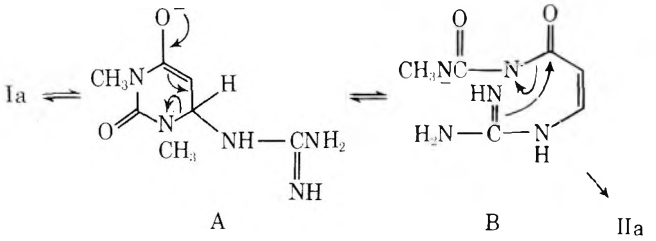
with which the reaction occurs depends on susceptibility of the pyrimidine C-6 position to nucleophilic reagents. Therefore the electronic nature of the substituent at C-5 and C-6 as well as the steric environment at C-6 will affect the ease of the reaction. Thus 5-fluoro-1,3-dimethyluracil (Id) was converted readily into 5-fluoroisocytosine (IId) in a few hours in refluxing ethanol, whereas transformation of 1,3-dimethylthymine (Ib) to 5-methylisocytosine (IIb) required more stringent conditions (such as fusion with guanidine at 80–90 °C). Also, while conversion of 1,3,6-trimethyluracil (Ic) into 6-methylisocytosine (IIc) required fusion conditions with guanidine, 5-bromo-1,3,6-trimethyluracil (Ie) was readily converted into 5-bromo-6-methylisocytosine (IIe) by treatment with guanidine in refluxing ethanol. In the case of Id or Ie, the isolated yield of the product was poor (~20%) due probably to participation of the C-5 halogen substituent in side reactions with guanidine.

Reaction of 1,3-dimethyluracil (Ia) with methylguanidine in refluxing ethanol gave a mixture from which 2-*N*-methylisocytosine (III) (59%) and 1-methylisocytosine (IV) (19%) were isolated. The isomer, 3-methylisocytosine, was not detected in the reaction mixture.

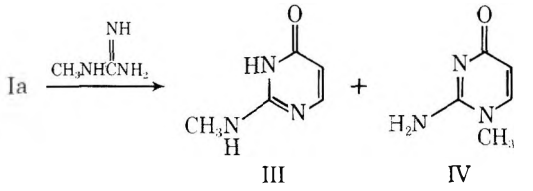
A plausible mechanism[14] to explain the above results may be formulated as shown for the conversion of Ia to IIa via postulated intermediates A and B. The mechanism proposed



A B IIa

above has close similarity to the one proposed for the conversion of 1-methylpyrimidinium iodide into a 2-substituted pyrimidine with an amidine nucleophile.[13]

Formation of two products (III and IV) in the reaction of Ia and methylguanidine is probably due to competition for

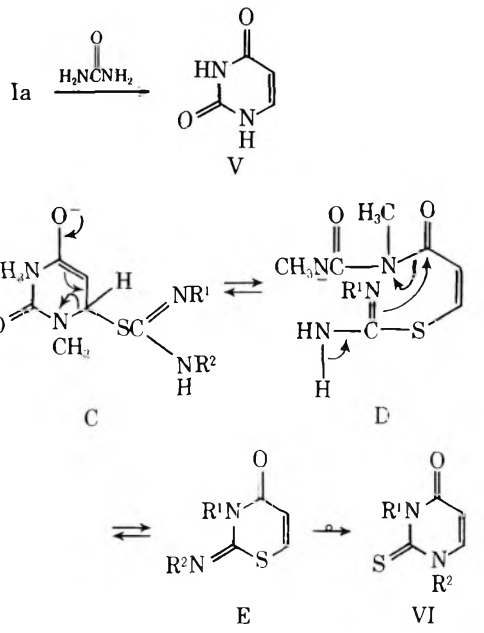


III IV

attack on C-6 of Ia between the stronger nucleophile (CH_3NH group) and sterically less-hindered nucleophile (NH_2 group) of the reagent.

Urea and thiourea, which are weaker bases than guanidine, did not react with Ia in ethanol. In the presence of sodium ethoxide, however, the reaction with these reagents proceeded smoothly with the formation of uracil (V) and 2-thiouracil (VIa), which were isolated in high yields. Reaction of Ia with 1-methylthiourea or 1-*n*-butylthiourea was also investigated. The major products were 1-methyl-2-thiouracil (VIb) and 1-*n*-butyl-2-thiouracil (VIc). The presence of 3-substituted-2-thiouracils was detected in the reaction mixture by ^1H NMR, but attempts to isolate these minor products failed. This method of synthesis of 1-alkyl-2-thiouracils is much simpler than the known multistep procedures.[19] Also, treatment of Ia with 1,3-dimethylthiourea in ethanolic sodium ethoxide gave 1,3-dimethyl-2-thiouracil (VId).

The reaction of I with thioureas probably proceeds via initial attack on C-6 of I by the sulfur nucleophile (which is more nucleophilic than nitrogen) to give C followed by ring opening at the N_1–C_6 bond to D. Subsequent attack by the sterically less-hindered nitrogen nucleophile in D on C-4 with

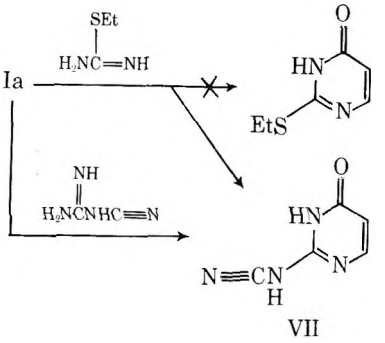


V C D E VI

a, $R^1 = R^2 = H$
b, $R^1 = H$; $R^2 = CH_3$
c, $R^1 = H$; $R^2 = n$-Bu
d, $R^1 = R^2 = CH_3$

liberation of 1,3-dimethylurea would result in the formation of the 1,3-thiazine intermediate E which, then, would rearrange to 2-thiouracils (VI) in the presence of excess alkali. Alkali-catalyzed rearrangements of 1,3-thiazines to 2-thiopyrimidines are known.[20]

Treatment of Ia with excess *S*-ethylthiuronium bromide in ethanolic sodium ethoxide afforded a crystalline product with the following characteristics. The UV spectral behavior was similar to that of isocytosine, but different from that of 2-alkylthiouracil.[21] The IR spectrum of the product showed the presence of a CN group (2190 cm^{-1}). Elemental analyses (C, H, N) were consistent with 2-*N*-cyanoisocytosine (VII). The same compound VII was obtained by treatment of Ia with

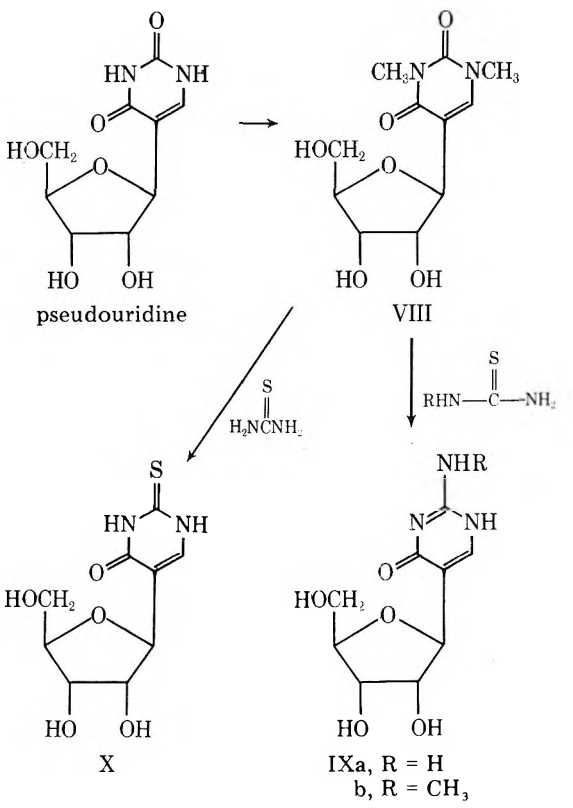


VII

cyanoguanidine. The formation of VII from the reaction of Ia with *S*-ethylthiuronium bromide in base may be explained by the instability of *S*-ethylisothiourea, which readily decomposes into cyanamide and ethyl sulfide.[22] Dimerization of cyanamide afforded cyanoguanidine, which then reacted with Ia to give VII.

Treatment of Ia with formamidine, acetamidine, or 1,1-dimethylurea in base caused decomposition of the nucleophilic reagents and unchanged Ia was recovered from the reaction mixture. Attempts to convert uracil, 1-methyluracil, or 3-methyluracil to isocytosine by treatment with guanidine under various conditions were uniformly unsuccessful. These failures are probably due to the anion formation by these uracils in a strongly basic media and which inhibits attack by nucleophiles.

5-(β-D-Ribofuranosyl)isocytosine (IXa, pseudoisocytidine)



was synthesized in our laboratory[23] and was found to be active against certain mouse leukemias.[24] This *C*-nucleoside IXa is currently under phase I clinical investigation at this center. The original synthesis of IXa consists of four or five reactions from D-ribose.[23] Application of this pyrimidine to pyrimidine transformation reaction to 1,3-dimethylpseudouridine (VIII), which was obtained in good yield by treatment of pseudouridine with dimethylformamide dimethyl acetal,[25] afforded pseudoisocytidine (IXa) in one step and the product was isolated as the crystalline hydrochloride salt in ~60% yield. Reaction of VIII with methylguanidine gave crystalline 2-*N*-methylpseudoisocytidine (IXb), which would be difficult to synthesize by other methods. A small amount of the α isomer of IXb was also isolated in crystalline form.

Treatment of VIII with thiourea in ethanolic sodium ethoxide solution under reflux gave crystalline 2-thiopseudouridine sodium salt (X) in good yield. The ^{1}H NMR spectrum of the salt, however, showed the product was contaminated with ~5% of the α isomer. After removal of the sodium ion, pure 2-thiopseudouridine (β) was obtained as a powder. The ^{1}H NMR and UV spectra of this sample were identical with those of 2-thiopseudouridine prepared previously from D-ribose.[23]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are corrected. ^{1}H NMR spectra were obtained on a JEOL J1M-PET-100 spectrometer, spectrometer, and Me_4Si was the internal standard for organic solvents and $Me_3Si(CH_2)_3SO_3Na$ for D_2O; chemical shifts are reported in parts per million (δ) and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet); δ and J values are first order. TLC was performed on a microscope slides coated with silica gel GF_{254} (Merck) and column chromatography on silica gel G. UV spectra were measured on a Cary Model 15 spectrometer and IR spectra were recorded on a Perkin-Elmer Infracord using pressed KBr pellets. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Conversion of 1,3-Dimethyluracils (I) into Isocytosines (II). Method A. Guanidine HCl (10 g) was stirred in 0.7 M ethanolic sodium ethoxide for 10 min and insoluble NaCl was removed by filtration. To the filtrate was added 0.01 mol of I and the mixture was refluxed under nitrogen. The reaction was followed by TLC ($CHCl_3$–MeOH, 5:1) and after the starting material disappeared the solvent was removed in vacuo. The residue was processed, depending on the dimethyluracil (I) employed, as described below.

Isocytosine (IIa). The residue of the reaction of Ia with guanidine was dissolved in 20 mL of water and the solution was passed through a column of Amberlite IRC-50 (H^+) (50 × 5.5 cm). The column was washed with water and the UV absorbing fractions were combined and evaporated in vacuo. The residue was triturated with ethanol and the solid was recrystallized from water to give 0.73 g of IIa (66%): mp 245–247 °C. The IR spectrum of this product was identical with that of an authentic sample.

5-Fluoroisocytosine (IId). The residue of the reaction of 1,3-dimethyl-5-fluorouracil[26] (Id) was dissolved in water (20 mL), the solution was poured on a column of Amberlite IRC-50 (H^+) (50 × 5.5 cm), and the product was eluted with water. The UV absorbing fractions were combined and evaporated in vacuo and the residue was further dried by several coevaporations with ethanol and chromatographed on a silica gel column (20 × 2.2 cm) using $CHCl_3$–MeOH (10:1) as the eluent. 5-Fluoroisocytosine (IId) was obtained after evaporation of the UV absorbing fractions and recrystallization of the residue from water: 230 mg (18%); mp 274–276 °C dec (lit.[27] mp 271–274 °C dec).

5-Bromo-6-methylisocytosine (IIe). The residue of the reaction of Ie and guanidine was triturated with water to give a solid which was crystallized from water. Crystalline IIe (430 mg, 22%) was obtained: mp 250 °C dec (lit.[28] mp 250 °C dec).

Isolation of 1,3-Dimethylurea. The residue of the reaction of Ia with guanidine was dissolved in 20 mL of water. The solution was neutralized with dry ice and extracted with $CHCl_3$ (3 × 50 mL). The combined extacts were dried over Na_2SO_4 and evaporated in vacuo and the residue was triturated with a small amount of benzene. Crystalline 1,3-dimethylurea (205 mg) was obtained, mp 102–103 °C, which was not depressed on admixture of an authentic sample.

Method B. 5-Methylisocytosine (IIb) and 6-Methylisocytosine (IIc). Guanidine hydrochloride (10 g) was stirred in 0.7 M sodium ethoxide in ethanol (100 mL) for 10 min, and then insoluble NaCl was removed by filtration. The filtrate was concentrated in vacuo to a thin syrup. Trimethyluracil (Ib or Ic) (800 mg) was added to the syrup and the mixture was heated to 80–90 °C with stirring for 6 h under nitrogen. The reaction mixture was diluted with water (20 mL), the solution was neutralized with Amberlite IRC-50 (H^+), and the neutral solution was evaporated to dryness in vacuo. The residue was crystallized from water. 5-Methylisocytosine (IIb) (590 mg, 91%) had mp 281–283 °C dec (lit.[28] mp 277–279 °C dec). 6-Methylisocytosine (IIc) was obtained in 45% yield (320 mg), mp 290–292 °C dec (lit.[29] mp 285–290 °C dec).

Reaction of Ia with Methylguanidine. To an ethanolic sodium ethoxide solution (prepared by dissolving 2.2 g of Na in 60 mL of ethanol) were added Ia (1.4 g, 0.01 mol) and methylguanidine sulfate (12.2 g, 0.1 mol). The mixture was refluxed overnight and then was allowed to cool to room temperature. Precipitated sodium sulfate was removed by filtration and the filtrate was evaporated in vacuo to a syrup which was dissolved in 20 mL of water and passed through a column of Amberlite IRC-50 (H^+) (55 × 5.5 cm). The eluate was evaporated to give a solid residue (1.16 g). TLC ($CHCl_3$–MeOH, 5:1) showed the residue contained one major and one minor component. Separation of the components was performed by silica gel column chromatography (50 × 2.2 cm) using $CHCl_3$–MeOH (10:1) as the eluent. The major product, 2-*N*-methylisocytosine (III) (790 mg, 59%), was obtained after recrystallization of the first fraction from ethanol: mp 214–215 °C (lit.[30] mp 214–215 °C). From the second fraction, 250 mg (19%) of 1-methylisocytosine (IV) was obtained after recrystallization from ethanol: mp 283–285 °C (lit.[30] mp 283–285 °C).

Conversion of Ia into Uracil (V). To a solution of ethanolic sodium ethoxide (1 M, 100 mL) were added Ia (1.4 g, 0.01 mol) and urea (6.0 g, 0.1 mol). The mixture was refluxed with stirring overnight and then the solvent was removed by evaporation in vacuo. The residue was dissolved in water (50 mL) and the solution was acidified with concentrated HCl to precipitate uracil (V), 0.7 g (64%), which was identical with an authentic sample of uracil with respect to UV and IR spectra.

Reaction of Ia with *n*-Butylurea. A mixture of Ia (700 mg) and *n*-butylurea (5.8 g) in ethanolic sodium ethoxide (prepared by dissolving 2.0 g of Na in 50 mL of ethanol) was refluxed for 20 h and the solvent was removed in vacuo. The residue was dissolved in water (50 mL) and the solution was extracted with $CHCl_3$ (2 × 50 mL). The aqueous layer was acidified with concentrated HCl and then extracted with $CHCl_3$ (2 × 50 mL). The latter $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated in vacuo to a syrup which was triturated with water. 3-*n*-Butyluracil (120 mg) crystallized and was collected by filtration: mp 151–152 °C (lit.[31] mp 152–153 °C).

The filtrate was concentrated in vacuo to a syrup which was triturated with ether to give crystalline 1-*n*-butyluracil (125 mg): mp 101–103°C (lit.[32] mp 100–102 °C).

Conversion of Ia into 2-Thiouracils (VI). A mixture of Ia (0.01 mol) and thiourea derivative (0.03 mol) in ethanolic sodium ethoxide (prepared by dissolving 700 mg of Na in 50 mL of ethanol) was refluxed overnight, after which the solution was evaporated in vacuo. The residue was processed, depending on the thiourea employed, as described below.

2-Thiouracil (VIa). The residue was dissolved in water (20 mL) and the solution was acidified with concentrated HCl. The precipitate was collected by filtration and recrystallized from water to give 1.16 g (91%) of VIa, identical with an authentic sample of 2-thiouracil with respect to LV and IR spectral characteristics.

1-Methyl-2-thiouracil (VIb). When *N*-methylthiourea was employed, the residue was not soluble in water (20 mL). The suspension was acidified with concentrated HCl and the solid was collected by filtration. Recrystallization of the solid from ethanol gave VIb: 1.04 g (95%); mp 226–227 °C (lit.[19] mp 228 °C).

1-*n*-Butyl-2-thiouracil (VIc). The residue of the reaction of Ia with *N*-*n*-butylthiourea was dissolved in water (50 mL) and the solution was acidified with concentrated HCl. The oily precipitates were extracted with ether (2 × 50 mL) and the extracts were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on a silica gel column (50 × 2.2 cm) using benzene–ethyl acetate (5:1) as the eluent. Crude 1-*n*-butyl-2-thiouracil (VIc) was recrystallized from water: 1.5 g (81%); mp 132–133 °C; UV λ_{max} (pH 1–7) 269, 290 (sh) nm (ϵ 12 300, 10 300), λ_{min} (pH 1–7) 242 (4600), λ_{max} (pH 13) 236, 270 (20 300, 14 500), λ_{min} (pH 13) 255 (12 400); ^1H NMR ($CDCl_3$) δ 0.98 (3, H, t, CH_3, spacing ~7.6 Hz), 1.20–1.94 (4 H, m, $CH_2CH_2CH_2CH_3$), 4.18 (2 H, t, NCH_2, spacing ~7.6 Hz), 6.00 (1 H, dd, H-5, $J_{5,6} \sim 8.0$, $J_{3,5} \sim 2.2$ Hz; the latter coupling disappeared upon addition of D_2O), 7.24 (1 H, d, H-6).

Anal. Calcd for $C_8H_{12}N_2OS$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.10; H, 6.62; N, 15.16.

The mother liquor of recrystallization was evaporated to dryness. The ^1H NMR spectrum ($CDCl_3$) of the residue showed that it contained a small amount of 3-*n*-butyl isomer. In addition to all the signals for VIc, the following signals were observed: δ 4.37 (t, NCH_2, spacing ~7.6 Hz), 5.96 (d, H-5, $J_{5,6} \sim 8.0$ Hz), 7.10 (d, H-6).

1,3-Dimethyl-2-thiouracil (VId). When dimethylthiourea was used as the nucleophile, TLC ($CHCl_3$–MeOH, 5:1) of the reaction mixture showed three UV spots corresponding to VId, Ia, and 1,3-dimethylthiourea. The residue was dissolved in water (20 mL) and the aqueous solution was acidified with concentrated HCl and extracted with ether (2 × 50 mL). The ether extracts were dried (Na_2SO_4) and evaporated and the residue was chromatographed on a silica gel column (50 × 2.2 cm) using benzene–ethyl acetate (5:1) as the eluent. Compound VId (274 mg, 18%) obtained had mp 107–108 °C (lit.[19b] mp 109 °C).

2-Thiothymine from 1,3-Dimethylthymine (Ib). A mixture of 770 mg of Ib and 1.5 g of thiourea in ethanolic sodium ethoxide (prepared by dissolving 400 mg of Na in 30 mL of ethanol) was refluxed for 48 h. The solvent was removed by evaporation in vacuo and the residue was dissolved in water (10 mL). The aqueous solution was acidified with concentrated HCl. 2-Thiothymine which precipitated was collected and recrystallized from methanol: 470 mg; mp 264–267 °C dec (lit.[33] mp 265–267 °C dec).

Reaction of Ia with *S*-Ethylisothiourea. Isolation of 2-*N*-Cyanoisocytosine (VII). A mixture of Ia (1.4 g, 0.01 mol) and *S*-ethylthiuronium bromide (9.3 g, 0.05 mol) in 100 mL of 1 N ethanolic sodium ethoxide was stirred for 10 min at room temperature and insoluble NaBr was removed by filtration. The filtrate was refluxed for 24 h. On cooling the mixture, 530 mg of crystals separated, which were collected by filtration, dissolved in water (5 mL), and acidified with glacial acetic acid. The crystals that precipitated were collected: 480 mg; mp 295–300 °C (eff). The IR spectrum of this sample was identical with that of authentic 2-*N*-cyanoisocytosine (VII) prepared as described below.

2-*N*-Cyanoisocytosine (VII). A mixture of Ia (0.7 g, 5 mmol) and cyanoguanidine (1.26 g) in ethanolic sodium ethoxide (prepared by dissolving 0.35 g of Na in 50 mL of ethanol) was refluxed for 24 h and then evaporated in vacuo. The residue was dissolved in water (30 mL) and the solution was acidified with glacial acetic acid. Compound VII (640 mg, 93%) precipitated and was collected by filtration: mp 295–300 °C (eff); UV λ_{max} (pH 1) 241, 265 (sh) nm (ϵ 16 400, 8700), λ_{min} (pH 1) 219 (7300), λ_{max} (pH 7) 295, 243 (6900, 15 400), λ_{min} (pH 7) 268 (3000), λ_{max} (pH 13) 282, 246 (6400, 13 900), λ_{min} (pH 13) 267, 230 (5300, 9800).

Anal. Calcd for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.17. Found: C, 43.97; H, 3.06; N, 40.95.

1,3-Dimethylpseudouridine (VIII). A suspension of pseudouridine (1.0 g) in dimethylformamide dimethyl acetal (7 mL) was refluxed until a clear solution was obtained (~30 min). The solution was concentrated in vacuo to a syrup which was triturated with a small amount of acetone to give a solid (910 mg, 82%). Recrystallization of the crude precipitate from ethanol gave analytically pure VIII: mp 174 °C.

Anal. Calcd for $C_{11}H_{16}N_2O_6$: C, 48.52; H, 5.92; N, 10.29. Found: C, 48.63; H, 6.02; N, 10.38.

Pseudoisocytidine (IXa) from VIII. Guanidine hydrochloride (10.0 g, 0.1 mol) was added to 0.7 M sodium ethoxide in ethanol (100 mL) and the mixture was stirred at room temperature for 10 min and then filtered from sodium chloride. The filtrate was concentrated in vacuo below 30 °C. To the residue was added VIII (300 mg), and the mixture was heated at 80–90 °C under nitrogen for 50 min. Water (20 mL) was added and, after removal of a small amount of insoluble impurities by filtration, the filtrate was passed through a column of Amberlite IRC-50 (H^+) (30 × 3 cm) and the column was washed with water. The UV absorbing fractions were collected and evaporated in vacuo, and the residue was dissolved in a small amount of ethanol. Crystalline IXa (6 mg) precipitated and was collected by filtration: mp 192–192.5 °C (sintered), 193–194 °C (eff). The ^1H NMR (D_2O) spectrum of this sample was identical with that of pseudoisocytidine hydrochloride.[23]

The filtrate was evaporated to dryness in vacuo and the residue was dissolved in ~10% methanolic hydrogen chloride. Crystalline pseudoisocytidine hydrochloride, which precipitated out, was collected by filtration: mp 215–216 °C dec; 185 mg (60%). The ^1H NMR, UV, and IR spectra of this sample were identical with those of authentic pseudoisocytidine hydrochloride.[23]

2-*N*-Methylpseudosiocytidine (IXb). Methylguanidine sulfate (24.4 g) was stirred in 1.3 M ethanolic sodium ethoxide (150 mL) for 10 min and then Na_2SO_4 was removed by filtration. To the filtrate was added VIII (816 mg, 3 mmol), and the solvent was removed in vacuo to a syrup below 35 °C. The syrup was diluted with 10 mL of ethanol and the mixture was heated at 85–90 °C for 3 h under nitrogen and then concentrated to a syrup in vacuo. The residue was dissolved in water (30 mL) and neutralized by passing it through a column of Amberlite IRC-50 (H^+) (20 × 2.2 cm). The neutral solution was evaporated to dryness in vacuo and the residue was triturated with acetone. The solid obtained showed two spots on TLC ($CHCl_3$–MeOH, 4:1). After purification by silica gel column chromatography (50 × 2.2 cm) ($CHCl_3$–MeOH, 4:1), two UV absorbing fractions were obtained. Evaporation of the solvent of the first fraction gave 205 mg of the β isomer (IXb) as a powder. The HCl salt of IXb had: mp 207–208 °C dec; UV λ_{max} (pH 1) 265, 222 nm (ϵ 7200, 11 900), λ_{min} (pH 1) 244 (4500), λ_{max} (pH 7) 293, 222 (5500, 14 600), λ_{min} (pH 7) 252 (2400), λ_{max} (pH 13) 281, 233 (6200, 10 600), λ_{min} (pH 13) 257 (2800); ^1H NMR (D_2O) δ 2.87 (3 H, s, NCH_3), 3.77 (2 H, m, H-5′,5″), 4.03 (1 H, m, H-4′), 4.17 (1 H, t, H-3′, $J_{2',3'} \sim J_{3',4'} \sim 4.9$ Hz), 4.34 (1 H, t, H-2′, $J_{1',2'} \sim J_{2',3'} \sim 4.9$ Hz), 4.65 (1 H, d, H-1′), 7.73 (1 H, s, H-6).

Anal. Calcd for $C_{10}H_{15}N_3O_5$·HCl: C, 40.89; H, 5.49; N, 14.28. Found: C 40.86; H, 5.62; N, 13.89.

From the second fraction, the α isomer (75 mg) was obtained. After recrystallization from methanol, it had: mp 210 °C; UV λ_{max} (pH 1) 265, 223 nm (ϵ 6900, 11 900), λ_{min} (pH 1) 245 (4400), λ_{max} (pH 7) 295, 220 (4400, 16 200), λ_{min} (pH 7) 253 (2200), λ_{max} (pH 13) 282, 233 (6400, 10 800), λ_{min} (pH 13) 257 (2700); ^1H NMR (D_2O) δ 2.87 (3, H, s, NCH_3), 5.01 (1 H, narrow q, H-1′, $J_{1',2'} \sim 2.2$, $J_{1',6} < 0.5$ Hz), 7.64 (1 H, d, H-6, $J_{1',6}$). The overall spectral pattern was quite similar with that of α-pseudoisocytidine.[23]

Anal. Calcd for $C_{10}H_{15}N_3O_5 \cdot {}^1/_4H_2O$: C, 45.89; H, 5.97; N, 16.05. Found: C, 46.06; H, 6.16; N, 15.74.

2-Thiopseudouridine (X) from VIII. A mixture of VIII (544 mg, 2 mmol) and thiourea (760 mg, 10 mmol) in 1 M ethanolic sodium ethoxide (20 mL) was refluxed with stirring for 2 h. After cooling the mixture, the crystalline sodium salt of X (519 mg, 92%) was collected by filtration. The ^1H NMR (D_2O) spectrum showed that the crystalline sodium salt of X was contaminated with a small amount of the α isomer. The salt (100 mg) was dissolved in water (5 mL), the solution was placed on a column of Amberlite IRC-50 (H^+) (5 × 3 cm), and the column was washed with water. The UV absorbing fractions were combined and evaporated to dryness. The residue was triturated with cold ethanol. The white precipitate of X was collected by filtration. The ^1H NMR spectrum of X was identical with that of an authentic sample of 2-thiopseudouridine.[23]

Acknowledgment. The authors wish to thank Kyowa Hakko Kogyo Co., Ltd., Tokyo, for pseudouridine used in this study.

Registry No.—Ia, 874-14-6; Ib, 4401-71-2; Ic, 13509-52-9; Id, 3013-92-1; Ie, 15018-59-4; IIa, 674-97-5; IIb, 15981-91-6; IIc, 3977-29-5; IId, 1683-86-9; IIe, 6307-35-3; III, 22404-50-8; IV, 2080-17-3; V, 66-22-8; VIa, 141-90-2; VIb, 615-78-1; VIc, 64985-69-5; VIc (3-Bu isomer), 64975-70-8; VId, 1194-71-4; VII, 51741-99-2; VIII, 64272-68-0; IXa, 57100-18-2; IXa HCl, 59464-15-2; IXb HCl, 64975-71-9; IXb α isomer, 64999-53-7; X, 59464-18-5; guanidine hydrochloride, 14317-32-9; methylguanidine sulfate, 1866-88-2; urea, 57-13-6; butylurea, 592-31-4; 3-butyluracil, 28289-95-4; 1-butyluracil, 705-06-6; thiourea, 62-56-6; *N*-methylthiourea, 598-52-7; *N*-butylthiourea, 1516-32-1; 1,3-dimethylthiourea, 534-13-4; 2-thiothymine, 636-26-0; *S*-ethylthiuronium bromide, 1071-37-0; cyanoguanidine, 461-58-5; pseudouridine, 1445-07-4; dimethylformamide dimethyl acetal, 4637-24-5.

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Use of *o*- and *p*-Hydroxybenzyl Functions as Blocking Groups Which Are Removable with Base

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The successful development of the *o*- and *p*-hydroxybenzyl functions and the corresponding esters thereof as blocking groups which are removable with base is described. Specific illustrative examples include protecting and subsequently releasing 1-phenyl-2-tetrazoline-5-thione and thiosulfate anions.

In photography many compounds are used which react in some way with silver halide either as silver precipitants, complexers, or solvents. For example, 1-phenyl-5-mercaptotetrazole (PMT) (1) is a development restrainer and forms a very insoluble silver salt.[1] On the other hand, sodium thiosulfate (hypo) is a silver solvent and is used for fixing emulsions (dissolving undeveloped silver halide).[2] We became interested in preparing derivatives of these types of compounds which would be stable in a film system before processing the system with a highly alkaline developer fluid, but during such processing these same derivatives would have to release the active photographic species.

Esters of PMT are not hydrolytically stable. For example, the acetyl derivative readily hydrolyzes, since the PMT anion is a very good leaving group. PMT is a fairly strong acid, having a pK_a of 3.65.[3] In the solid state, the compound exists as the tautomeric 1-phenyl-2-tetrazoline-5-thione (2).[4]

There is considerable literature on the base instability of *o*- and *p*-hydroxybenzyl groups,[5] the decomposition going through quinone methide intermediates.[6] We decided to prepare *o*- and *p*-hydroxybenzyl chlorides or the corresponding esters as reagents to generate alkali-removable blocking groups for photographically active compounds.

The reagents with which we did the most work were *o*- and *p*-acetoxybenzyl chlorides **3**. These compounds are prepared in one step by reaction of the *o*- and *p*-hydroxymethylphenols with with acetyl chloride.[7] The isomeric *m*-hydroxymethylphenol does not undergo this reaction. It is desirable to have

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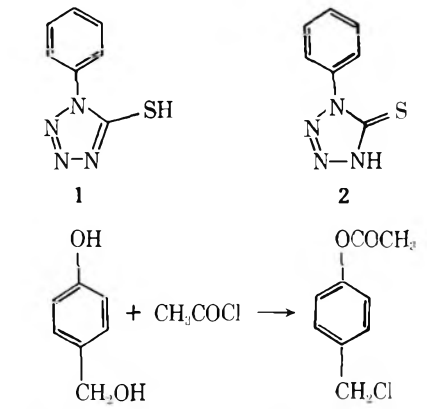


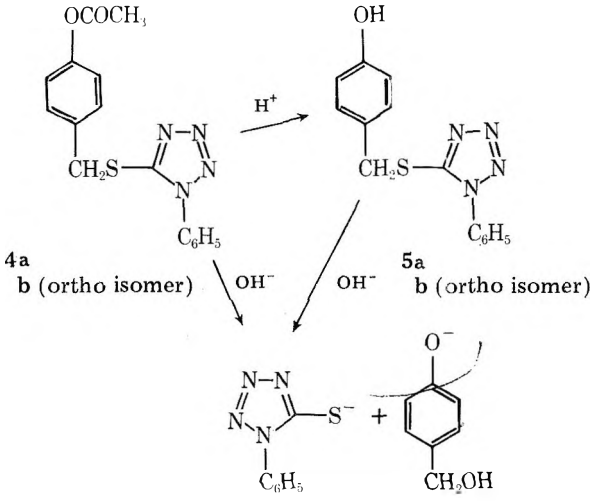
1 2

(also ortho isomer) 3a

b (ortho isomer)

these esters, since the unsubstituted chloromethylphenols readily decompose and polymerize.

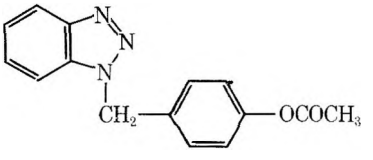
We found that the above compounds smoothly react to generate blocked PMT derivatives **4a,b**, which we formulate as the S-alkylated derivative. These ester derivatives can be hydrolyzed in acid to give the free hydroxybenzyl compounds **5a,b**. All of these compounds when treated with alkali rapidly



4a b (ortho isomer) 5a b (ortho isomer)

decompose to release the PMT anion. The quinone methide is converted to the anion of the hydroxymethylphenol. These reactions are readily followed by analysis of the products as well as by ^{1}H NMR and UV spectroscopy.

Although the cleavage reaction is very rapid in the case of PMT, a nitrogen analogue, 1-(*p*-acetoxybenzyl)benzotriazole (**6**), reacts much more slowly.



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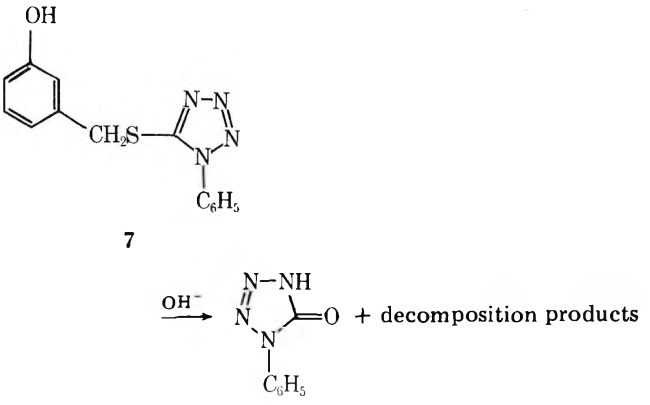
As a synthetic "proof" of the mechanism, we decided to prepare the meta derivative **7**. The intermediate, *m*-acetoxybenzyl chloride, was prepared in two steps.[8] The PMT derivative was found to undergo a very slow decomposition in alkali to yield a different product. Thus, instead of PMT anion being generated, the product was 1-phenyl-5-tetrazolone (**8**), the reaction most likely being attack of alkali on the tetrazole ring with cleavage of the sulfur bond in the opposite direction to that observed with the other isomers.

Another useful reagent was found to be the previously unreported 4-chloromethyl-2,6-dichlorophenol (**9**) readily prepared by chloromethylation of the phenol.[9] This compound



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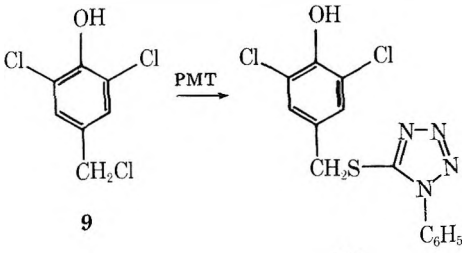
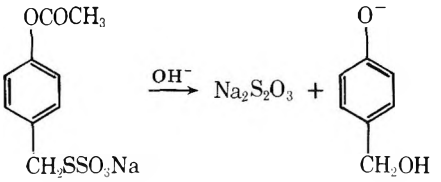
is quite stable and can be stored if kept dry. The PMT derivative **10** is readily prepared and deblocked with base.



9 10

We then focused on the special Bunte salts based on this chemistry, by reaction of sodium thiosulfate with *p*-acetoxybenzyl chloride. We succeeded in preparing sodium *S*-(*p*-acetoxybenzyl)thiosulfate (**11**), and this compound does indeed release hypo when treated with alkali while the corresponding sodium *S*-benzylthiosulfate does not.



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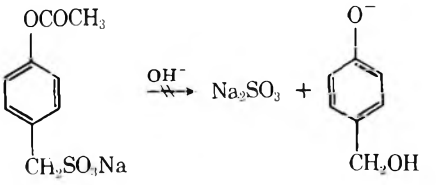
A similar release of sulfite ion was attempted. In this case, however, no sulfite ion could be detected after treatment for several hours with aqueous alkali.



12

Partial accounts of this work including applications have appeared in the patent literature.[10-13]

Experimental Section

p-Chloromethylphenyl Acetate (3a). Acetyl chloride (300 mL) was stirred in an open beaker with ice cooling. *p*-Hydroxybenzyl alcohol (99.3 g, 0.8 mol) was added in small portions so as to keep the evolution of HCl at a moderate rate. The excess of acetyl chloride was allowed to evaporate overnight, whereupon the remainder was neutralized with concentrated sodium bicarbonate solution. The organic phase was separated and the aqueous layer extracted twice with ether. The combined organic layers were filtered and dried over Drierite. Vacuum distillation through a 12-in. severed Vigreux column yielded 81 g (55%) of a colorless liquid; bp 104–106 °C (1.5 mm); n^{25}_D

1.5290.

Anal. Calcd for $C_9H_9ClO_2$: Cl, 19.3. Found: 19.3.

o-Chloromethylphenyl Acetate (3b). Acetyl chloride and o-hydroxybenzyl alcohol were reacted in the same manner as described above to yield o-chloromethylphenyl acetate, bp 98–100 °C (1.5 mm), n^{25}_D 1.5235, in 75% yield.

Anal. Calcd for $C_9H_9ClO_2$: Cl, 19.3. Found: 19.3.

5-(o-Acetoxybenzylthio)-1-phenyltetrazole (4b). Sodium 1-phenyltetrazole-5-thiolate (45 g, 0.225 mol) and o-chloromethylphenyl acetate (41.5 g, 0.225 mol) were dissolved in 600 mL of acetone. The solution was refluxed for 2 h and then filtered. The filtrate was evaporated to dryness and the residue extracted with 3% aqueous $NaHCO_3$ solution. The remaining solid was washed with water and dried to render 72 g (98%) of white crystals, mp 103–105 °C.

Anal. Calcd for $C_{16}H_{14}N_4O_2S$: C, 59.0; H, 4.3; N, 17.2; S, 9.8. Found: C, 58.8; H, 4.6; N, 16.9; S, 9.7.

5-(p-Acetoxybenzylthio)-1-phenyltetrazole (4a). Similarly, the reaction of sodium 1-phenyltetrazolethiolate with p-chloromethylphenyl acetate gave the corresponding thioether, mp 71–72 °C, in 80% yield.

Anal. Calcd for $C_{16}H_{14}N_4O_2S$: C, 59.0; H, 4.3; N, 17.2. Found: C, 58.9; H, 4.3; N, 17.3.

5-(o-Hydroxybenzylthio)-1-phenyltetrazole (5b). 5-(o-Acetoxybenzylthio)-1-phenyltetrazole (57 g, 0.175 mol) was dissolved in 1.3 L of methanol containing 0.2% concentrated HCl. The solution was stirred at 55–57 °C under nitrogen for 3 h followed by solvent evaporation. The residue was powdered, extracted with warm dilute $NaHCO_3$ solution, washed with water, and finally dried. Recrystallization from benzene/hexane gave 40 g (80%) of colorless crystals, mp 102–103 °C.

Anal. Calcd for $C_{14}H_{12}N_4OS$: C, 59.2; H, 4.2; N, 19.7; S, 11.8. Found: C, 59.2; H, 4.3; H, 19.7; S, 11.8.

5-(p-Hydroxybenzylthio)-1-phenyltetrazole (5a). Acid hydrolysis of the corresponding acetate in the previously described manner gave the free phenol, mp 130–131 °C, in 70% yield: ^1H NMR (Me_2SO) δ 4.40 (CH_2), 6.58, and 7.12 (arom protons), 7.83 (C_6H_5), 9.37 (OH); UV (50% *tert*-butyl alcohol) λ_{max} 228 nm, ϵ 17 000.

Anal. Calcd for $C_{14}H_{12}N_4OS$: C, 59.2; H, 4.2; N, 19.7. Found: C, 59.2; H, 4.4; N, 19.7.

Alkaline Hydrolysis of o- and p-Hydroxybenzylthio-1-phenyltetrazoles. The free phenols as well as their acetates were stirred in 5% aqueous NaOH at 25–30 °C for about 2 h. The reaction mixture was centrifuged and repeatedly extracted with ether. Acidification with HCl gave a voluminous, slightly yellow precipitate, which was recrystallized from benzene. The product was identified by means of elemental and spectral analysis as pure 1-phenyltetrazoline-5-thione. The ^1H NMR spectrum of the compounds in Me_2SO-d_6 containing KOD showed a complex aromatic signal and a shift of 0.3 ppm from δ 4.4 (CH_2S) to 4.1 ppm (CH_2O). Although in the parent compounds we have no direct proof of S-alkylation, we feel that not only is it the predictable isomer but also that the chemical shift for CH_2N would be more like that of compound **6**, δ 5.7.

1-(p-Acetoxybenzyl)benzotriazole (6). To a solution of 2.5 g (2.06 mmol) of 2,4,6-trimethylpyridine in 50 mL of diethyl ether was added with stirring a solution of 3.5 g (1.89 mmol) of p-acetoxybenzyl chloride in 10 mL of ether. The hazy reaction mixture was refluxed overnight, followed by solvent evaporation and extraction with 10 mL of water and 50 mL of ether. The ether phase was washed with water and dried with anhydrous Na_2SO_4. Solvent evaporation yielded a pale-yellow oil which solidified on treatment with a hexane/methanol mixture. Recrystallization from hexane/methanol gave 2 g (40%) of white crystals; mp 89 °C; ^1H NMR (CD_3OD) δ 2.0 (CH_3), 5.7 (CH_2N), multiple signals at 6.6, 7.0, 7.4, and 7.8 ppm (aromatic ring systems).

Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.4; H, 4.9; N, 15.8. Found: C, 67.3; H, 5.2; N, 15.6.

Alkaline cleavage: to the CD_3OD solution was added 5 wt % of KOD, followed by heating at 70 °C for 4 h. The following changes in the ^1H NMR spectrum were recorded: decrease in the intensity of the signal at δ 5.7 (CH_2N) and appearance of new signal at δ 4.1 ppm (CH_2O); signal strength ratio 3:1 (25% cleavage).

5-(m-Hydroxybenzylthio)-1-phenyltetrazole (7). A solution of sodium 1-phenyltetrazole-5-thiolate (4.5 g, 22.5 mmol) and m-chloromethylphenyl acetate[6] (4.15 g, 22.5 mmol) in acetone (200 mL) was heated to reflux for 2 h. Filtration and solvent evaporation yielded a pale-yellow oil. The latter was heated at 54 °C in methanol in the presence of HCl to give a solid which was recrystallized from benzene: white crystals, mp 111 °C, yield 2 g (31%).

Anal. Calcd for $C_{14}H_{12}N_4OS$: C, 59.2; H, 4.2; N, 19.7. Found: C, 59.1; H, 4.2; N, 19.8.

Alkaline Hydrolysis of m-Hydroxybenzylthio-1-phenyltetrazole. Unlike the ortho and para isomer, the meta-substituted derivative was not changed by dilute aqueous NaOH at room temperature. Heating at 50–60 °C with 10% NaOH gave a clear odorous solution. The pH was adjusted to 8, followed by ether extraction. The aqueous layer was evaporated to dryness, and the solid was extracted with ether and recrystallized from 2-propanol/water. The colorless crystalline product melted at 190 °C and was found to be identical with 1-phenyl-5-tetrazolone (8).[14]

Anal. Calcd for $C_7H_6N_4O$: C, 51.9; H, 3.7; N, 34.6. Found: C, 52.2; H, 3.7; N, 34.5.

4-Chloromethyl-2,6-dichlorophenol (9). 2,6-Dichlorophenol (41.8 g, 0.256 mol) was dissolved in heptane (300 mL) with heating and stirring under a nitrogen blanket. A mixture of 37% aqueous formaldehyde solution (250 mL, 3.1 mol) and concentrated HCl (500 mL) was prepared, three quarters of which was added to the phenol solution. The remainder was introduced after letting the reaction mixture reflux for 8 h. Simultaneously, the introduction of HCl gas was started. The reflux conditions were maintained for a total of 24 h. The organic layer was separated, the aqueous layer was extracted with ether, and the extracts were combined with the oil phase. Recrystallization of the evaporation residue gave 35 g (64%) of white needles, mp 87.5–89 °C.

Anal. Calcd for $C_7H_5Cl_3O$: C, 39.7; H, 2.4; Cl, 50.3. Found: C, 39.4; H, 2.4; Cl, 50.6.

5-(3,5-Dichloro-4-hydroxybenzylthio)-1-phenyltetrazole (10). A solution of sodium 1-phenyltetrazole-5-thiolate (3 g, 0.015 mol) in acetone (20 mL) was treated with 4-chloromethyl-2,6-dichlorophenol (3.2 g, 0.015 mol) in acetone (20 mL). Immediate precipitation of NaCl was noticed. The mixture was refluxed for 2 h and then filtered and evaporated to yield a white solid, mp 127–130 °C. Recrystallization from benzene/hexane gave the pure compound, mp 132–134 °C, in 90% yield (4.8 g).

Anal. Calcd for $C_{14}H_{10}Cl_2N_4OS$: C, 47.6; H, 2.9; N, 15.8; Cl, 20.2; S, 9.0. Found: C, 47.7; H, 3.0; N, 15.7; Cl, 19.9; S, 8.9.

Sodium S-(p-Acetoxybenzyl) Thiosulfate (11). To a solution of $Na_2S_2O_3 \cdot 5H_2O$ (27.3 g, 0.11 mol) in H_2O (60 mL) was added ethanol (5 mL). The mixture was heated at 55–65 °C and p-chloromethylphenyl acetate (18.45 g, 0.1 mol) in 60 mL of ethanol was added from a dropping funnel over a period of 45 min. The clear solution was stirred at 65–70 °C for another 45 min. Then the solvent was evaporated and the residue extracted with hot ethanol (about 700 mL). The extract was filtered hot and refrigerated to give a crystalline material (19 g, 75%): mp 220 °C (decomposition); UV (in ethanol) λ_{max} 265, 272 nm (ϵ 435, 325).

Anal. Calcd for $C_9H_9S_2O_5Na$: C, 38.1; H, 3.2; S, 22.5. Found: C, 37.9; H, 3.2; S, 22.4.

Treatment of the compound with aqueous NaOH gave a white precipitate. The supernatant liquid acted as silver complexing agent, solubilizing silver ion in alkaline solution.

Sodium S-Benzyl Thiosulfate. By use of the above procedure substituting p-chloromethylphenyl acetate with benzyl chloride, sodium S-benzyl thiosulfate was isolated as white platelets, mp ~210 °C (decomposition). Aqueous NaOH caused an oily brown precipitate to form. Silver ion was not solubilized, indicating hypo was not released.

Sodium p-Acetoxybenzyl Sulfonate (12). To a solution of 6 g (0.048 mol) of Na_2SO_3 in 30 mL of water was added at 70–73 °C a solution of 8.8 g (0.048 mol) of p-chloromethylphenyl acetate in 30 mL of ethanol. The hazy solution was diluted with 50 mL of ethanol and stirred at 75 °C for 2 h. A small amount of a white solid settled out. The clear supernatant was freed of solvent to render a white crystalline residue which was recrystallized twice from ethanol. The yield was 2 g of an extremely hygroscopic solid. The IR spectrum showed only a very weak carbonyl absorption band at 1720 cm^{-1}. Elemental analysis showed the solid to be a mixture of the p-acetoxy and p-hydroxybenzyl sulfonates. When the solid was treated with aqueous alkali, no evidence of sulfite release was found, as evidenced by a negative iodine test. Since neither the hydroxy compound nor its acetate released sulfite, no further work was done to separate these compounds into pure components.

Registry No.—**3a**, 39720-27-9; **3b**, 15068-08-3; **4a**, 39720-25-7; **4b**, 39720-28-0; **5a**, 39720-23-5; **5b**, 39720-24-6; **6**, 64706-07-6; **7**, 64706-08-7; **8**, 5097-82-5; **9**, 45952-61-2; **10**, 64706-09-8; **11**, 39941-32-7; **12**, 64706-10-1; acetyl chloride, 75-36-5; p-hydroxybenzyl alcohol, 623-05-2; o-hydroxybenzyl alcohol, 90-01-7; sodium 1-phenyltetrazole-5-thiolate, 15052-19-4; 1-phenyltetrazoline-5-thione, 86-93-1; m-chloromethylphenyl acetate, 4530-44-3; 2,6-dichlorophenol, 87-65-0; formaldehyde, 50-00-0.

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Synthesis of γ- and δ-(1,3-Dithianyl) β-Keto Esters[1]

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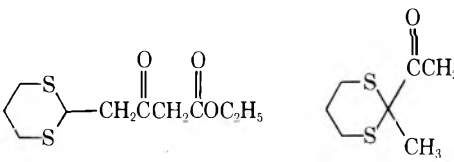
The preparations of ethyl γ-(1,3-dithian-2-yl)acetoacetate (**1**), *tert*-butyl 3-oxo-4-trimethylenedithiopentanoate (**2**), and ethyl 5-benzyloxy-3-oxopentanoate (**3**) are described. Some additional reactions relevant to the chemistry of dithiane are also discussed.

Previous papers from this laboratory have described an unambiguous approach to the synthesis of 6-substituted pteridines by guanidine cyclization of 2-amino-3-cyano (or alkoxycarbonyl) pyrazines suitably substituted at position 5. These latter critical intermediates were prepared in turn by cyclization of aminomalononitrile (or esters of α-aminocyanoacetic acid) with an α-ketoaldoxime, followed by deoxygenation of the resulting pyrazine 1-oxide (see Scheme I).[3] In this sequence, the group α to the carbonyl of the α-ketoaldoxime becomes the C-6 substituent on the final pteridine. Since the α-ketoaldoximes are themselves prepared from β-keto esters by hydrolysis, oximation, and subsequent decarboxylation, the preparation of a specific C-6 substituted pteridine requires an appropriately substituted β-keto ester. Our current interest in the preparation of certain 2,4-diaminopteridines carrying side chains at position 6 substituted with carbonyl groups thus necessitated the preparation of a variety of β-keto esters containing a (potential) carbonyl at either the γ or δ position. This paper describes our efforts to prepare β-keto esters **1**, **2**, and **3**.



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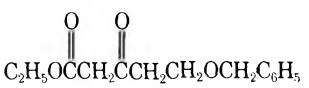
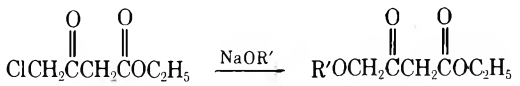


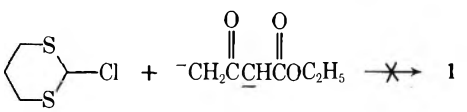
3

Initial approaches to **1** attempted to attach the dithiane moiety directly to the γ position of an appropriately substituted acetoacetic ester. A promising model was the successful conversion of ethyl γ-chloroacetoacetate (**4**) with excess alkoxide to yield γ-alkoxy derivatives in good yield.[4] Unfortunately, however, no reaction occurred between 2-lithio-1,3-dithiane and **4** (as its sodium salt). The dithiane anion is apparently not sufficiently nucleophilic to displace the γ-chloro substituent.[5] Attempts to carry out this reaction in the presence of 1 equiv of sodium iodide[6] resulted only in self-condensation of **4**.



4

An alternative approach to **1** involves treatment of 2-chloro-1,3-dithiane (**5**)[7] with the dianion of ethyl acetoacetate.[8] No displacement of halide ion occurred; instead, the dianion was protonated by **5**, leading to the recovery of ethyl acetoacetate and to the decomposition of the dithiane moiety.



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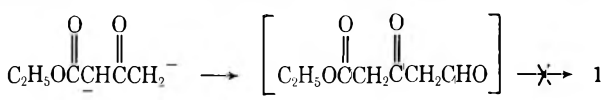
Since direct linkage of 1,3-dithiane with the γ position of ethyl acetoacetate did not seem feasible, an attempt was made to incorporate this moiety indirectly. Treatment of the dianion of ethyl acetoacetate with methyl formate gave the unstable aldehyde **6**,[9] but attempted reaction of this material with



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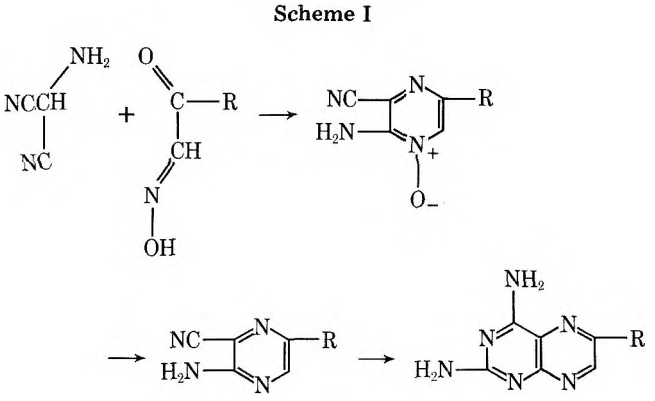
propane-1,3-dithiol resulted only in the formation of an intractable tar; no **1** could be isolated.

Scheme I



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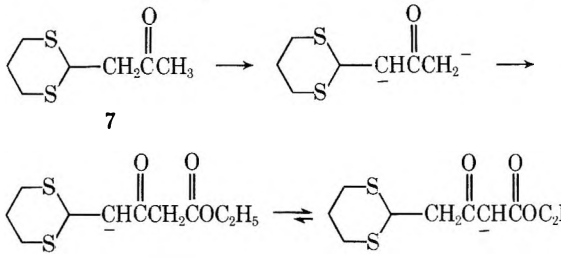
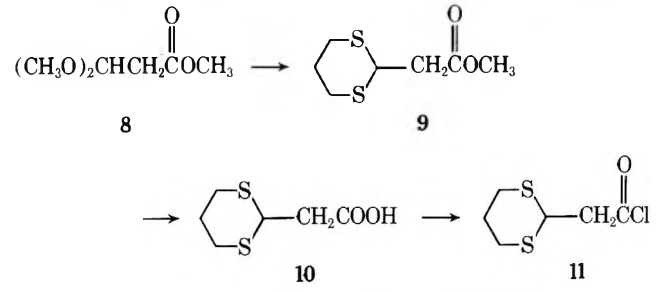
An alternative conceptual approach to **1** would utilize a 1,3-dithiane unit already possessing a carbon substituent at position 2 capable of elaboration to the desired β-keto ester. Thus, α-(1,3-dithian-2-yl)acetone (**7**), although an unsymmetrical ketone, would be expected to undergo selective functionalization on the methyl group (kinetically favored product).[10] Treatment of **7** with 2 equiv of lithium diethylamide, followed by quenching with ethyl chloroformate, indeed gave the desired β-keto ester **1** but only in 15% yield. All attempts to improve this reaction by the use of different solvents or alternate bases failed.

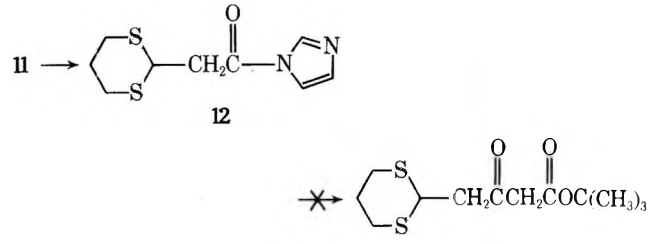


The use of diketene as a β-keto ester synthon was then briefly examined. It is known that diketene reacts with chlorine to give γ-chloroacetoacetyl chloride which, on treatment with alcohols, affords esters of γ-chloroacetoacetic acid.[11] It therefore seems reasonable to anticipate that treatment of diketene with 2-chloro-1,3-dithiane using titanium tetrachloride as catalyst, followed by addition of ethanol, might yield the desired β-keto ester **1**. Instead, ethyl acetoacetate was recovered from the reaction mixture, and it appears that 2-chloro-1,3-dithiane is completely unreactive toward diketene. Only tar formation was observed upon attempts to react diketene with triethyl orthoformate in the presence of boron trifluoride as catalyst.[12]

A stepwise approach to **1** was then considered. Treatment of methyl 3,3-dimethoxypropanoate (**8**)[13] with propane-1,3-dithiol gave methyl (1,3-dithian-2-yl)acetate (**9**) in 81% yield. Hydrolysis of **9** to the corresponding carboxylic acid **10**,

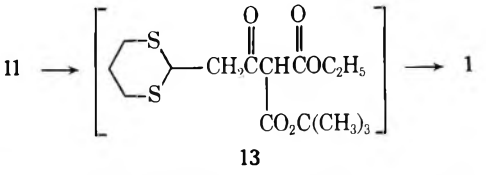


followed by treatment with oxalyl chloride, gave the corresponding acid chloride **11** in 93% overall yield. Surprisingly, however, attempts to convert **11** directly to the desired β-keto ester **1** were unsuccessful. For example, only decomposition was observed when **11** was treated with 1 equiv of lithio *tert*-butyl acetate in the presence of 1 equiv of lithium diethylamide.[14] Since this may have been the result of deprotonation of **11** by the strongly basic nucleophile, **11** was converted to the acyl imidazole **12**, which was then treated with lithio *tert*-butyl trimethylsilylacetate, a reagent developed by Rathke for the preparation of β-keto esters.[15] Unexpectedly,

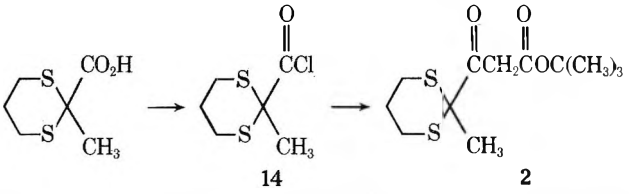


however, *tert*-butyl trimethylsilylacetate was obtained in quantitative yield from this reaction; no trace of acylation by **12** was observed.

In order to avoid the use of a nucleophilic reagent which was also strongly basic, **11** was treated with the magnesium ethoxide salt of *tert*-butyl ethyl malonate,[16] and the resulting adduct **13** was then heated under reflux in xylene in the presence of *p*-toluenesulfonic acid as catalyst. The desired β-keto ester **1** was thus finally obtained in 44% overall yield from **9**.

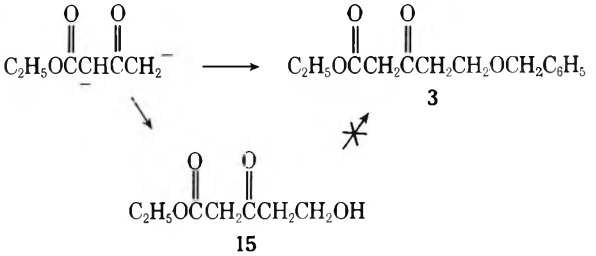


Preparation of the desired β-keto esters **2** and **3** proved to be more straightforward. Thus, **2** was obtained from 2-methyl-1,3-dithiane-2-carboxylic acid[5] by initial conversion with oxalyl chloride to its acid chloride **14**, followed by reaction



with lithio *tert*-butyl acetate (65% overall yield). The success of this reaction, in contrast to the failure of the corresponding attempted acylation of lithio *tert*-butyl acetate with the acid chloride **11**, is consistent with our assumption that monosubstituted dithiane substrates are incompatible with nucleophiles which are strong bases.

Finally, the desired β-keto ester **3** was prepared directly by alkylation of the dianion of ethyl acetoacetate with chloromethyl benzyl ether. This method proved to be superior to an alternative route which involved condensation of the dianion of ethyl acetoacetate with formaldehyde to give **15**, followed by attempted alkylation of the hydroxyl group with benzyl chloride; this latter step was complicated by competitive alkylation on the enol oxygen.

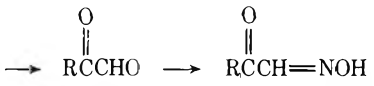


Although the preparation of **1**, **2**, and **3** completed this phase of the project, some additional reactions relevant to the chemistry of dithiane were carried out which are reported briefly below.

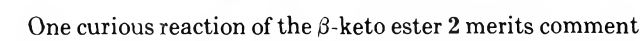
Since our purpose in preparing various γ-substituted β-keto esters was to convert them subsequently to α-ketoaldoximes, an alternative synthesis of these latter key intermediates for pteridine synthesis was explored in which the dithiane moiety was designed to serve as the potential α-keto functionality. Thus, it was envisioned that a 2-substituted dithiane might then, by selective trans-oximation with acetone oxime,[17] give the desired α-ketoaldoxime. Treatment of 2-lithio-1,3-dithiane with bromoacetaldehyde diethylacetal gave the known acetal **16**.[5] Formylation of **16** then gave the aldehyde **17** in good yield, but all attempts to deprotect this latter intermediate (NBS in aqueous acetone, NCS, $AgNO_3$ in aqueous ac-

etonitrile,[18] SO_2Cl_2, silica gel[19]) failed. Attempted conversion of the aldehyde functionality to its corresponding acetal led only to polymerization.

16, R = $CH_2CH(OC_2H_5)_2$ 17, R = $CH_2CH(OC_2H_5)_2$

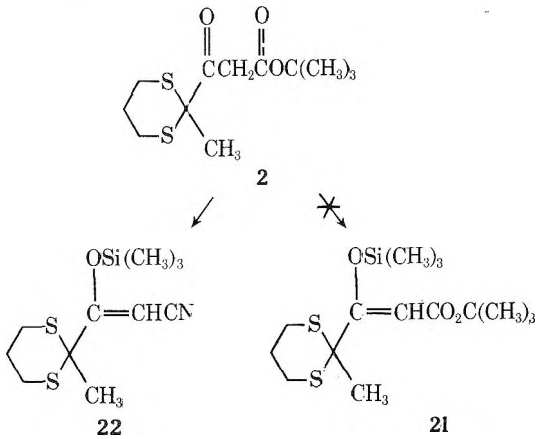


In view of this failure to convert the substituted dithiane 17 to the corresponding α-ketoaldehyde, we briefly explored the possible utilization in this reaction scheme of an alternative acyl anion equivalent, ethyl ethylthiomethyl sulfoxide, 18.[20] We have found, as have others,[21] that 18 could not be prepared by $NaIO_4$ oxidation of bis(ethylthio)methane (19) as had been reported:[20] instead, 18 was prepared by peracid oxidation of 19.[21] However, attempted reaction of the anion of 18 (under conditions identical to those successfully employed in the formation of 16) with bromoacetaldehyde diethylacetal was unsuccessful, and only starting materials were recovered. It appears that bromoacetaldehyde diethyl acetal is an unpredictable electrophile; although no reaction took place with the dianion of ethyl acetoacetate, it did react successfully with the anion of bis(ethylthio)methane (19) to give the expected product 20.



19 20

One curious reaction of the β-keto ester 2 merits comment at this time. We were interested in the conversion of 2 to its *O*-trimethylsilyl derivative 21, which was to serve as a substrate for a subsequent oximation. A recent procedure[22] for the preparation of such derivatives from methyl β-keto esters uses hexamethyldisilazane and a catalytic amount of imidazole. Reaction of 2 under these conditions gave a product which, although it possessed the expected trimethylsilyl grouping, had lost the *tert*-butyl group and apparently possessed a nitrile substituent (IR band at 2210 cm^{-1}). The presence of nitrogen was confirmed by combustion analysis which indicated a molecular formula of $C_{11}H_{19}NOS_2Si$. It thus appeared that the product of this reaction was 1-cyano-2-trimethylsilyloxy-3-trimethylenedithio-1-butene (22), and this was confirmed by an independent synthesis from the acid chloride 14. Thus, treatment of 14 with lithioacetonitrile[23] gave the β-ketonitrile 23, which underwent normal O-trimethylsilation to give 22 upon treatment with hexamethyldisilazane in the presence of imidazole. The mechanism of this unusual transformation of 2 to 22 is unclear, but it may not represent a general reaction, since the ester moiety of *tert*-butyl acetoacetate remains intact under the same reaction conditions.



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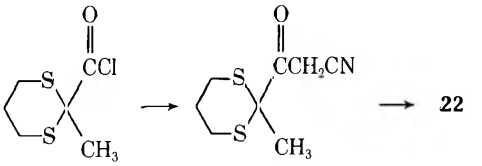

14 23 22

Experimental Section

Methyl (1,3-Dithian-2-yl)acetate (9). A mixture of 17.2 g (0.116 mol) of methyl 3,3-dimethoxypropanoate, 1.25 g (0.166 mol) of propane-1,3-dithiol, 0.2 g of *p*-toluenesulfonic acid, and 200 mL of benzene was heated at reflux for 25 h. The mixture was concentrated and the residue distilled under reduced pressure. After a small amount of forerun was collected, the product distilled at 108–109 °C (0.3 Torr); yield 18.0 g (81%). NMR ($CDCl_3$) δ 1.8–2.3 (m, 2), 2.8–3.1 (m, 6), 3.79 (s, 3), 4.49 (t, 1); IR (neat) 1735 (ester) cm^{-1}.

Anal. Calcd for $C_7H_{12}O_2S_2$: C, 43.72; H, 6.29; S, 33.35. Found: C, 43.67; H, 6.02; S, 33.42.

(1,3-Dithian-2-yl)acetic Acid (10). A mixture of 14.8 g (77 mmol) of **9**, 6.16 g (154 mmol) of sodium hydroxide, and 50 mL of water was heated at reflux for 0.5 h. The mixture was cooled to room temperature and then acidified with concentrated HCl. After cooling, the mixture was filtered, washed with cold water, and then dried in vacuo to afford 13.3 g (97%) of **10** as a white fluffy solid, mp 109–110 °C. This material was used without further purification, although it could be recrystallized from CCl_4: NMR ($CDCl_3$) δ 1.8–2.3 (m, 2), 2.8–3.1 (m, 4), 4.42 (t, 1), 9.90 (s, 1); IR (KBr) 3200–2800 (OH), 1690 (carbonyl) cm^{-1}.

Anal. Calcd for $C_6H_{10}O_2S_2$: C, 41.42; H, 5.65; S, 35.97. Found: C, 41.13; H, 5.19; S, 35.35.

(1,3-Dithian-2-yl)acetyl Chloride (11). A mixture of 1.78 g (10 mmol) of **10**, 0.40 g (10 mmol) of sodium hydroxide, and 10 mL of water was gently heated until homogeneous and then concentrated under reduced pressure. The resulting sodium salt was dried in vacuo [100 °C (0.5 Torr) for 2 h] and then added slowly to a stirred solution of 1.52 g (12 mmol) of oxalyl chloride in 40 mL of benzene at room temperature. After addition was complete, the mixture was heated at reflux for 2 h, cooled, filtered to remove NaCl, and concentrated under reduced pressure to give 1.9 g (100%) of **11** as a light brown liquid. This material was used without further purification: NMR ($CDCl_3$) δ 1.7–2.1 (m, 2), 2.7–3.1 (m, 4), 3.27 (d, 2), 4.30 (t, 1); IR (neat) 1790 (carbonyl) cm^{-1}.

(1,3-Dithian-2-yl)acetylimidazole (12). To a stirred solution of 2.45 g (36 mmol) of imidazole in 25 mL of dry THF at room temperature was added a solution of 3.5 g (18 mmol) of **11** in 10 mL of THF. The mixture was heated at reflux for 0.5 h, cooled, and filtered, and the filtrate was concentrated under reduced pressure to give an oil which solidified while being dried in vacuo overnight. Recrystallization from CCl_4 afforded 3.05 g of **12** as a white solid, mp 79–80 °C.

Anal. Calcd for $C_9H_{12}N_2OS_2$: C, 47.34; H, 5.30; N, 12.27; S, 28.09. Found: C, 47.44; H, 5.52; N, 12.08; S, 27.88.

Ethyl γ-(1,3-Dithian-2-yl)acetoacetate (1). Method A. Freshly prepared magnesium ethoxide (9.12 g, 80 mmol) was added to a 500-mL three-necked round-bottomed flask fitted with a gas-inlet tube, condenser, and magnetic stirrer, and containing 150 mL of sodium-dried ether. While stirring under nitrogen, 13.1 g (80 mmol) of *tert*-butyl ethyl malonate was added. The mixture was heated at reflux for 15 min, and then a solution of 15.7 g (80 mmol) of **11** in 50 mL of ether was cautiously added. The mixture was again heated at reflux for 3 h. After cooling, 100 mL of 10% H_2SO_4 was slowly added. The ether layer was separated and the aqueous solution was extracted twice with 20-mL portions of ether. The combined ether layers were dried (Na_2SO_4), filtered, and evaporated, leaving a light yellow oil. The oil was dissolved in 150 mL of xylene, 0.35 g of *p*-toluenesulfonic acid was added, and the mixture was heated at reflux for 3.5 h. The mixture was concentrated and the residual dark oil was scratched to induce crystallization. Recrystallization of this crude solid from cyclohexane (Norite) afforded 8.74 g (44%) of 1 as an off-white solid: mp 64–65 °C; NMR ($CDCl_3$) δ 1.32 (t, 3), 1.9–2.3 (m, 6), 3.58 (s, 2), 4.25 (q, 2), 4.54 (t, 1) (these last two sets of signals overlap); IR (KBr) 1740 (ester), 1715 (ketone) cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_3S_2$: C, 48.36; H, 6.49; S, 25.82. Found: C, 48.59; H, 6.30; S, 25.68.

Method B. A solution of lithium diisopropylamide was prepared by adding, *via syringe*, 4.4 mL (10.5 mmol) of 2.4 M *n*-butyllithium

to a stirring solution of 1.06 g (10.5 mmol) of diisopropylamine in 15 mL of dry THF under nitrogen at −78 °C. This was stirred at −78 °C for 0.5 h. To the base solution was added dropwise a solution of 1.76 g (10.0 mmol) of α-(1,3-dithian-2-yl)acetone (**7**) in 15 mL of dry THF. After addition was complete, the mixture was stirred at −78 °C for 45 min. To the anion solution was added 1.14 g (10.5 mmol) of freshly distilled ethyl chloroformate. The mixture was stirred at −78 °C for 5 min and then allowed to warm to room temperature for 0.5 h. The mixture was poured into 100 mL of saturated NaCl, and the organic layer was separated from the basic aqueous solution. The aqueous solution was acidified with 10% HCl, and then extracted three times with a total of 100 mL of $CHCl_3$. The combined $CHCl_3$ layers were dried (Na_2SO_4), filtered, and evaporated, leaving 0.35 g (15%) of a light yellow oil which solidified on standing. Recrystallization from 2-propanol afforded a white fluffy solid, mp 64–65 °C, identical in all respects with the material prepared by method A. Attempts to improve the yield by using excess base (i.e., 2 equiv of LDA) led to lower yields.

α,α-Trimethylenedithiopropionyl Chloride (14). A mixture of 1.78 g (10 mmol) of 2-methyl-1,3-dithiane-2-carboxylic acid, 0.40 g (10 mmol) of sodium hydroxide, and 15 mL of water was gently heated until homogeneous and then concentrated under reduced pressure. The resulting sodium salt was dried in vacuo (100 °C, 0.5 Torr) for 2 h) and then added slowly to a solution of 1.52 g (12 mmol) of oxalyl chloride in 40 mL of benzene at room temperature. After addition was complete, the mixture was heated to reflux for 2 h, cooled, filtered to remove NaCl, and concentrated under reduced pressure to give 1.9 g (100%) of **14** as a light orange oil. This material was used without further purification: NMR ($CDCl_3$) δ 1.70 (s, 3), 1.8–3.3 (m, 6); IR (neat) 1755 (carbonyl) cm^{-1}.

***tert*-Butyl 3-Oxo-4-trimethylenedithiopentanoate (2).** A three-necked 250-mL round-bottomed flask fitted with a gas-inlet tube, addition funnel, and magnetic stirring bar was charged with 52 mL (0.126 mol) of 2.4 M *n*-butyllithium. While stirring under nitrogen, the flask was cooled (ice bath) and a solution of 12.7 g (0.126 mol) of diisopropylamine in 50 mL of dry THF was added over 15 min. This solution of LDA was cooled to −70 °C and 7.3 g (63 mmol) of *tert*-butyl acetate in 25 mL of dry THF was added. After stirring at −70 °C for 0.5 h, a solution of 63 mmol of **14** in 50 mL of dry THF was added dropwise to the anion solution. This mixture was stirred at −70 °C for 0.5 h, allowed to warm to room temperature over 0.5 h, and quenched with 100 mL of 10% HCl. The organic layer was separated and the aqueous solution extracted twice with 50-mL portions of ether. The combined organic layers were washed six times with saturated aqueous NaCl (to remove traces of acid), dried over Na_2SO_4, and filtered, and the filtrate was evaporated. The residual brown liquid was distilled under reduced pressure to give 11.2 g (64%) of **2** as a colorless liquid: bp 122–124 °C (0.01 Torr); NMR ($CDCl_3$) δ 1.38 (s, 9), 1.56 (s, 3), 1.8–3.3 (m, 6), 3.51 (s, 2); IR (neat) 1735 (ester), 1700 (ketone) cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_3S_2$: C, 52.14; H, 7.30. Found: C, 52.02; H, 7.17.

Ethyl 5-Hydroxy-3-oxopentanoate (15). A mixture of 2.6 g (0.11 mol) of sodium hydride (prepared by washing 5.2 g of 50% NaH/paraffin oil with pentane) and 75 mL of dry THF was stirred at 0 °C under nitrogen in a 250-mL round-bottomed flask fitted with an addition funnel, gas-inlet tube, and septum. To this was added dropwise a solution of 13.0 g (0.10 mol) of ethyl acetoacetate in 75 mL of dry THF. Stirring was continued at 0 °C for 0.5 h after addition was complete. To this anion solution was added 42 mL (0.10 mol) of a 2.4 M solution of *n*-butyllithium and the resulting dianion solution was stirred at 0 °C for 1 h. A side-armed flask containing 3.0 g (0.10 mol) of paraformaldehyde was inserted between the nitrogen source and the reaction vessel. The paraformaldehyde was vaporized by heating with a heat gun, and these vapors were carried into the reaction flask by the nitrogen stream. After 0.5 h, no paraformaldehyde remained. The reaction mixture was stirred at room temperature for 15 min, neutralized with 10% HCl, and extracted three times with a total of 100 mL of $CHCl_3$. The combined $CHCl_3$ layers were dried (Na_2SO_4), filtered, and evaporated to give a light brown liquid. Distillation under reduced pressure afforded 1.8 g (14%) of ethyl acetoacetate followed by 4.75 g (30%) of colorless **15**: bp 106–108 °C (0.3 Torr). The remaining material decomposed during distillation: NMR ($CDCl_3$) δ 1.17 (t, 3), 2.66 (t, 2), 3.40 (s, 2), 3.73 (t, 2), 4.07 (q, 2); IR (neat) 3200–3600 (OH), 1750 (ester), 1710 (ketone) cm^{-1}.

Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.29; H, 7.74.

4,4-Diethoxy-2-trimethylenedithiobutanal (17). A solution of 29.7 g (0.126 mol) of 1,1-diethoxy-3,3-trimethylenedithiopropane (**16**)[4] in 200 mL of dry THF was stirred at −30 °C under nitrogen in a 500-mL round-bottomed flask fitted with an addition funnel with septum and a thermometer. To this solution was added dropwise 54 mL (0.13 mol) of 2.4 M *n*-butyllithium. After addition was complete, the light brown solution was stirred at −20 °C for 2 h and poured into a mixture of 36.6 g (0.50 mol) of DMF (distilled from CaH_2) and 100 mL of dry THF, and the resulting yellow solution was stirred at −15 °C for 18 h. It was then added to 400 mL of water, and the organic layer was separated. The aqueous solution was extracted with three 50-mL portions of ether, the combined organic layers were washed twice with water, once with aqueous 7% KOH solution, once more with water, and then dried over Na_2SO_4, filtered, and evaporated. Vacuum distillation of the residual brown oil afforded 25.2 g (78%) of **17** as a colorless oil: bp 109 °C (0.05 Torr); NMR ($CDCl_3$) δ 1.15 (t, 6), 1.8–3.8 (m, 12), 4.70 (t, 1), 8.88 (s, 1); IR (neat) 2700 (CHO), 1710 (carbonyl) cm^{-1}.

Anal. Calcd for $C_{11}H_{20}O_3S_2$: C, 49.97; H, 7.62; S, 24.25. Found: C, 50.17; H, 7.37; S, 24.31.

1,1-Diethoxy-3,3-diethylthiopropane (20). A solution of 6.8 g (50 mmol) of bis(ethylthio)methane in 50 mL of dry THF was stirred at −30 °C under nitrogen in a 250-mL three-necked round-bottomed flask fitted with a thermometer, gas-inlet tube, addition funnel, and magnetic stirring bar. *n*-Butyllithium (21.6 mL, 52 mmol, as a 2.4 M solution) was added dropwise, with the temperature maintained below −20 °C. After addition was complete, the mixture was stirred at −20 °C for 1.5 h, and bromoacetaldehyde diethyl acetal (10.8 g, 55 mmol) was added. The mixture was stirred at −15 °C for 46 h and poured into 200 mL of water, and the organic layer was separated. The aqueous phase was washed with three 30-mL portions of ether. The combined organic layers were washed with water, aqueous 7% KOH, and saturated NaCl solution, and then dried over Na_2SO_4, filtered, and evaporated. Vacuum distillation of the residual light brown oil afforded 3.9 g (31%) of **20** as a colorless oil: bp 108 °C (0.15 Torr); NMR (neat) δ 0.9–1.3 (m, 12), 1.92 (q, 2), 2.50 (m, 4), 3.2–3.9 (m, 5), 4.70 (t, 1).

Anal. Calcd for $C_{11}H_{24}O_2S_2$: C, 52.34; H, 9.58; S, 25.40. Found: C, 52.34; H, 9.71; S, 25.67.

Ethyl 5-Benzyloxy-3-oxopentanoate (3). Sodium hydride, as a 50% paraffin oil dispersion (1.3 g, 27.5 mmol), was washed with pentane and added to a three-necked 250-mL round-bottomed flask fitted with a gas inlet tube, addition funnel, magnetic stirring bar, and septum. Dry THF (20 mL) was added, the slurry was stirred under nitrogen at −5 °C, and a solution of ethyl acetoacetate (3.25 g, 25 mmol) in 20 mL of dry THF was added dropwise. After addition was complete, the mixture was stirred for 10 min, 11.2 mL (26 mmol) of a 2.4 M solution of *n*-butyllithium was added dropwise, and the dianion solution was stirred for 10 min at 0 °C. A solution of 3.91 g (25 mmol) of benzyl chloromethyl ether in 10 mL of dry THF was then added, and the mixture was stirred at 0 °C for 1 h and then poured into 50 mL of saturated NaCl solution. The mixture was acidified with 10% HCl and the organic layer separated. The aqueous solution was extracted twice with 25-mL portions of ether, and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated to give 6.3 g of a light yellow oil. The material was purified by passing through a silica gel column (35 × 3.5 cm), with $CHCl_3$ as the eluent, to give 4.42 g (70%) of **3** as a colorless oil. The material could be further purified by distillation [bp 135 °C (0.01 Torr)].

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.00; H, 7.13.

3-Oxo-4-trimethylenedithiovaleronitrile (23). To a solution of 16.7 mL (40 mmol) of a 2.4 M solution of *n*-butyllithium in 10 mL of dry THF, stirred under nitrogen at −70 °C, was added dropwise a solution of 1.64 g (40 mmol) of dry acetonitrile in 10 mL of dry THF. After addition was complete, the mixture was stirred at −70 °C for 1 h, during which time a milky white suspension formed. To this was added a solution of 3.92 g (20 mmol) of acid chloride **14** in 10 mL of dry THF. After addition was complete, the mixture was stirred at −70 °C for 0.5 h, allowed to warm to room temperature over 0.5 h, and poured into 50 mL of 10% HCl. The organic layer was separated, and the aqueous phase was extracted twice with a total of 25 mL of ether. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated, leaving a brown oil. Distillation under reduced pressure afforded 3.46 g (86%) of a colorless oil, bp 148–150 °C (0.05 Torr), which solidified upon cooling; mp 50–53 °C. Recrystallization from benzene/cyclohexane afforded **23** as white needles, mp 59–60 °C.

Anal. Calcd for $C_8H_{11}NOS_2$: C, 47.73; H, 5.51; N, 6.96; S, 31.86. Found: C, 47.92; H, 5.53; N, 6.77; S, 31.90.

1-Cyano-2-trimethylsilyloxy-3-trimethylenedithio-1-butene (22). Method A. In a dry 50-mL three-necked flask, swept with dry nitrogen and equipped with a magnetic stirrer and condenser, was placed 2.01 g (10.0 mmol) of **23** and 0.04 g (0.6 mmol) of recrystallized

imidazole. Hexamethyldisilazane (10 mL, 43 mmol) was then added and the mixture was heated at reflux for 2 h. The mixture was concentrated and the residue distilled under reduced pressure, affording 2.29 g (84%) of a colorless oil, bp 124 °C (0.05 Torr), which solidified on scratching. Recrystallization from cyclohexane afforded **22** as a white solid: mp 57–58 °C; NMR ($CDCl_3$) δ 0.32 (s, 9), 1.52 (s, 3), 1.7–2.9 (m, 6), 5.50 (s, 1); IR (neat) 2210 (nitrile) cm^{-1}. Satisfactory microanalytical values could not be obtained for this compound, since it hydrolyzed back to **23** with extreme ease (Found: C, 47.63; H, 5.30; N, 6.96; S, 32.32; *m/e* 201).

Method B. In a dry 50-mL three-necked round-bottomed flask, swept with dry nitrogen and equipped with a magnetic stirrer and condenser, was placed 2.76 g (10.0 mmol) of keto ester **2** and 0.04 g (0.06 mmol) of recrystallized imidazole. Hexamethyldisilazane (10 mL, 43 mmol) was then added and the mixture was heated at reflux for 2 h. The mixture was concentrated and the residue was distilled at reduced pressure, affording 2.70 g of a colorless oil, bp 127 °C (0.08 Torr), which solidified on scratching. Recrystallization from cyclohexane afforded a white solid, mp 57–58 °C, identical in all respects with the material prepared by method A.

Registry No.—**1**, 64714-77-8; **2**, 64714-78-9. **3**, 64714-79-0; **7**, 18554-39-7; **8**, 7424-91-1; **9**, 64714-80-3; **10**, 64714-81-4; **11**, 64714-82-5; **12**, 65714-83-6; **14**, 64714-84-7; **15**, 64714-85-8; **16**, 5849-13-8; **17**, 64714-86-9; **20**, 64714,87-0; **22**, 64714-88-1; **23**, 64714-89-2; propane-1,3-dithiol, 109-80-8; imidazole, 288-32-4; *tert*-butyl ethyl malonate, 32864-38-3; ethyl chloroformate, 541-41-3; 2-methyl-1,3-dithiane-2-carboxylic acid, 4901-19-3; *tert*-butyl acetate, 540-88-5; ethyl acetoacetate, 141-97-9; bis(ethylthio)methane, 4396-19-4; bromoacetaldehyde diethyl acetal, 2032-35-1; benzyl chloromethyl ether, 3587-60-8; acetonitrile, 75-05-8; hexamethyldisilazane, 999-97-3.

References and Notes

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A Convenient One-Flask Synthesis of Dialkyl Selenides and Diselenides via Lithium Triethylborohydride Reduction of Se_x

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Commercially available $Li(C_2H_5)_3BH$ rapidly and quantitatively cleaves gray elemental Se_x in THF to Li_2Se or Li_2Se_2, depending upon stoichiometry. Only volatile byproducts (H_2 and $(C_2H_5)_3B$) are formed. The heterogeneous Li_2Se and Li_2Se_2 preparations may be alkylated in 50–95% yield, optimally in the presence of *tert*-butyl alcohol cosolvent. This one-flask procedure constitutes a substantial improvement over conventional dialkyl selenide and dialkyl diselenide syntheses. $Li(C_2H_5)_3BH$ (2 equiv) also effects reduction of diselenides to selenolates, which may be alkylated to give unsymmetrical selenides.

During the last few years, organoselenium compounds[1] have emerged as important reagents and intermediates in organic synthesis.[2] Starting materials for their preparation are often symmetrical selenides (R_2Se) and diselenides (R_2Se_2). Hence, convenient high-yield syntheses of these key parent molecules are desirable. Current methodology,[3-14] however, suffers from various combinations of (a) low yields, (b) lack of demonstrated generality, (c) cumbersome manipulations, and (d) the use of toxic and malodorous H_2Se.

During the course of another research project underway in this laboratory, it was discovered that commercially available trialkylborohydrides such as $Li(C_2H_5)_3BH$ effect rapid reductive cleavage of several types of metal–metal bonds in THF at room temperature.[15] As a result, we were able to develop a preparation for metal carbonyl monoanions from the corresponding metal–metal dimers (eq 1)[15] which is substantially more convenient than existing procedures.[16]

$$L_n(CO)_xM\text{–}M(CO)_xL_n + 2Li(C_2H_5)_3BH \rightarrow 2Li[L_n(CO)_xM] + 2(C_2H_5)_3B + H_2 \quad (1)$$

Consequently, one objective of this study was to determine if trialkylborohydrides could be used in *metalloid* anion synthesis. Due to the independent need for several organoselenium compounds in our laboratory, we decided to investigate the feasibility of Li_2Se and Li_2Se_2 syntheses from gray elemental selenium. Dialkyl selenides and dialkyl diselenides would be available via the transformations depicted in eq 2–5.

$$Se + 2Li(C_2H_5)_3BH \rightarrow Li_2Se + 2(C_2H_5)_3B + H_2 \quad (2)$$

$$Li_2Se + 2RX \rightarrow R_2Se \quad (3)$$

$$2Se + 2Li(C_2H_5)_3BH \rightarrow Li_2Se_2 + 2(C_2H_5)_3B + H_2 \quad (4)$$

$$Li_2Se_2 + 2RX \rightarrow R_2Se_2 \quad (5)$$

We report in this paper that symmetrical dialkyl selenides and diselenides can be conveniently prepared in a one-flask operation in good to high yields via the simple sequences depicted above. Unsymmetrical dialkyl selenides are also easily

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Table I. Dialkyl Selenides and Dialkyl Diselenides Prepared

R	Yield,[a] %	Previous ref
	Selenides, R_2Se	
n-Pentyl	61	17
Benzyl	88 (66)	5
p-Chlorobenzyl	78 (53)	18
2-Phenylethyl	95 (88)	*b*
	Diselenides, R_2Se_2	
Methyl	73[c]	4
Ethyl	69	4
n-Propyl	50 (40)	19
n-Pentyl	64	14
Cyclohexyl	60 (46)	14
Benzyl	77 (75)	5
p-Chlorobenzyl	66 (58)	14

[a] Isolated yields are in brackets; other yields are by ^1H NMR with reference to toluene or *p*-xylene internal standard, unless noted. [b] New compound; spectral characterization is in Experimental Section. [c] Determined by GC with reference to an internal standard and corrected for detector response factor

synthesized when a slight procedural modification is employed.

Results

The addition of 1.0 equiv of gray powdered selenium to 2.1 equiv of $Li(C_2H_5)_3BH$ in THF (sold as a 1.0 M THF solution under the trade name Super Hydride) under dry N_2 with stirring resulted in gas evolution, lasting ca. 2 min (eq 2). Stirring was continued for at least 20 min, during which time the reaction mixture became a heterogeneous milky white. The subsequent efficaciousness of this Li_2Se preparation was not diminished by overnight stirring.

Addition of THF solutions of alkyl halides (2.1 equiv) to the Li_2Se preparation did afford dialkyl selenides (eq 3). Slightly superior yields, however, resulted when some *tert*-butyl alcohol (1.7–5.3 equiv) was added with the alkyl halide as cosolvent or directly to the Li_2Se just prior to the addition of alkyl halide. Reaction time depended upon alkyl halide reactivity, and workup consisted of ether extraction, washing, and drying. Subsequent solvent evaporation removed the triethylborane byproduct. Yields were obtained by reference to a ^1H NMR internal standard, or by isolating the product by recrystallization or distillation. Product deterioration was noted upon column chromatography. Yields are given in Table I.

The addition of 1.0 equiv of gray powdered selenium to 1.05 equiv of stirred $Li(C_2H_5)_3BH$ in THF resulted in gas evolution and the formation of a dark brown-red suspension (eq 4). After a minimum of 20 min stirring, a THF solution containing alkyl halide (usually 1.05 equiv) and 1.7–5.3 equiv of *tert*-butyl alcohol was added to the Li_2Se_2 preparation (eq 5). Alternately, the *tert*-butyl alcohol could be added to the Li_2Se_2 just prior to the alkyl halide. Workup was analogous to that used with the selenides, and the diselenides that were prepared are listed in Table I.

When two side-by-side preparations of dibenzyl diselenide were attempted, one with *tert*-butyl alcohol and the other without, product yields (^1H NMR) were 77 and 42%, respectively. When pyridine was used instead of *tert*-butyl alcohol, a 41% yield of dibenzyl diselenide was obtained.

Unsymmetrical selenides and diselenides could not be synthesized via sequential addition of RX and R'X to the Li_2Se and the Li_2Se_2 preparations. Only symmetrical products were detected. The addition of 2.1 equiv of $Li(C_2H_5)_3BH$ to symmetrical diselenide reaction mixtures as prepared in eq 5 followed by the addition of 2.1 equiv of a second alkyl halide did not afford clean yields of unsymmetrical dialkyl selenides (eq 6 and 7). Presumably the *tert*-butyl alcohol present now plays a deliterious role by reacting with the $Li(C_2H_5)_3BH$ faster than the diselenide. However, rapid formation of lithium alkylselenolates or arylselenolates (eq 6) was observed when *isolated* diselenides were treated with 2.1 equiv of $Li(C_2H_5)_3BH$ in THF alone. Addition of 2.1 equiv of benzyl chloride to 2.0 equiv of lithium phenylselenolate prepared from diphenyl diselenide afforded a 92% yield (^1H NMR) of benzyl phenyl selenide. By an identical procedure, benzyl methyl selenide was prepared from dibenzyl diselenide and methyl iodide in 92% yield (^1H NMR).

$$RSeSeR + 2Li(C_2H_5)_3BH \rightarrow 2RSeLi + 2(C_2H_5)_3B + H_2 \quad (6)$$

$$2RSeLi + 2R'X \rightarrow RSeR' \quad (7)$$

Scheme I. Syntheses of Symmetrical Dialkyl Selenides

$$Se \xrightarrow{Na/NH_3} Na_2Se \xrightarrow{2RX} R_2Se \quad (8)^3$$

$$Se \xrightarrow[\text{aq NaOH}]{HOCH_2SO_2Na} Na_2Se \xrightarrow{2RX} R_2Se \quad (9)^4$$

$$Se \xrightarrow[H_2O \text{ or } C_2H_5OH]{NaBH_4} NaHSe \text{ and } Na_2Se \xrightarrow{2RX} R_2Se \quad (10)^5$$

$$SeO_2 + RMgX \text{ or } RLi \rightarrow R_2Se \quad (11)^{6a}$$

$$SeO_2 + R_3B \xrightarrow{THF} R_2Se \quad (12)^{6b}$$

$$H_2Se + CH_2CH_2 \xrightarrow[350\ ^\circ C]{12\ atm} (CH_3CH_2)_2Se \quad (13)^7$$

$$SeCl_2 + 2CHCl{=}CHCl \rightarrow (CHCl_2CHCl)_2Se \quad (14)^8$$

Scheme II. Syntheses of Symmetrical Dialkyl Diselenides

$$Se \xrightarrow[NH_3]{Na \text{ or } Li} Se_2^{2-} \xrightarrow{2RX} R_2Se_2 \quad (15)^{3a,9}$$

$$Se \xrightarrow[\text{aq NaOH}]{HOCH_2SO_2Na} Na_2Se_2 \xrightarrow{2RX} R_2Se_2 \quad (16)^{10}$$

$$Se \xrightarrow[H_2O \text{ or } C_2H_5OH]{NaBH_4} Na_2Se_2 \xrightarrow{2RX} R_2Se_2 \quad (17)^5$$

$$Se \xrightarrow[CH_3OH]{Mg} (CH_3OMg)_2Se \xrightarrow{2RX} R_2Se_2 \quad (18)^{11}$$

$$KSeCN + RX \rightarrow RSeCN \xrightarrow{-OH} R_2Se_2 \quad (19)^{12}$$

$$H_2Se + 2RCOR \xrightarrow[\text{pyridine/}(C^2H^5)^3N,]{HCl \text{ or}} (R_2CH)_2Se_2 \quad (20)^{13,14}$$

Discussion

The dialkyl selenide and diselenide syntheses described herein have the following attributes: (a) only a single reaction flask is required, and most reactions proceed satisfactorily at room temperature; (b) starting materials are conveniently handled and inexpensive on moderate scales ($Li(C_2H_5)_3BH$ costs $42/mol); (c) no detectable byproducts are formed, and workup procedures are simple.

The yields presented in Table I are by no means optimized. However, in nearly every case the best reported literature yield is matched or exceeded. The pervasive odor of diethyl diselenide, dipropyl diselenide, and dipentyl diselenide deterred us from further experimentation strictly for yield's sake. Benzyl organoselenium compounds were prepared from benzyl chlorides, and alkyl organoselenium compounds were prepared from alkyl bromides or iodides. Only in the case of dicyclohexyl diselenide was the starting alkyl halide (cyclohexyl bromide) unreactive enough to require a reflux period.

Representative synthetic routes to symmetrical dialkyl selenides and diselenides are listed in Schemes I and II, re-

spectively, While Se^{2-} and Se_2^{2-} can be readily prepared by alkali metal–ammonia reduction of Se_x (eq 8 and 15), this procedure is operationally cumbersome. Sodium formaldehyde sulfoxylate or "Rongalite" can effect identical reductions (eq 9 and 16), but aqueous solvent systems are required. Several selenide syntheses employ SeO_2 and carbon nucleophiles (eq 11 and 12), and the addition of Se–H and Se–Cl bonds across olefins has been observed (eq 13 and 14). These methods lack in convenience, generality, and yield. A recently developed route to secondary alkyl diselenides utilizes ketones as starting materials but requires the use of H_2Se (eq 20).

The $NaBH_4$ reduction of Se_x recently described by Klayman and Griffin (eq 10 and 17) is related to our procedure and has many attributes in common. However, water or ethanol were required as solvents, and due to their reactivity only one hydride per BH_4^- could be utilized. In water, Na_2Se_2 was not prepared directly as depicted in eq 17 but via addition of further Se_x to NaHSe (eq 10). In ethanol, Na_2Se_2 formation was accompanied by an equivalent amount of H_2Se. While only benzyl selenides and diselenides were prepared by this procedure, it may have generality similar to ours and be superior for large scale preparations.

The exact role of the *tert*-butyl alcohol cosolvent in the Li_2Se and Li_2Se_2 alkylation steps is uncertain. Since the K_a of NaHSe is 10^{-15} (22 °C),[20] Li_2Se is probably not significantly protonated by *tert*-butyl alcohol in THF. Any excess trialkylborohydride would be quenched by *tert*-butyl alcohol and thus prevented from depleting the alkyl halide pool by nucleophilic attack.[21] However, this should result in only a slight increase in yield. The *tert*-butyl alcohol could act in part by increasing the polarity of the reaction medium and the concentration of dissolved Li_2Se and Li_2Se_2. We have also considered the possibility of *tert*-butyl alcohol or *t*-alkoxide catalysis by addition to selenium to form a hypervalent species of enhanced nucleophilicity. In the alkylation of selenolates (RSe^-) prepared from diselenides (eq 6 and 7), *tert*-butyl alcohol is not needed. We emphasize that *tert*-butyl alcohol is not in any way required for the actual production of Li_2Se and Li_2Se_2 suspensions from $Li(C_2H_5)_3BH$ and Se_x.

In aprotic solvents, $NaBH_4$ is incorporated into chalcogens to form products such as $NaBH_2S_3$, $NaBH_2Te_3$, and H_2.[22] Gray elemental selenium consists of polymeric, unbranched helical chains[23] which are apparently broken down completely by $Li(C_2H_5)_3BH$ in THF. The enhanced nucleophilicity of trialkylborohydrides relative to other boron and aluminum hydride reagents has been previously noted.[21]

The $(C_2H_5)_3B$ which is produced as a byproduct in these reactions is removed as a codistillate with THF and workup solvents. These solvent mixtures are not pyrophoric,[21c] and we have handled all product workups detailed herein and elsewhere[15] without special precaution and without incident. Other researchers have suggested[21d] that rotary evaporator vacuums be broken with N_2 when $(C_2H_5)_3B$ is among the volatiles. Since $Li(C_2H_5)_3B$ is readily formed from LiH and $(C_2H_5)_3$,[21e] Li_2Se and Li_2Se_2 might be equally well produced from LiH and a catalytic amount of $(C_2H_5)_3B$.

Unsymmetrical selenides are generally prepared by reduction of symmetrical diselenides to selenolates (RSe^-) and subsequent alkylation.[24] Although this can be accomplished with $NaBH_4$,[2a,24a] we have found $Li(C_2H_5)_3BH$ to be equally effective (eq 6). Unsymmetrical selenides, however, cannot be prepared in one flask from Se_x unless the *tert*-butyl alcohol is omitted from the initial symmetrical diselenide synthesis (eq 5). Since this adversely affects the diselenide yield, we recommend diselenide isolation before further reaction with $Li(C_2H_5)_3BH$.

At this time, we have not yet extended our methodology to the preparation of diaryl selenides or diselenides. However, arylation of carbon nucleophiles through use of transition metal catalysts is becoming increasingly common,[25] and a similar approach may prove effective with Li_2Se and Li_2Se_2. We also envision no difficulty in reacting our Li_2Se and Li_2Se_2 preparations with other classes of electrophiles such as esters or epoxides.

In conclusion, on scales where the moderate expense of $Li(C_2H_5)_3BH$ is inconsequential, we believe the procedure reported herein for dialkyl selenide and diselenide syntheses is the method of choice. Further applications of trialkylborohydrides to transition metal and metalloid anion syntheses are under active investigation.

Experimental Section

General. All experiments were carried out under an atmosphere of dry N_2. Selenium was used in its powdered gray form and stored in a desiccator. Tetrahydrofuran was dried and deoxygenated by distillation from sodium benzophenone ketyl. In initial experiments, *tert*-butyl alcohol was dried by distillation from magnesium turnings and subsequently deoxygenated by either a freeze–thaw cycle or by passage of dry N_2 through the alcohol. The alkyl halides were purified by distillation and subsequent deoxygenation with a stream of dry N_2. $Li(C_2H_5)_3BH$ (Super Hydride) was obtained from Aldrich as a 1.0 M THF solution and used at the stated bottle concentration. Melting points were taken on a Büchi Schmeltzpunktbestimmungsapparat and are uncorrected. ^1H NMR spectra were taken on a Varian T-60 spectrometer; NMR yields are with reference to toluene or *p*-xylene and are based on the starting amount of lithium selenide or diselenide. ^{13}C NMR spectra were taken on a Varian CFT-20 spectrometer. ^1H and ^{13}C NMR chemical shifts are reported with reference to Me_4Si. Mass spectra were taken on an AEI MS-9 instrument. All products were identified either by comparison to authentic samples or by analysis of spectral data.

Preparation of Lithium Selenide Suspension in THF. A representative procedure is as follows. Gray selenium (0.220 g, 2.780 mmol) was added portionwise to 5.80 mL of $Li(C_2H_5)_3BH$ solution (5.80 mmol) with magnetic stirring. Gas evolution occurred and ceased within 2 min; the solution gradually turned a heterogeneous milky white. THF (3 mL) was added, and the suspension was allowed to stir for at least 20 min.

General Method of Product Workup. After the specified reaction between alkyl halide and Li_2Se (or Li_2Se_2), the reaction mixture was taken up in ethyl ether/water. After separation, the aqueous layer was extracted twice more with ether. The organic phases were combined and dried with $MgSO_4$ or Na_2SO_4. After filtration, the solvent was removed under vacuum. If a ^1H NMR yield was desired, the internal standard was added at this point. This procedure was followed in all cases unless noted. *Caution!* Flammable byproducts [H_2, $(C_2H_5)_3B$] are produced during these reactions. Larger scale reactions may require cautionary measures in addition to those discussed.

Dipentyl Selenide. A solution of 1-bromopentane (0.725 mL, 5.85 mmol) and *tert*-butyl alcohol (0.5 mL, 5.3 mmol) in 5 mL of THF was added overnight to Li_2Se (2.78 mmol) suspended in 9 mL of THF. When the addition was completed, the reaction mixture was worked up as previously described. The yield of product, as determined by ^1H NMR, was 61%: ^1H NMR ($CDCl_3$) δ 0.92 (t, 3 H), 1.43 (m, 6 H), 2.50 (t, 2 H); ^{13}C NMR ($CDCl_3$) 14.0, 22.3, 24.0, 30.5, 32.3 ppm; mass spectrum, *m/e* 222 (M^+, ^{80}Se).

Dibenzyl Selenide. Benzyl chloride (0.69 mL, 6.00 mmol) in 5 mL of THF was added dropwise to Li_2Se (2.94 mmol) suspended in 0.5 mL (4.3 mmol) of *tert*-butyl alcohol and 11 mL of THF. After the addition was completed, the reaction mixture was stirred overnight and worked up as previously described. The product yield was 88% by ^1H NMR. Recrystallization from hexane yielded 0.501 g (66%) of white crystals, mp 44–45 °C (lit.[5,25] mp 45.5 °C): ^1H NMR ($CDCl_3$) δ 3.67 (s, 2 H), 7.25 (s, 5 H); ^{13}C NMR ($CDCl_3$) 27.5, 126.7, 128.4, 129.0 ppm (no pulse delay; one arene carbon absent).

Di(*p*-chlorobenzyl) Selenide. α-*p*-Dichlorotoluene (0.966 g, 6.00 mmol) in 7 mL of THF was added dropwise to Li_2Se (2.79 mmol) suspended in 0.5 mL (5.3 mmol) of *tert*-butyl alcohol and 11 mL of THF. After addition was completed, the reaction mixture was stirred overnight and worked up as previously described. The product yield was 78% by ^1H NMR. Recrystallization from hexane afforded 0.486 g (53%) of fluffy white crystals, mp 49.5–51 °C (lit.[18] mp 57.5 °C), which were recrystallized a second time, mp 51.5–52 °C: ^1H NMR ($CDCl_3$) δ 3.63 (s, 4 H), 7.23 (s, 8 H); ^{13}C NMR ($CDCl_3$) 26.7, 128.7, 130.3, 132.6 (weak), 137.4 (weak) ppm; mass spectrum, *m/e* 330 (M^+, $^{35}Cl_2$, ^{80}Se).

Di(2-phenylethyl) Selenide. (2-Iodoethyl)benzene (1.458 g, 6.28 mmol) in 4 mL of THF was added overnight to Li_2Se (2.79 mmol) in 0.5 mL (5.3 mmol) of *tert*-butyl alcohol and 7 mL of THF. Following workup as previously described, the product yield by ^1H NMR was 95%. In a separate experiment, (2-iodoethyl)benzene (1.439 g, 6.2 mmol) in 5 mL of THF was added over a 0.5-h period to Li_2Se (2.96 mmol) suspended in 0.5 mL (5.3 mmol) of *tert*-butyl alcohol and 11 mL of THF. After stirring overnight, the reaction mixture was worked up as previously described, and the resulting light yellow oil was washed with 50 mL of hot hexane. Solvent removal under high vacuum afforded 0.761 g (89%) of a light yellow liquid that was pure by ^1H NMR analysis. The compound could not be induced to crystallize. ^1H NMR (CCl_4) δ 2.77 (m, 4 H), 7.13 (s, 5 H); ^{13}C NMR ($CDCl_3$) 25.0, 37.2, 126.3, 128.39, 128.42, 141.2 ppm; mass spectrum, *m/e* 290 (M^+, ^{80}Se); exact mass (calcd) 290.0574; exact mass (found) 290.0569 ± 0.001; IR ($CHCl_3$) 3085 w, 3063 w, 3009 w, 2967 w, 2936 w, 1495 s, 1453 s, 1259 br, 696 vs cm^{-1}.

Preparation of Lithium Diselenide Suspension in THF. Gray selenium (0.319 g, 4.04 mmol) was added portionwise to a solution of 4.15 mmol of $Li(C_2H_5)_3BH$ in THF with magnetic stirring. Gas evolution occurred, and the suspension turned a dark brown-red. The Li_2Se_2 reaction mixture was allowed to stir for at least 20 min before proceeding.

Dimethyl Diselenide. Iodomethane (0.265 mL, 4.25 mmol) in 5 mL of THF was added over a period of 5 h to a suspension of Li_2Se_2 (2.02 mmol) in 0.5 mL (5.3 mmol) of *tert*-butyl alcohol and 6 mL of THF prepared in the manner described above. After workup as previously indicated, gas chromatography with reference to an internal standard and a commercial (Alfa-Ventron) authentic product indicated a yield of 73%;

Diethyl Diselenide. Iodoethane (0.726 mL, 9.01 mmol) in 5 mL of THF was added dropwise to a suspension of Li_2Se_2 (2.145 mmol) in 0.5 mL (5.3 mmol) of *tert*-butyl alcohol and 9.9 mL of THF, and the reaction mixture was stirred overnight. Workup as previously described afforded the product as a foul-smelling yellow oil (yield 69% by ^1H NMR). Subsequent experiments showed the excess iodoethane employed in this preparation to have only a slight influence on the yield. ^1H NMR (CCl_4) δ 1.45 (t, 3 H), 2.88 (q, 2 H); mass spectrum, *m/e* 218 (M^+, $^{80}Se_2$).

Dipropyl Diselenide. 1-Iodopropane (0.22 mL, 2.30 mmol) in 5 mL of THF was added dropwise to Li_2Se_2 (2.12 mmol) suspended in 0.5 mL (5.3 mmol) of *tert*-butyl alcohol and 9.7 mL of THF. After stirring overnight, workup as previously described afforded a yellow oil in 50% yield by ^1H NMR (92% yield if based upon 1-iodopropane). In a separate experiment, 1-iodopropane (0.41 mL, 4.2 mmol) in 3 mL of THF was added slowly to a suspension of Li_2Se_2 (1.01 mmol) in 0.5 mL (5.3 mmol) of *tert*-butyl alcohol and 2 mL of THF. Workup as previously described and vacuum distillation afforded 0.10 g (40%) of product as a red-brown foul-smelling liquid. ^1H NMR ($CDCl_3$) δ 0.98 (t, 3, H), 1.70 (m, 2 H), 2.90 (t, 2 H); mass spectrum, *m/e* 246 (M^+, $^{80}Se_2$).

Dipentyl Diselenide. 1-Bromopentane (0.350 mL, 2.83 mmol) in 0.5 mL (5.3 mmol) of *tert*-butyl alcohol and 5 mL of THF was added over a period of 2 h to a solution of Li_2Se_2 (1.35 mmol) in 5 mL of THF. After workup, ^1H NMR revealed a 64% yield of product as well as 15% unreacted halide (to account for 94% of the mass balance). Chromatography on silica gel with 25% v/v ethyl acetate in hexane as the eluent yielded pure product for spectral analysis. ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H), 1.35 (m, 4 H), 1.72 (m, 2 H), 2.92 (t, 2 H); ^{13}C NMR ($CDCl_3$) 13.9, 22.2, 30.4, 30.8, 31.8 ppm; mass spectrum, *m/e* 302 (M^+, $^{80}Se_2$).

Dicyclohexyl Diselenide. Bromocyclohexane (0.345 mL, 2.83 mmol) in 5 mL of THF was added over a 1-h period to a solution of Li_2Se_2 (1.33 mmol) in 0.5 mL (5.3 mmol) of *tert*-butyl alcohol and 5 mL of THF. The absence of a color change upon completion of the addition suggested that no reaction had taken place. After 13 h of stirring at room temperature, the reaction flask was heated to 45 °C for 11 h and then to 70 °C for 8 days. After workup in the usual way, ^1H NMR indicated a 60% yield. Distillation under reduced pressure yielded 0.20 g (46%) of product: ^1H NMR (CCl_4) δ 1.62 (broad multiplet, 10 H), 2.97 (m, 1 H); ^{13}C NMR ($CDCl_3$) 25.7, 27.0, 34.6, 43.4 ppm (area ratios ca. 1:2:2:1); mass spectrum, *m/e* 326 (M^+, $^{80}Se_2$).

Dibenzyl Diselenide. Benzyl chloride (0.310 mL, 2.69 mmol) in 3 mL of THF was added over a period of 1.5 h to a suspension of Li_2Se_2 (1.29 mmol) in 0.6 mL (6.4 mmol) of *tert*-butyl alcohol and 3 mL of THF. After stirring overnight, the reaction mixture was worked up by the addition of 4 mL of $CHCl_3$ and 1 mL of water to the flask, separation of the aqueous phase, and drying of the organic phase with $MgSO_4$. After filtration, the solution was evaporated to dryness. The crude dibenzyl diselenide was recrystallized from hexane. Several crops were obtained, giving a combined yield of 0.330 g (75%) of product, mp 91.0–92.0 °C (lit.[27] mp 92–93 °C).

The use of pyridine as a cosolvent was attempted. Benzyl chloride (0.310 mL, 2.69 mmol) in 5 mL of THF was added over a 2-h period to a solution of Li_2Se_2 (1.28 mmol) in 0.6 mL (7.4 mmol) of dry pyridine and 3 mL of THF. The workup was identical to that in the previous paragraph. Recrystallization from hexane yielded 0.179 g (41%) of product, obtained in several crops, mp 90.0–91.0 °C.

Two side-by-side experiments were conducted, one with and one without *tert*-butyl alcohol. In one reaction, benzyl chloride (0.168 mL, 1.46 mmol) in 5 mL of THF was added dropwise to a suspension of Li_2Se_2 (1.33 mmol) in 8 mL of THF and 0.5 mL (5.3 mmol) of *tert*-butyl alcohol. In another experiment, benzyl chloride (0.168 mL, 1.46 mmol) in 5 mL of THF was added dropwise to a suspension of Li_2Se_2 (1.4 mmol) in 8 mL of THF. After stirring overnight and employing the general method of product workup previously described, ^1H NMR analysis indicated the yield of the reaction done with *tert*-butyl alcohol to be 77% and the yield of the reaction done without it to be 42%; ^1H NMR ($CDCl_3$) δ 3.83 (s, 2 H), 7.27 (s, 5 H).

Di(*p*-chlorobenzyl) Diselenide. α-*p*-dichlorotoluene (0.5766 g, 3.58 mmol) in 5 mL of THF was added over a 2.5-h period to a suspension of Li_2Se_2 (1.78 mmol) in 0.5 mL (5.3 mmol) of *tert*-butyl alcohol and 6 mL of THF. The reaction mixture was then heated to 67 °C for 20 h. After workup, ^1H NMR analysis indicated a 66% yield of product. In a separate experiment, α-*p*-dichlorotoluene (0.699 g, 4.34 mmol) in 5 mL of THF was added slowly to Li_2Se_2 (2.12 mmol) suspended in 0.5 mL (5.3 mmol) of *tert*-butyl alcohol and 9.6 ml of THF. After stirring overnight, workup as previously described and recrystallization from hexane afforded 0.501 g (58%) of fluffy yellow crystals, mp 73.5–75 °C (lit. mp 76.5–77 °C,[18] 82 °C[28]), and subsequent recrystallizations increased the melting point to 77–78 °C: ^1H NMR ($CDCl_3$) δ 3.82 (s, 4 H), 7.25 (m, 8 H); ^{13}C NMR ($CDCl_3$) 31.7, 128.6, 130.3, 133.0 (weak), 137.5 (weak) ppm; mass spectrum, *m/e* 410 (M^+, $^{35}Cl_2$, $^{80}Se_2$). Anal. Calcd for $C_{14}H_{12}Cl_2Se_2$: C, 41.11; H, 2.96; Cl, 17.33; Se, 38.60. Found: C, 41.22; H, 2.90; Cl, 17.14; Se, 38.72.

Phenyl Benzyl Selenide. Diphenyl diselenide (2.11 mmol, 0.6585 g) in 5 mL of THF was treated with 4.4 mL of $Li(C_2H_5)_3BH$ solution (4.4 mmol), and the mixture was stirred for 0.5 h. THF (5 mL) and 0.5 mL of *tert*-butyl alcohol were added followed by 4.22 mmol (0.486 mL) of benzyl chloride in 2 mL of THF. The reaction was stirred for 4 h and worked up as previously described. ^1H NMR analysis indicated a product yield of 92%. The crude oil was recrystallized from hexane to afford white crystals, mp 33–34 °C (lit.[29] mp 32.5 °C): ^1H NMR ($CDCl_3$) δ 4.08 (s, 2 H), 7.3 (m, 10 H); ^{13}C NMR ($CDCl_3$) 32.3, 126.8, 127.3, 128.4, 128.8, 128.9, 133.6 ppm; mass spectrum, *m/e* 248 (M^+, ^{80}Se).

Benzyl Methyl Selenide. Dibenzyl diselenide (1.02 mmol, 0.348 g) in 5 mL of THF was treated with 2.2 mL of $Li(C_2H_5)_3BH$ solution (2.2 mmol). After stirring for 0.5 h, 2.04 mmol (0.128 mL) of iodomethane in 2 mL of THF was added, and the reaction mixture was stirred for 4 h. Workup as previously described afforded a yellow oil.[30] ^1H NMR analysis indicated a 92% yield: ^1H NMR ($CDCl_3$) δ 2.23 (s, 3 H), 4.07 (s, 2 H), 7.63 (s, 5 H); mass spectrum, *m/e* 186 (M^+, ^{80}Se).

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Registry No.—Li_2Se, 12136-60-6; Li_2Se_2, 65027-50-1; $Li(C_2H_5)_3BH$, 22560-16-3; selenium, 7782-49-2; dipentyl selenide, 14835-67-7; 1-bromopentane, 110-53-2; dibenzyl selenide, 1842-38-2; benzyl chloride, 100-44-7; di(*p*-chlorobenzyl) selenide, 56344-10-6; α-*p*-dichlorotoluene, 104-83-6; di(2-phenylethyl) selenide, 65027-51-2; (2-iodoethyl)benzene, 17376-04-4; diethyl diselenide, 628-39-7; iodoethane, 75-03-6; dipropyl diselenide, 7361-89-9; 1-iodopropane, 107-08-4; dipentyl diselenide, 52056-07-2; dicyclohexyl diselenide, 56592-97-3; bromocyclohexane, 108-85-0; dibenzyl diselenide, 1482-82-2; di(*p*-chlorobenzyl) diselenide, 56344-11-7; phenyl benzyl selenide, 18255-05-5; diphenyl diselenide, 1666-13-3; benzyl methyl selenide, 5925-78-0; dimethyl diselenide, 7101-31-7.

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Chlorosulfenylation–Dehydrochlorination Reactions. New and Improved Methodology for the Synthesis of Unsaturated Aryl Sulfides and Aryl Sulfones

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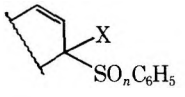
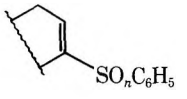
An improved procedure has been developed for the chlorosulfenylation of olefins. The method utilized is based on the quantitative reaction of aryl thiols with *N*-chlorosuccinimide to afford a reagent solution (A) which contains arylsulfenyl chloride as well as the "inert" co-product succinimide. Reaction of this reagent with a representative group of olefins (ethylene, cyclopentene, cyclohexene, cycloheptene, norbornene, butadiene, cyclohexadiene, Δ^2-cholestene, 1,2-dimethylcyclohexene, 1-methylcyclohexene, and 3-sulfolene) generates β-chlorophenyl sulfides in nearly quantitative yield. Aryl-substituted olefins react with reagent A in the presence of sodium carbonate to produce allylic or vinylic sulfides. The β-chloroaryl sulfides produced in the chlorosulfenylation reaction can be dehydrohalogenated with DBU to yield allyl, vinyl, or dienyl sulfides. Alternatively, the β-chloro sulfides can be oxidized to β-chloro sulfones, which may then be dehydrochlorinated with DBU under very mild conditions to afford excellent yields of α,β-unsaturated sulfones.

Unsaturated sulfur systems are valuable weapons in the arsenal of the synthetic organic chemist. Deprotonation reactions, fostered by the propensity of the sulfur moiety to stabilize an adjacent negative charge of allyl sulfides[3,4] (**1a**), allyl sulfoxides[4] (**1b**), and allyl sulfones[5,6] (**1c**), provide thioallylic anions (**2a–c**) of exceptional synthetic utility. A



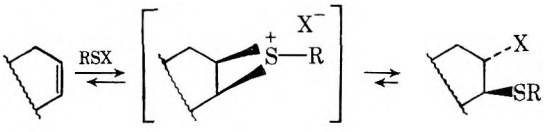
1a, X = H; n = 0
b, X = H; n = 1
c, X = H; n = 2
2a, X = Li; n = 0
b, X = Li; n = 1
c, X = Li; n = 2



3a, n = 0
b, n = 1
c, n = 2

related area of growing interest involves the chemistry of vinyl sulfides[7–9] (**3a**), sulfoxides[8] (**3b**), and sulfones[10] (**3c**). In connection with our synthetic program, we have been investigating methods of producing several of these unsaturated sulfur systems (**1, 3**) based upon chlorosulfenylation–dehydrochlorination reactions.

The reaction of aryl- and alkylsulfenyl halides with olefins (**4**) to produce *trans*-β-haloaryl (alkyl) sulfides (**6**) is a very well-known process.[11] The reaction proceeds through an episulfonium salt intermediate (**5**)[12] which yields products



4 **5** **6**

R = aryl or alkyl

usually resulting from predominant or exclusive attack of the halide ion at the more positively polarized carbon atom.[11,13–16] The β-halo sulfides so formed have been shown to undergo retrosulfenylation reactions (at elevated temperatures) as well as secondary rearrangements.[16–18] The facility with which these rearrangements occur is directly related to the electron

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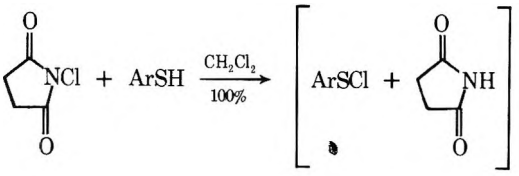
density on sulfur, the β-haloalkyl sulfides being far more labile.[17]

The greater stability of β-haloaryl sulfides, coupled with their higher molecular weight (better crystallinity, lower odor), fostered our decision to limit our initial investigation to the chemistry of arylsulfenyl chlorides. As previously indicated, the reaction of olefins with phenylsulfenyl chloride has been shown to produce 1:1 adducts in excellent yield.[11] A major synthetic disadvantage which accompanies this reaction as traditionally conducted stems from the inconvenience which attends the isolation and purification of the hygroscopic arylsulfenyl halides[11,19] (particularly in multimolar quantities).

We find that the difficulties associated with manipulations of arylsulfenyl chlorides can be completely avoided simply by generating and subsequently using the reagent in a methylene chloride solution. The reagent **7** is prepared by a modification



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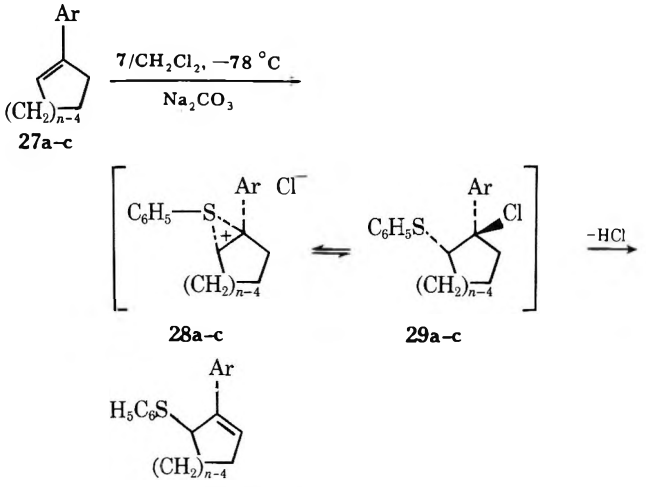
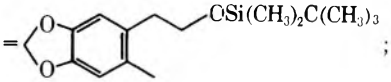
of the method of Harpp[19] via the quantitative reaction of the aryl thiol with a suspension of *N*-chlorosuccinimide in methylene chloride. The chlorosulfenylation reaction is normally conducted by simply adding the olefinic substrate to the reagent solution (−78 °C) and allowing the reaction to warm to room temperature; aryl-substituted olefins are best sulfenylated by the inverse addition mode. The co-product, succinimide, which is produced in the reagent generation step, is conveniently removed (usually by filtration) at the stage of isolation of the β-chlorophenyl sulfide. The β-chlorophenyl sulfides thus prepared are produced in excellent yields and can usually be used in subsequent reactions without any purification (see Table I).

Reaction of phenylsulfenyl chloride with 1-phenylcyclohexene (**27a**) generates adduct **29a** which is too labile to be



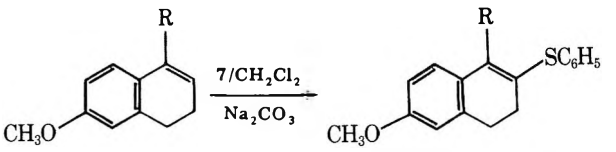
27a–c **28a–c** **29a–c**

30a, *n* = 6; Ar = C_6H_5; 63%
30b, *n* = 5; Ar = C_6H_5; 79%

30c, *n* = 5; Ar =  ; 66%

conveniently isolated and purified. Therefore, a modified procedure was developed for chlorosulfenylation–dehydrochlorination of aryl-substituted olefins. In these instances, the phenylsulfenyl chloride reagent solution (**7**) is added to a cooled methylene chloride solution of olefins **27a–c** containing excess anhydrous sodium carbonate. This expedient directly affords allylic sulfides **30a–c**.

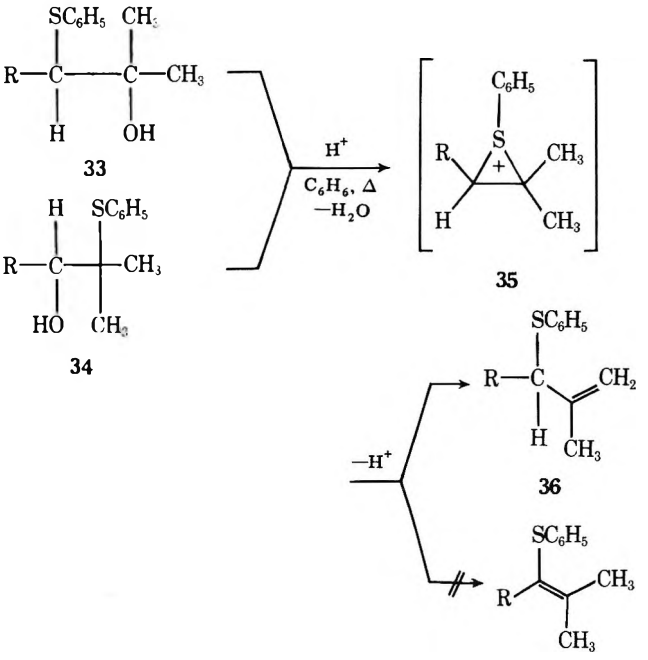
Chlorosulfenylation–dehydrochlorination of dihydronaphthol derivatives **31a,b** under the same reaction conditions produce vinylic sulfides **32a,b**.



31a, R = H
31b, R = CH_3

32a, R = H; 80%
32b, R = CH_3; 99%

Although a proper mechanistic understanding of the factors which determine the production of allylic vs. vinylic sulfides in these reactions must necessarily await further experimental investigation, several points are worthy of mention. Trost[21] and Warren[22] have shown that dehydration of β-hydroxy sulfides **33**[21] and **34**[22] affords only allylic sulfide **36**, possibly



33 **34** **35** **36**

because the external C–H bonds are more easily able to attain an anti periplanar relationship to the departing C–S bond in episulfonium ion intermediate **35**.[22] Analogous allylic sulfides are formed from β-haloalkyl sulfides.[23]

A similar rationale would seem to accommodate the formation of allylic sulfides **30a–c** through the intermediacy of ions **28a–c**. The difficulty of extending this analogy too far is rapidly seen in the case of aryl olefin **31b**. In this instance, the product **32b** is a vinylic sulfide.

It is tempting to invoke oxonium ion **37** as the progenitor of vinyl sulfide **32b**. A highly delocalized ion of this type would not be expected to gain much additional stabilization by formation of an episulfonium ion. Therefore, instead of tending to promote formation of allyl sulfide via an episulfonium ion, the "free" aryl sulfide moiety (of ion **37**) is available for α-CH acidification[24] which assists in formation of the observed vinyl sulfide **32b**. Clearly, the reactions of additional substrates

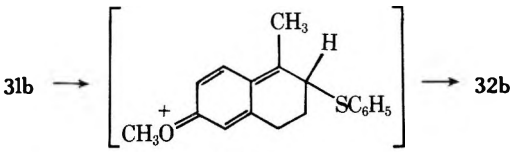


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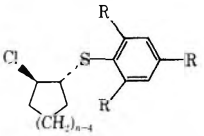
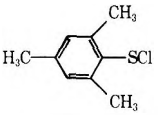
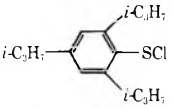
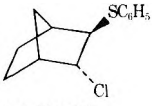
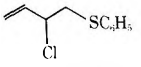
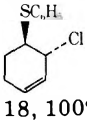
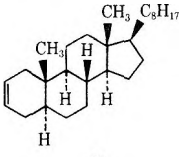
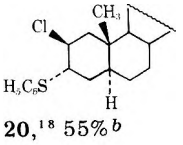
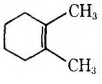
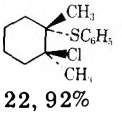
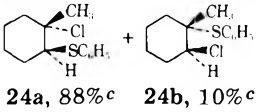
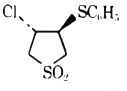
Table I

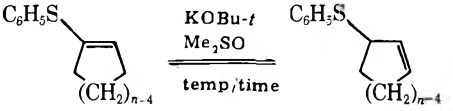
Olefin	Registry no.	In situ arylsulfenyl chloride	Registry no.	β-Chlorosulfide yield[a]	Registry no.
$CH_2=CH_2$ **8**	74-85-1	C_6H_5SCl	931-59-9	$ClCH_2CH_2SC_6H_5$ **9**, 98%	5535-49-9
 **10a** (n = 5)	142-29-0	C_6H_5SCl		 **11a** (n = 5; R = H), 99%	64741-03-3
10a (n = 5)			14575-12-3	**12a** (n = 5; R = CH_3), 98%	64741-04-4
10a (n = 5)			64741-02-2	**12b** (n = 5; R = i-C_3H_7), 80% (54%)[b]	64741-05-5
10b (n = 6)	110-83-8	C_6H_5SCl		**11b**[20] (n = 6; R = H), 96%	51704-77-9
10c (n = 7)	628-92-2	C_6H_5SCl		**11c** (n = 7; R = H), 100%	64741-06-6
 **13**	498-66-8	C_6H_5SCl		 **14**,[14] 99%	13204-36-9
 **15**	106-99-0	C_6H_5SCl		 **16**,[16] 100%	16728-08-8
 **17**	592-57-4	C_6H_5SCl		 18, 100%	64741-07-7
 **19**	570-73-0	C_6H_5SCl		 **20**,[18] 55%[b]	17150-04-8
 **21**	1674-70-8	C_6H_5SCl		 22, 92%	64741-08-8
 **23**	591-49-1	C_6H_5SCl		 **24a**, 88%[c] **24b**, 10%[c]	
 **25**	77-79-2	C_6H_5SCl		 **26**,[29] 81%[b]	15507-87-6

[a] Yield refers to "crude" material of >95% purity. [b] Recrystallized material. [c] Obtained by thermal equilibration of an original 3:1 mixture of 24a/24b. Registry no: 24a, 64741-09-9; 24b, 64741-10-2.

must be examined to test the validity of these hypotheses.[25]

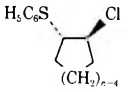
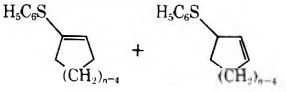
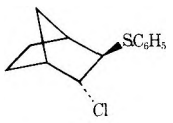
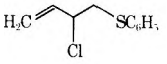
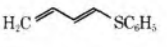
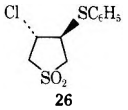
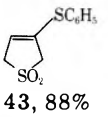
Less activated β-chloroaryl sulfides may also be conveniently dehydrochlorinated by briefly heating with the amidine base 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU).[26,27]

As can be seen in Table II, although the β-chlorocyclohexyl phenyl sulfide (**11b**) yields almost exclusively the allyl sulfide **40b**, the dehydrochlorination reactions of the cyclopentyl and cycloheptyl derivatives are nonspecific, producing about an equal mixture of vinyl (**39a,c**) and allyl sulfides (**40a,c**). The products **39a–c** and **40a–c** were individually resubjected to the conditions of this reaction and were recovered unchanged (see Experimental Section). Furthermore, the equilibrium (**39** ⇄ **40**) was established by potassium *tert*-butoxide/dimethyl sulfoxide[21] treatment of allyl isomers **40a–c**. The finding that



39a–c		**40a–c**
a (n = 5) 90%	60 °C/4 h	10%
b (n = 6) 92%	25 °C/20 h	8%
c (n = 7) 92%	60 °C/2 h	8%

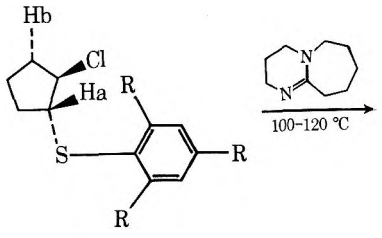
Table II

β-Chloro sulfide	DBU temp/time	Olefin, yield[a]	Registry no.
$ClCH_2CH_2SC_6H_5$ 9	100 °C/0.25 h	$H_2C{=}CHSC_6H_5$ 38, 88%	
			
11a (n = 5)	120 °C/3 h	39a, 40%[b] 40a, 40%[b]	
11b (n = 6)	120 °C/9 h	39b, 4%[b] 40b, 77%[b]	
11c (n = 7)	120 °C/9 h	39c, 36%[b] 40c, 24%[b]	
 14	170 °C/1 h	No reaction (91%, 14 recovered)	
 16	100 °C/0.2 h	 41, 81%	53097-28-2
 18	100 °C/0.2 h	 42, 73%	64691-42-5
 26	−40 °C/2 h $CHCl_3$	 43, 88%	64741-13-5

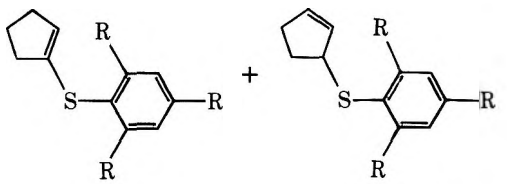
[a] Yield refers to isolated material of >95% purity. [b] Registry no: 39a, 37053-16-0; 39b, 4922-47-8; 39c, 64741-11-3; 40a, 3467-68-3; 40b, 3467-73-0; 40c, 64741-12-4.

the vinyl sulfide predominates at equilibrium is in accord with previous observations by Trost[21] et al. and O'Connor and Lyness.[28]

Having established that the **39/40** product mixture was a kinetic one, we felt that ortho substitution of the aryl sulfide moiety should favor production of the allylic isomer by retarding approach of the DBU to the methine hydrogen H_a relative to the *trans*-β-chloro hydrogen H_b. To this end, we compared the DBU-induced dehydrochlorination reaction of β-chloroaryl sulfides **12a** and **12b** with the parent β-chlo-



11a, R = H
12a, R = CH_3
12b, R = i-C_3H_7

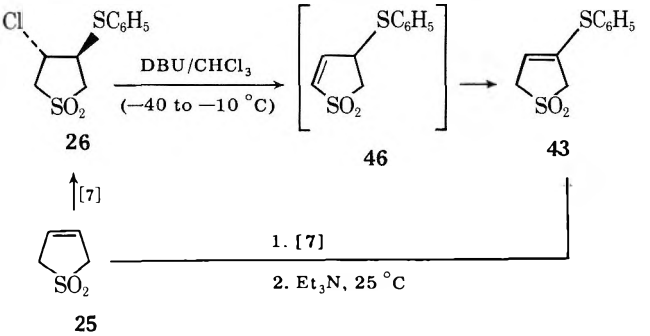


39a, 50% **40a**, 50%
44a, 20% **45a**, 80%
44b, 20% **45b**, 80%

rophenyl sulfide **11a**. While the ratio changes are in the desired direction, at this point the added selectivity is not sufficient to be synthetically useful.

The use of DBU for synthesis of vinyl and dienyl sulfides is especially convenient. The conversion of chloro sulfide **16** to 1-thiophenylbutadiene **41** had been previously achieved by Evans et al. by utilization of potassium *tert*-butoxide as base.[8] Our experience with the *tert*-butoxide reaction indicates that considerable experimental care (freshly prepared *tert*-butoxide) is necessary to consistently achieve satisfactory results. Simple use of commercial DBU for this reaction has been far more rewarding. (See Table II).

A considerable improvement in the ease of synthesis of 3-thiophenyl-3-sulfolene (**43**) has also been achieved. Gundermann and Holtmann have used triethylamine in hot (90 °C) Me_2SO to convert chloride **26** to vinyl sulfide **43**.[29] We find the same transformation can be more cleanly achieved using DBU in chloroform at −40 to −10 °C. The reaction proceeds through the intermediacy of isomer **46** which is further deconjugated to vinyl sulfide **43**.[29] Moreover, we further find that



26 **46** **43**

25

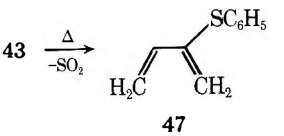


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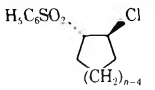
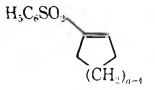
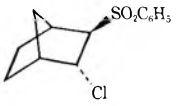
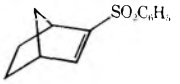
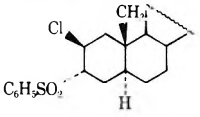
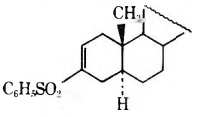
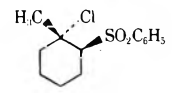
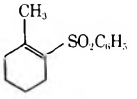
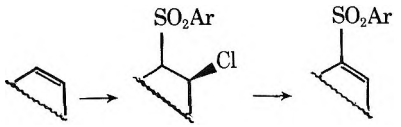
Table III

β-Chloro sulfide	RCO_3H R =	β-Chloro sulfone, yield	Registry no.	DBU solvent/temp/time	α,β-Unsaturated Sulfone, yield (recrystallized yield)	Registry no.
						
11a (n = 5)	3-ClC_6H_4	51a (n = 5), 99%	64741-14-6	CH_2Cl_2/0 °C/0.5 h	52a, 100% (86%)	64740-90-5
11a (n = 5)	CH_3	51a (n = 5), 93%				
11b (n = 6)	3-ClC_6H_4	51b (n = 6), 99%	33995-48-1	CH_2Cl_2/0 °C/0.5 h	52b, 98% (81%)	59059-70-0
11b (n = 6)	CH_3	51b (n = 6), 85%				
11c (n = 7)	3-ClC_6H_4	51c (n = 7), 99%	64740-86-9	CH_2Cl_2/0 °C/0.5 h	52c, 99% (84%)	64740-91-6
11c (n = 7)	CH_3	51c (n = 7), 90%				
14	3-ClC_6H_4			$CHCl_3$/61 °C/0.25 h		
		53, 99%	64740-87-0		54, 97% (68%)	64740-92-7
18	3-ClC_6H_4			CH_2Cl_2/25 °C/0.25 h		
		55, 99%	64740-88-1		56, 98% (83%)	26211-03-0
20	3-ClC_6H_4			CH_2Cl_2/25 °C/1 h		
		57, 96%	17150-06-0		58, (93%)	64740-93-8
24a/24b	3-ClC_6H_5			CH_2Cl_2/40 °C/1.5 h		
		59, 63%[a]	64740-89-2		60, 99% (oil)	64740-94-9

[a] Recrystallized yield, based on amount of 2-chloro-2-methyl-1-cyclohexenylphenyl sulfide in the original 24a/24b mixture.

43 may be synthesized (2.5-mol scale) in a one-pot chlorosulfenylation–dehydrochlorination reaction (using the less expensive triethylamine as the base) in an overall yield of 85% from sulfolene (**25**). Sulfolene **43** is an excellent source of 2-thiophenylbutadiene **47**[29] (and related compounds[30]) via thermolytic SO_2 extrusion reactions.[31]

The conversion of olefins **48** to α,β-unsaturated aryl sulfones **50** has been accomplished in a two-step sequence: (1)



48 **49** **50**

Cu-catalyzed chlorosulfonylation followed by (2) dehydrochlorination of the β-halo sulfone (**49**) with triethylamine (often at elevated temperature).[32]

In view of several of our eventual applications for natural product synthesis, we felt that a milder and higher overall yield procedure could be developed based on the kinetic work of Goering.[33] He found that β-halophenyl sulfides could be oxidized to sulfones **49** and then subsequently dehydrochlorinated (to **50**) with aqueous hydroxide ion by an E1cB mechanism.[33]

We find that simply oxidizing the "crude" β-chloroaryl sulfides from the chlorosulfenylation reaction with *m*-chloroperoxybenzoic acid provides β-halo sulfones in essentially quantitative yield. [For preparative purposes (>0.4-mol scale), we employ the more economical peracetic acid in the oxidation step]. Dehydrochlorination of these β-halo sulfones with DBU smoothly generates the unsaturated sulfones in outstanding overall yield (see Table III).

Experimental Section

General. Melting points were taken on a Fisher-Johns melting-point apparatus. All melting and boiling points are uncorrected. Infrared spectra were recorded neat or as a melt on a Perkin-Elmer Infracord or 137 spectrophotometer. NMR spectra were determined in chloroform-d_1 solution on a Varian A60A or Perkin-Elmer R-32 spectrometer; chemical shifts are reported in δ with tetramethylsilane as an internal standard. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Coupling constants are given in hertz. Mass spectra were recorded on CEC-21-110-B high-resolution mass spectrometer at an ionizing voltage of 70 eV and an ionizing current of 100 μA. Exact mass determinations were obtained on the CEC-21-110-B instrument.

All experiments were carried out under a positive pressure of dry nitrogen. During workup of the reactions, anhydrous magnesium sulfate was used for general solvent drying. Precoated thin-layer Sil G-25 UV_{254} plates were obtained from Brinkman Instruments, Inc.; thick-layer plates were made from silica gel PF-254 containing $CaSO_4$ from EM reagents. Products were recovered from the silica gel by washing with ethyl acetate.

Preparation of Arylsulfenyl Chloride Solutions: Phenylsulfenyl Chloride. The highly unpleasant odor of volatile aryl thiols necessitates that this reaction be conducted in a well-ventillated hood. To a rapidly stirred suspension of 68.1 g (0.510 mol) of *N*-chlorosuccinimide[34] in 500 mL of dry methylene chloride at room temperature in a 1-L flask equipped with a pressure-equalizing dropping funnel, thermometer, and an efficient water-cooled condenser was added about 5 g of a total 55.1 g (0.500 mol) of thiophenol.[34] Initiation of sulfenyl chloride formation is indicated by the intense orange coloration of the suspension accompanied by gentle boiling of the solvent. Gentle heating on a steam bath for 1 to 2 min may be required to initiate the reaction. Addition of substantially larger quantities of thiophenol prior to initiation will invariably result in an uncontrollably exothermic initiation. Once initiated, the reaction vessel was immersed in an ice bath and the remaining thiophenol added dropwise at a rate sufficient to maintain the solvent at reflux, the addition requiring approximately 15 min. When the addition was complete, the ice bath was immediately removed and the homogeneous orange so-

lution was stirred at room temperature for an additional 30 min. During this time, succinimide precipitated in most runs. The resulting solution contains 0.500 mol of phenylsulfenyl chloride.

Appropriate changes in reagent quantities in the above procedure have allowed convenient preparation of from 30 μmol to 2.5 mol of arylsulfenyl chloride solutions in methylene chloride. Preparation of less than 25 mmol of arylsulfenyl chloride may be accomplished without a dropping funnel, internal thermometer, or reflux condenser via slow syringe addition of thiophenol to a suspension of *N*-chlorosuccinimide in methylene chloride. This procedure has also been used to prepare solutions of 2,4,6-trimethylphenylsulfenyl chloride and 2,4,6-triisopropylphenylsulfenyl chloride from the corresponding thiols.[35]

The subsequently described solutions of arylsulfenyl chlorides are all generated in the manner described above and necessarily contain an equimolar quantity of succinimide, which is removed during reaction workup.

Preparation of 2-Chloroethyl Phenyl Sulfide (9). Ethene (**8**)[36] was bubbled through a solution of 2.00 mmol of phenylsulfenyl chloride at room temperature until the solution was colorless. Concentration in vacuo, stirring for 1 h with 1 mL of carbon tetrachloride, filtration, and concentration of the filtrate in vacuo gave rise to 0.34 g (98%) of **9** as a colorless oil: NMR δ 7.1–7.4 (m, 5 H), 3.4–3.9 (m, 2 H), 2.9–3.3 (m, 2 H). M^+ Calcd for C_8H_9ClS: 172.011. Found: 172.012.

Preparation of *trans*-2-Chloro-1-cyclopentyl Phenyl Sulfide (11a). A solution of 0.600 mol of phenylsulfenyl chloride was cooled to −50 °C and 42.6 g (0.625 mol) of cyclopentene (**10a**)[34] was added rapidly via a dropping funnel. The orange solution was instantly decolorized upon completion of the addition. The temperature rose to 0 °C during the addition, and the cold, colorless solution was filtered to remove the majority of the succinimide as a white solid, which was washed with 50 mL of methylene chloride. Concentration of the combined filtrates in vacuo afforded a light yellow oil to which 200 mL of carbon tetrachloride was added to precipitate the last traces of succinimide. This solution was stirred for 1 h and then filtered, and the filtrate was concentrated in vacuo to yield 126.9 g (99%) of **11a** as an oil: NMR δ 7.1–7.5 (m, 5 H), 4.1–4.4 (m, 1 H), 3.6–4.0 (m, 1 H), 1.4–2.7 (m, 6 H). M^+ Calcd for $C_{11}H_{13}ClS$: 212.043. Found: 212.042.

Preparation of *trans*-2-Chloro-1-cyclopentyl 1-(2,4,6-Trimethyl)phenyl Sulfide (12a). To a solution of 5.0 mmol of 2,4,6-trimethylphenylsulfenyl chloride at −78 °C was added via syringe 0.375 g (5.5 mmol) of cyclopentene (**10a**).[34c] The mixture was allowed to warm to room temperature and concentrated in vacuo. The residue was diluted with 5 mL of carbon tetrachloride, stirred for 1 h, and filtered to remove the succinimide as a white solid. Concentration of the filtrate in vacuo afforded 1.25 g (98%) of **12a** as a colorless oil: NMR δ 6.9 (brs, 2 H), 4.1 (m, 1 H), 3.5 (m, 1 H), 1.4–2.8 (m, 6 H), 2.5 (s, 6 H), 2.3 (s, 3 H). M^+ Calcd for $C_{14}H_{19}ClS$: 254.090. Found: 254.089.

Preparation of *trans*-2-Chloro-1-cyclopentyl 1-(2,4,6-Triisopropyl)phenyl Sulfide (12b). To a solution of 5.00 mmol of 2,4,6-triisopropylphenylsulfenyl chloride at −78 °C was added via syringe 0.375 g (5.5 mmol) of cyclopentene (**10a**).[34] The mixture was allowed to warm to room temperature and poured in 100 mL of ether. The organic layer was extracted with 25 mL of water, followed by 25 mL of saturated aqueous sodium chloride. Drying ($MgSO_4$) and concentration in vacuo afforded 1.36 g (80%) of a solid which was recrystallized from pentane to yield 0.92 g (54%) of **12b** as a white solid: mp 80.5–82 °C; NMR δ 7.0 (s, 2 H), 4.1 (m, 1 H), 3.9 (m, 2 H), 3.5 (m, 1 H), 2.8 (m, 1 H), 1.5–2.8 (m, 6 H), 1.2 (m, 18 H). M^+ Calcd for $C_{20}H_{31}ClS$: 338.184. Found: 338.185.

Preparation of *trans*-2-Chloro-1-cyclohexyl Phenyl Sulfide (11b).[20] In the procedure for the preparation of **11a**, 51.3 g (0.625 mol) of cyclohexene (**10b**)[34] was used in place of cyclopentene to afford 131.0 g (96%) of **11b** as a light yellow oil: NMR δ 7.2–7.5 (m, 5 H), 3.8–4.2 (m, 1 H), 3.1–3.5 (m, 1 H), 1.2–2.5 (m, 8 H). M^+ Calcd for $C_{12}H_{15}ClS$: 226.058. Found: 226.056.

Preparation of *trans*-2-Chloro-1-cycloheptyl Phenyl Sulfide (11c). In the procedure for the preparation of **11a**, 61.8 g (.610 mol) of 95% cycloheptene (**10c**)[34] was substituted for cyclopentene. Workup gave 147.5 g (102%) of **11c** as a crude oil, presumably contaminated with impurities present in the original cycloheptene: NMR δ 7.2–7.5 (m, 5 H), 4.2–4.4 (m, 1 H), 3.5–3.7 (m, 1 H), 1.2–2.3 (m, 10 H). M^+ Calcd for $C_{13}H_{17}ClS$: 240.074. Found: 240.075.

Preparation of *endo*-3-Chloro-*exo*-2-bicyclo[2.2.1]heptyl Phenyl Sulfide (14).[14] To a solution of 0.100 mol of phenylsulfenyl chloride at −78 °C was added via syringe a solution of 9.4 g (0.100 mol) of norbornylene (**13**)[34] in 50 mL of dry methylene chloride. The mixture was allowed to warm to room temperature and concentrated in vacuo. The resulting residue was diluted with 50 mL of carbon tetrachloride, stirred for 1 h, and filtered to remove the succinimide as a white solid. Concentration of the filtrate in vacuo afforded 23.6 g (99%) of **14** as an oil: NMR δ 7.1–7.5 (m, 5 H), 3.9–4.2 (dd, J = 4 and 4 Hz, 1 H), 3.0–3.2 (dd, J = 4 and 3 Hz, 1 H), 2.2–2.3 (m, 2 H), 1.2–2.2 (m, 6 H). M^+ Calcd for $C_{13}H_{15}ClS$: 238.058. Found: 238.058.

Preparation of 2-Chloro-3-buten-1-yl Phenyl Sulfide (16).[16] Freshly distilled 1,3-butadiene (**15**)[37] (5.4 g, 0.100 mol) cooled to −25 °C was added via syringe to a solution of 0.025 mol of phenylsulfenyl chloride at −78 °C. This mixture was allowed to warm to room temperature, concentrated in vacuo, diluted with 12.5 mL of carbon tetrachloride, and stirred for 1 h. Filtration and concentration of the filtrate in vacuo produced 4.95 g (100%) of **16** as an oil: NMR δ 7.1–7.5 (m, 5 H), 5.9 (ddd, J = 8, 8, and 18 Hz, 1 H), 5.2 (dd, J = 2 and 18 Hz, 1 H), 5.2 (dd, J = 2 and 8 Hz, 1 H), 4.4 (ddd, J = 6, 8, and 8 Hz, 1 H), 3.3 (dd, J = 6 and 14 Hz, 1 H), 3.2 (dd, J = 8 and 14 Hz, 1 H). M^+ Calcd for $C_{10}H_{11}ClS$: 198.027. Found: 198.028.

Preparation of *trans*-2-Chloro-3-cyclohexen-1-yl Phenyl Sulfide (18). In the preparation of **16**, 2.20 g (27.5 mmol) of 1,3-cyclohexadiene (**17**)[34] at room temperature was used in place of cold 1,3-butadiene. Workup afforded 5.6 g (100%) of **18**, a colorless oil: NMR δ 7.1–7.5 (m, 5 H), 6.7–6.9 (m, 2 H), 4.4–4.6 (m, 1 H), 3.5–3.8 (m, 1 H), 1.2–2.7 (m, 4 H). M^+ Calcd for $C_{12}H_{13}ClS$: 224.043. Found: 224.044.

Preparation of Δ²-Cholestene (19). To a solution of 7.77 g (20 mmol) of dihydrocholesterol[38] and 2.78 g (27.5 mmol) of triethylamine[39] in 125 mL of methylene chloride at −20 °C was added dropwise, over a period of 15 min, 2.86 g (25 mmol) of methanesulfonyl chloride.[40] The mixture was allowed to warm to 0 °C and stirred for 1 h and then transferred to a separatory funnel and washed successively with 50 mL of 10% aqueous hydrochloric acid, 50 mL of water, and 50 mL of saturated aqueous sodium chloride. Drying ($MgSO_4$) and concentration in vacuo afforded 9.15 g (98%) of crude mesylate which was used without further purification: NMR δ 4.2–4.9 (m, 1 H), 3.0 (s, 3 H), 0.6–2.3 (m, 46 H).

A 7.00-g (15 mmol) portion of the crude mesylate was rapidly added to 4.6 g (30 mmol) of rapidly stirred DBU[34] at 150 °C. The mixture was stirred 0.5 h at this temperature and then cooled to room temperature, and 100 mL of 2% aqueous hydrochloric acid was added. This mixture was extracted with three 100-mL portions of ether and the combined organic layers were washed with 50 mL of saturated aqueous sodium chloride. Drying ($MgSO_4$) and concentration in vacuo afforded a colorless oil which was recrystallized from ethanol to yield 4.25 g (77%) of **19** as a white solid: mp 69.5–70.5 °C; NMR δ 5.6 (m, 2 H), 0.6–2.2 (m, 44 H).

Preparation of 3α-Phenylthio-2β-chlorocholestane (20).[18] A 1.48-g (4.00 mmol) portion of Δ²-cholestene (**19**) was added to 4.0 mmol of phenylsulfenyl chloride solution at −50 °C. The mixture was decolorized over a period of 15 min. After complete decolorization, the solvent was concentrated in vacuo and the residue was stirred with 5.0 mL of carbon tetrachloride. Filtration and concentration of the filtrate in vacuo afforded **20** as a crude oil; recrystallization from acetone afforded 1.13 g (55%) of **20** as a colorless needles: mp 113.5–114.5 °C; NMR δ 7.3–7.5 (m, 5 H), 4.4 (m, 1 H), 3.7 (m, 1 H), 0.6–2.5 (m, 44 H).

Preparation of 2-Chloro-1,2-dimethylcyclohexyl Phenyl Sulfide (22). A solution of 0.83 g (0.75 mmol) of 1,2-dimethylcyclohexene (**21**)[41] in 3 mL of methylene chloride was added all at once to a solution of 0.75 mmol of phenylsulfenyl chloride at −78 °C. The mixture was diluted with 25 mL of ether, washed with 10 mL of water and then 10 mL of saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to yield 0.175 g (92%) of **22** as an oil: NMR δ 7.1–7.6 (m, 5 H), 1.1–2.5 (m, 8 H), 1.8 (s, 3 H), 1.3 (s, 3 H). M^+ Calcd for $C_{14}H_{19}ClS$: 254.090. Found: 254.090.

Chlorosulfenylation of 1-Methylcyclohexene (23). 1-Methylcyclohexene (**23**),[42] 5.0 g (52 mmol), was added via syringe to a solution of 0.050 mol of phenylsulfenyl chloride such that the temperature did not exceed −70 °C. Addition required about 15 min, after which time, the reaction was warmed to room temperature and concentrated in vacuo, and 25 mL of carbon tetrachloride was added. The mixture was stirred for 1 h and filtered, and the filtrate was concentrated in vacuo to afford 11.80 g (98%) of a product, which was demonstrated by NMR to be a 3:1 mixture of 2-chloro-2-methyl-1-cyclohexyl phenyl sulfide (**24a**) and 2-chloro-1-methyl-1-cyclohexyl phenyl sulfide (**24b**). This mixture was taken up in 50 mL of methylene chloride and heated under reflux for 1.5 h, to yield, after concentration in vacuo, a 90:10 mixture of **24a** and **24b**, respectively. This ratio was unchanged on further heating. The mixture was not separated: NMR δ 7.1–7.6 (m, 5 H), 3.8–4.0 (m, 1 H, due to **24b**), 3.3–3.6 (m, 1 H, due to **24a**), 1.2–1.3

(m, 11 H). M^+ Calcd for $C_{13}H_{17}ClS$: 240.074. Found: None. $M^+ - HCl$ Calcd for $C_{13}H_{16}S$: 204.097. Found: 204.098.

Preparation of *trans*-3-Chloro-4-phenylthiotetrahydrothiophene 1,1-Dioxide (26).[29] A 29.5-g (0.250 mol) portion of 2,5-dihydrothiophene 1,1-dioxide (**25**)[43] was added to a solution of 0.250 mol of phenylsulfenyl chloride at room temperature. This mixture was stirred for 48 h at room temperature then washed with 100 mL of water followed by 100 mL of saturated aqueous sodium chloride. Drying ($MgSO_4$) and concentration in vacuo afforded an orange oil which was crystallized from 9:1 (v/v) ether/hexane at 0 °C to yield 53.2 g (81%) of **26** as a white solid: mp 74.5–75.5 °C; NMR δ 7.1–7.6 (m, 5 H), 2.9–4.6 (m, 6 H). M^+ Calcd for $C_{10}H_{11}ClO_2S_2$: 261.989. Found: 261.988.

Preparation of Phenyl 2-Phenyl-2-cyclopenten-1-yl Sulfide (30b). A solution of 0.025 mol of phenyl sulfenyl chloride cooled to −78 °C was added dropwise via syringe over a period of 15 min to a rapidly stirred suspension of 13.25 g (0.125 mol) of anhydrous sodium carbonate in 25 mL of methylene chloride containing 3.61 g (0.025 mol) of 1-phenylcyclopentene (**27b**)[42] which was maintained at about −25 °C. The resulting suspension was then heated under reflux for a period of 24 h to complete the dehydrochlorination. After cooling to room temperature, the mixture was poured into 200 mL of ethyl acetate, and the organic layer was extracted twice with 100-mL portions of water and then with 50 mL of saturated aqueous sodium chloride solution, dried ($MgSO_4$), and concentrated in vacuo to afford 2.5 g (99%) of **30b** as an oil. This oil was recrystallized from ether to yield 5.0 g (79%) of **30b** as light brown cryrstals: mp 80.5–82 °C; NMR δ 7.2–7.7 (m, 10 H), 6.2 (m, 1 H), 4.5–4.7 (m, 1 H), 2.3–2.5 (m, 4 H). M^+ Calcd for $C_{17}H_{16}S$: 252.097. Found: 252.099.

Preparation of Phenyl 2-Phenyl-2-cyclohexen-1-yl Sulfide (30a). In the preparation of **30b**, 3.96 g (0.025 mol) of 1-phenylcyclohexene (**27a**)[34] was substituted for 1-phenylcyclopentene to afford, after recrystallization, 4.2 g (63%) of **30a** as light yellow crystals: mp 46–48 °C; NMR δ 7.2–7.6 (m, 10 H), 6.2 (m, 1 H), 4.3 (m, 1 H), 1.5–2.4 (m, 6 H). M^+ Calcd for $C_{18}H_{18}S$: 266.113. Found: 266.114.

Omission of the 24-h reflux period gave a product which decomposed at room temperature; the NMR showed, in addition to signals due to **30a**, a signal at δ 3.95 (m), which vanished upon the addition of an excess of DBU to the NMR sample with a corresponding increase in the intensity of the signals due to **30a**. The structure was thus assigned as **29a**, containing about 10 mol % **30a**.

Preparation of 1-(3,4-Methylenedioxy-6-[2′-*tert*-butyldimethylsiloxyethyl]phenyl)-5-phenylthio-1-cyclopentene (30c). To a solution of 0.20 mmol of phenylsulfenyl chloride rapidly stirred over 0.21 g (2.0 mmol) of anhydrous sodium carbonate cooled to −78 °C was added in one portion 0.069 g (0.20 mmol) of 1(3,4-methylenedioxy-6-[2′-*tert*-butyldimethylsiloxyethyl]phenyl-1-cyclopentene (**27c**).[44] The colorless suspension was filtered and the filtrate was chromatographed on silica (10% THF/hexane) to yield 0.060 g (66%) of **30c** as a colorless oil: NMR (in ppm relative to CH_3Si of TBDMS group) δ 7.1–7.3 (m, 5 H), 6.65 (s, 2 H), 5.85 (s, 2 H), 5.75 (brs, 1 H), 4.2–4.6 (m, 1 H), 3.7 (t, J = 7 Hz, 2 H), 2–2.9 (m, 6 H), 0.9 (s, 9 H), 0.0 (s, 6 H). M^+ Calcd for $C_{26}H_{34}O_3SSi$: 454.200. Found: 454.200.

Preparation of 6-Methoxy-3,4-dihydronaphthalene (31a).[45] A solution of 17.6 g (0.100 mol) of 6-methoxy-1-tetralone[34] in 300 mL of ether was added dropwise over a period of 0.5 h to a suspension of 3.8 g (.050 mol) of lithium aluminum hydride in 150 mL of ether, the temperature of the reaction mixture being maintained at 5 °C during the entire addition. After stirring an additional 15 min, 3.8 mL of water was added dropwise over a period of 0.5 h, followed by the cautious addition of 3.8 mL of 10% aqueous sodium hydroxide, and, finally, 10.5 mL of water. The mixture was stirred for 10 min and filtered to remove the aluminum salts, and the salts were washed with an additional 50 mL of ether.[46] The combined organic layers were washed with 100 mL of water and then with 100 mL of saturated aqueous sodium chloride. Drying ($MgSO_4$) and concentration in vacuo afforded 17.8 g (100%) of 6-methoxy-1,2,3,4-tetrahydro-1-naphthol as a light brown oil: NMR δ 7.3 (ddd, J = 9, 2, and 2 Hz, 1 H), 6.7 (ddd, J = 9, 2, and 2 Hz, 1 H), 6.6 (dd, J = 2 and 2 Hz, 1 H), 4.6 (m, 1 H), 3.75 (s, 3 H), 2.7 (m, 2 H), 1.4–2.2 (m, 5 H). M^+ Calcd for $C_{11}H_{14}O_2$: 178.099. Found: 178.100.

A solution of 16.93 g (0.095 mol) of the crude alcohol and 0.266 g (1.40 mmol) of *p*-toluenesulfonic acid monohydrate[34] in 0.5 L of benzene was heated under reflux for 0.5 h. (Longer reaction times and higher boiling solvents produced low yields of the desired olefin due to dimer formation.)[47] The mixture was cooled to room temperature, washed with 100 mL of water and 100 mL of saturated aqueous sodium chloride, and dried ($MgSO_4$). Concentration in vacuo gave 14.75 g (97%) of **31a** as an orange oil of sufficient purity for the subsequent chlorosulfenylation. Kugelrohr distillation of 0.860 g of this oil at 112 °C (0.6 mm) afforded 0.846 g of **31a** as a colorless oil, for a distilled overall yield of 95% from 6-methoxy-1-tetralone: NMR δ 6.9 (d, J = 9 Hz, 1 H), 6.65 (m, 2 H), 6.4 (m, 1 H), 5.85 (dt, J = 10 and 4 Hz, 1 H), 3.75 (s, 3 H), 2.75 (m, 2 H), 2.0–2.4 (m, 2 H). M^+ Calcd for $C_{11}H_{12}O$: 160.089. Found: 160.089.

Preparation of 6-Methoxy-2-phenylthio-3,4-dihydronaphthalene (32a). A solution of 5.0 mmol of phenylsulfenyl chloride cooled to −78 °C was transferred dropwise, via a cannula, over a period of 1 min to a rapidly stirred suspension of 2.65 g (25 mmol) of anhydrous sodium carbonate in 5 mL of methylene chloride containing 0.80 g (5.0 mmol) of 6-methoxy-3,4-dihydronaphthalene (**31a**) at −78 °C. The colorless mixture was then heated at reflux for a period of 2 h to effect complete dehydrochlorination. The mixture was cooled to room temperature and poured into 100 mL of ether, and the organic layer was washed with 50 mL of water and then with 50 mL of saturated aqueous sodium chloride. Drying ($MgSO_4$) and concentration in vacuo afforded 1.33 g (99%) of **32a** as a colorless oil. Crystallization from 50 mL of methanol at 0 °C provided 0.80 g of **32a** as a white solid, mp 51–52 °C; concentration of the filtrate to a volume of 25 mL and cooling to 0 °C afforded a second crop of 0.27 g for a total recrystallized yield of 80%: NMR δ 7.2–7.6 (m, 5 H), 6.5–7.0 (m, 4 H), 3.8 (s, 3 H), 2.85 (t, J = 7 Hz, 2 H), 2.4 (t, J = 7 Hz, 2 H). M^+ Calcd for $C_{17}H_{16}OS$: 268.092. Found: 268.095.

Deletion of the 2-h period at reflux resulted in a product which decomposed at room temperature; the NMR had, in addition to signals due to **32a**, signals at 5.2 (m) and 4.0 (m) which vanished upon addition of excess DBU to the NMR sample and thus were attributed to *trans*-1-chloro-6-methoxy-2-phenylthio-3,4-dihydronaphthalene.

Preparation of 6-Methoxy-1-methyl-2-phenylthio-3,4-dihydronaphthalene (32b). In the preparation of **32b**, 0.87 g (5.0 mmol) of 6-methoxy-1-methyl-3,4-dihydronaphthalene (**31b**)[48] was substituted for 6-methoxy-3,4-dihydronaphthalene, and the reflux period was unnecessary. Workup provided 1.40 g (93%) of **32b** as a brown oil: NMR δ 7.0–7.5 (m, 6 H), 6.5–6.8 (m, 2 H), 3.75 (s, 3 H), 2.1–2.9 (m, 7 H). M^+ Calcd for $C_{18}H_{18}OS$: 282.108. Found: 282.106.

Preparation of Phenyl Vinyl Sulfide (38). To 1.52 g (10.0 mmol) of DBU[34] at 100 °C was added via syringe 0.86 g (5.0 mmol) of 2-chloroethyl phenyl sulfide (**9**). The mixture was stirred for 15 min at 100 °C, then cooled rapidly to room temperature, and diluted with 25 mL of 2% aqueous hydrochloric acid. Extraction with 50 mL of ether, washing of the ether layer with 25 mL of saturated aqueous sodium chloride, drying ($MgSO_4$), and concentration in vacuo afforded a light yellow oil. Kugelrohr distillation at 27 °C (0.5 mm) yielded 0.60 g (88%) of **38**: NMR δ 7.2–7.5 (m, 5 H), 6.5 (ddd, J = 17, 8, and 5 Hz, 1 H), 5.3 (d, J = 17 Hz, 1 H), 5.3 (d, J = 8.5 Hz, 1 H). M^+ Calcd for C_8H_8S: 136.035. Found: 136.036.

Preparation of 1- and 2-Cyclopenten-1-yl Phenyl Sulfides (39a and 40a). A 1.06-g (5.0 mmol) portion of *trans*-2-chloro-1-cyclopentyl sulfide (**11a**) was added via syringe to 1.52 g (10.0 mmol) of DBU[34] at 120 °C. The mixture was stirred for 3 h at 120 °C, cooled to room temperature, diluted with 25 mL of 2% aqueous hydrochloric acid, and extracted with 50 mL of ether, and the organic layer was washed with 25 mL of saturated aqueous sodium chloride. Drying ($MgSO_4$) and concentration in vacuo left a light yellow oil which NMR showed to be a 1:1 mixture of **39a** and **40a**. Kugelrohr distillation at 95 °C (0.5 mm) provided 0.80 g (91%) of a colorless oil; this oil was separated by TLC on silica (hexane) to yield 0.35 g (40% overall from the chloride) of **39a** and 0.35 g (40% overall from the chloride) of **40a**. **39a:** NMR δ 7.1–7.5 (m, 5 H), 5.7 (t, J = 2, Hz, 1 H), 2.2–2.6 (m, 4 H), 1.7–2.2 (m, 2 H). M^+ Calcd for $C_{11}H_{12}S$: 176.066. Found: 176.065. **40a:** NMR δ 7.1–7.5 (m, 5 H), 5.8 (m, 2 H), 4.1–4.5 (m, 1 H), 1.9–2.5 (m, 4 H). M^+ Calcd for $C_{11}H_{12}S$: 176.066. Found: 176.066.

Preparation of 1- and 2-Cyclohexen-1-yl Phenyl Sulfides (39b and 40b). In the preparation of **39b** and **40b**, 1.13 g (5.0 mmol) of *trans*-2-chloro-1-cyclohexyl phenyl sulfide (**11b**) was substituted for *trans*-2-chloro-1-*trans*-2-chloro-1-cyclopentyl phenyl sulfide and the mixture was heated for 9 h at 120 °C. Kugelrohr distillation at 110 °C (0.2 mm) afforded 0.764 g (81%) of product which NMR showed to be almost exclusively **40**. Thin-layer chromatography on silica (hexane) afforded 0.58 g (62% from the chloride) of **40b** and 0.03 g (3% from the chloride) of **39b**. **39b:** NMR δ 7.3 (m, 5 H), 6.0 (m, 1 H), 2.0–2.4 (m, 4 H), 1.5–2.0 (m, 4 H). M^+ Calcd for $C_{12}H_{14}S$: 190.082. Found: 190.079. **40b:** NMR δ 7.1–7.5 (m, 5 H), 5.8 (m, 2 H), 3.7–4.0 (m, 1 H), 1.5–1.2 (m, 6 H). M^+ Calcd for $C_{12}H_{14}S$: 190.082. Found: 190.081.

Preparation of 1- and 2-Cyclohepten-1-yl Phenyl Sulfide (39c and 40c). In the preparation of **39c**, and **40c**, 1.20 g (5.0 mmol) of *trans*-2-chloro-1-cycloheptyl phenyl sulfide (**11c**) was substituted for *trans*-2-chloro-1-cyclopentyl phenyl sulfide, and the mixture was

heated to 120 °C for 9 h. Workup produced 0.72 g (71%) of an oil which by NMR was a 13:7 mixture of **39c** and **40c**, respectively. Kugelrohr distillation at 90 °C (0.15 mm) yielded 0.68 g (66%) of an oil which gave, after thin-layer chromatography, 0.34 g (36% from the chloride) of **39c** and 0.22 g (24% from the chloride) of **40c**. **39c:** NMR δ 7.1–7.3 (m, 5 H), 5.0 (t, J = 6 Hz, 1 H), 2.0–2.4 (m, 4 H), 1.4–1.8 (m, 6 H). M^+ Calcd for $C_{13}H_{16}S$: 204.097. Found: 204.097. **40c:** NMR δ 7.2–7.5 (m, 5 H), 4.8 (m, 2 H), 4.0 (m, 1 H), 1.5–2.4 (m, 8 H). M^+ Calcd for $C_{13}H_{16}S$: 204.097. Found: 204.097.

Equilibration of 1- and 2-Cycloalken-1-yl Phenyl Sulfides. A mixture of 1.76 g (10.0 mmol) of 2-cyclopenten-1-yl phenyl sulfide (**40a**), 0.22 g (2 mmol) of potasssium *tert*-butoxide,[49] and 10 mL of Me_2SO was heated to 60 °C for 4 h, cooled to room temperature, and quenched with 100 mL of 2% aqueous hydrochloric acid. This solution was extracted with 200 mL of ether and the ether layer washed with 100 mL of water followed by 100 mL of saturated aqueous sodium chloride. Drying ($MgSO_4$) and concentration in vacuo left 1.72 g (97%) of a light brown oil which was shown by NMR to be a 90:10 mixture of **39a** and **40a**, respectively.

Similar treatment of 1.90 g (10.0 mmol) of 2-cyclohexen-1-yl phenyl sulfide (**40b**) for 20 h at room temperature afforded 1.78 g (94%) of a light brown oil which NMR revealed to be a 92:8 mixture of **39b** and **40b**, respectively.

Equilibration of 2.04 g (10.0 mmol) of 2-cyclohepten-1-yl phenyl sulfide (**40c**) for 2 h at 60 °C led to a recovery of 1.96 g (96%) of a 92:8 mixture of **39c** and **40c**, respectively.

Longer reaction times produced no further change in the ratio of 1- to 2-cycloalken-1-yl phenyl sulfides, and it is thus assumed that these ratios represent the equilibrium value.

Demonstration of the Kinetic Stability of the 1- and 2-Cycloalken-1-yl Phenyl Sulfides. To a solution of 0.304 g (2.0 mmol) of DBU[34] in 5.0 mL of benzene at room temperature was added 83 μL (1.0 mmol) of concentrated hydrochloric acid. Concentration in vacuo produced a 1:1 mixture of DBU and DBU·HCl. This mixture was heated to 125 °C and a quantity (see Table IV) of cycloalkenyl phenyl sulfide was added. After heating for the specified period of time, the mixture was cooled to room temperature and diluted with 10 mL of 2% aqueous hydrochloric acid. Extraction with 25 mL of ether and washing of the organic layer with 10 mL of saturated aqueous sodium chloride furnished, after drying ($MgSO_4$) and concentration in vacuo, a product which by NMR showed no detectable equilibration.

Attempted Dehydrochlorination of *endo*-3-Chloro-*exo*-2-bicyclo[2.2.1]heptyl Phenyl Sulfide (14). To 0.304 g (2.0 mmol) of DBU[34] at 170 °C was added via syringe 0.24 g (1.0 mmol) of *endo*-3-chloro-*exo*-2-bicyclo[2.2.1]heptyl phenyl sulfide (**14**). The mixture was stirred for 1 h at 170 °C and then cooled to room temperature and diluted with 10 mL of 2% aqueous hydrochloric acid. This solution was extracted with 25 mL of ether, and the organic layer was washed with 10 mL of saturated aqueous sodium chloride. Drying ($MgSO_4$) and concentration in vacuo afforded 0.22 g (91%) of an oil which NMR showed to be exclusively **14**.

Preparation of *trans*-1,3-Butadien-1-yl Phenyl Sulfide (41).[8] A 1.99-g (10.0 mmol) portion of 2-chloro-3-buten-1-yl phenyl sulfide (**16**) was added via syringe to 3.04 g (20.0 mmol) of DBU[34] at 100 °C. The mixture was stirred for 10 min at 100 °C, cooled to room temperature, and diluted with 50 mL of 2% aqueous hydrochloric acid. Shaking with 50 mL of ether, washing the organic layer with 25 mL of saturated aqueous sodium chloride, drying ($MgSO_4$), and concentration in vacuo produced 1.50 g (92%) of **41** as a light yellow oil. Kugelrohr distillation at 60 °C (0.1 mm) furnished 1.31 g (81%) of **41** as a colorless oil: NMR δ 7.1–7.4 (m, 5 H), 6.0–6.5 (m, 3 H), 4.9–5.5 (m, 2 H); M^+ Calcd for $C_{10}H_{10}S$: 162.050. Found: 162.051.

Preparation of 1,3-Cyclohexadien-1-yl Phenyl Sulfide (42). In the preparation of **41**, 2.24 g (10.0 mmol) of *trans*-2-chloro-3-cyclohexadien-1-yl phenyl sulfide (**18**) was substituted for 2-chloro-3-buten-1-yl sulfide to yield 1.54 g (82%) of crude material which was Kugelrohr distilled at 92 °C (0.7 mm) to yield 1.37 g (73%) of **42** as a colorless oil: NMR δ 7.1–7.5 (m, 5 H), 6.6–6.0 (m, 3 H), 2.1–2.4 (m, 4 H). M^+ Calcd for $C_{12}H_{12}S$: 188.066. Found: 188.063.

Dehydrochlorination of *trans*-2-Chloro-1-cyclopentyl 1-(2,4,6-Trimethyl)phenyl Sulfide (12a). A 0.127-g (0.50 mmol) portion of *trans*-2-chloro-1-cyclopentyl 1-(2,4,6-trimethyl)phenyl sulfide (**12a**) and 0.15 g of DBU[34] were heated to 110–120 °C for 3 h. The mixture was cooled to room temperature, diluted with 50 mL of ether, and washed with 25 mL of 2% aqueous hydrochloric acid. Drying ($MgSO_4$) and concentration in vacuo afforded a dark oil which gave NMR signals at δ 5.8 (m), 5.65 (m) (olefinic protons of **45a**), and 4.95 (br s) (olefinic proton of **44a**) whose intensities indicated an 80:20 mixture of **45a** and **44a**, respectively. About 10 mol % of **12a** was also present in the sample.

Table IV. Kinetic Stability of the 1- and 2-Cycloalken-1-yl Phenyl Sulfides

Sulfide (wt, g; mmol)	Time, h	Product wt, g (% yield)
39a (0.083, 0.47)	3	0.075 (90)
40a (0.176, 1.0)	3	0.130 (74)
39b (0.062, 0.33)	9	0.058 (94)
40b (0.190, 1.0)	9	0.184 (97)
39c (0.063, 0.31)	9	0.045 (71)
40c (0.044, 0.22)	9	0.041 (94)

Dehydrochlorination of *trans*-2-Chloro-1-cyclopentyl 1-(2,4,6-Triisopropyl)phenyl Sulfide (12b). Treatment of 0.17 g (0.5 mmol) of *trans*-2-chloro-1-cyclopentyl 1-(2,4,6-triisopropyl)phenyl sulfide (**12b**) with 0.15 g (1.0 mmol) of DBU[34] for 2.5 h at 110–120 °C and workup identical to that for the dehydrochlorination of **12a** provided an oil whose NMR showed signals at δ 5.8 (m), 5.6 (m) (olefinic protons of **45b**), and 4.9 (br s) (olefinic proton of **44b**); the integrals indicated an 80:20 mixture of **45b** and **44b**, respectively, as well as about 10% recovered starting material **12b**.

Preparation of 3-Phenylthio-2,5-dihydrothiophene 1,1-Dioxide (43).[29] A solution of 12.72 g (48 mmol) of *trans*-3-chloro-4-phenylthio-2,5-dihydrothiophene 1,1-dioxide (**26**) in 250 mL of chloroform was cooled to −40 °C and 7.74 g (51 mmol) of DBU[34] in 5 mL of chloroform was added dropwise over a 5-min period. The resulting solution was stirred for 0.5 h at −40 °C, warmed to −10 °C, and quenched with 50 mL of 10% aqueous hydrochloric acid. The organic layer was then dried ($MgSO_4$) and concentrated in vacuo to afford an oil which was crystallized from ether/hexane to yield 9.7 g (88%) of **43** as white crystals: mp 55.5–56.5 °C; NMR δ 7.2–7.5 (m, 5 H), 5.75 (m, 1 H), 3.75–3.95 (m, 2 H), 3.6–3.75 (m, 2 H). M^+ Calcd for $C_{10}H_{10}O_2S_2$: 226.012. Found: 226.015.

Higher temperatures (75 °C, 1 h, sealed tube) convert **43** cleanly to 3-phenylthio-4,5-dihydrothiophene 1,1-dioxide, a white solid: mp 140.5–141.5 °C; NMR δ 7.5 (m, 5 H), 6.8 (m, 1 H), 3.2–3.6 (m, 2 H), 2.7–3.2 (m, 2 H). M^+ Calcd for $C_{10}H_{10}O_2S_2$: 226.012. Found: 226.012.

One-Pot Preparation of 3-Phenylthio-2,5-dihydrothiophene 1,1-Dioxide (43) from 2,5-Dihydrothiophene 1,1-Dioxide (25).[29] A 295.4-g (2.5 mol) portion of 2,5-dihydrothiophene 1,1-dioxide (**25**)[43] was added to a solution of 2.50 mol of phenylsulfenyl chloride, and the mixture was stirred for 24 h at room temperature. With ice-bath cooling to maintain the temperature below 25 °C, 265.6 g (2.63 mol) of triethylamine[39] was added over a period of 5 min. Intermittant cooling during the next hour was necessary to maintain a temperature of 25 °C, after which time the mixture was allowed to stir for 24 h at room temperature. The resulting brown solution was washed twice with 1-L portions of water, once with 0.5 L of 2% aqueous hydrochloric acid, and once with 0.5 L of saturated aqueous sodium chloride. Concentration in vacuo provided 515 g (91%) of a crude orange oil whose NMR was identical to that of the crystalline sample obtained in the two-step procedure. Crystallization from 2.5 L of ether/hexane provided a first crop of 422 g (75%) of **43** as slightly yellow solid, mp 56.5–57.5 °C. A second, more colored crop of 59 g (NMR identical to colorless crystals of **43**) was collected by concentration of the filtrate in vacuo and cooling to −40 °C. The total recrystallized yield of **43** was, thus, 481 g (85%). Spectral data was identical to that obtained for the two-step procedure.

Preparation of *trans*-2-Chloro-1-cyclopentyl Phenyl Sulfone (51a). Method A. To a solution of 1.06 g (5.0 mmol) of *trans*-2-chloro-1-cyclopentyl phenyl sulfide (**11a**) in 25 mL of methylene chloride immersed in an ice bath at 0 °C was added 2.44 g (12.0 mmol) of 85% *m*-chloroperoxybenzoic acid (MCPBA)[34] at a rate which caused gentle boiling of the solvent. After the addition, the ice bath was removed and the solution was stirred an additional 0.5 h at room temperature. A 10-mL portion of 10% aqueous sodium sulfite was added and the mixture was poured into 50 mL of ether. The organic layer was washed with 25 mL of 10% aqueous sodium carbonate and 25 mL of saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to yield 1.21 g (99%) of **51a** as a white solid: mp 81–82 °C; NMR δ 7.8–8.0 (m, 2 H), 7.5–7.8 (m, 3 H), 4.45–4.7 (m, 1 H), 3.5–3.9 (m, 1 H), 1.7–2.4 (m, 6 H). M^+ Calcd for $C_{11}H_{13}ClO_2S$: 244.032. Found: 244.033.

Preparation of *trans*-2-Chloro-1-cyclopentyl Phenyl Sulfone (51a). Method B. To a solution of 106.2 g (0.500 mol) of *trans*-2-chloro-1-cyclopentyl phenyl sulfide (**11a**) in 180 mL of glacial acetic acid at 20 °C in an ice bath was added dropwise over a 1-h period 171

mL (1.20 mol) of 7 M peracetic acid[50] in acetic acid which had been previously treated with 15 g (0.183 mol) of anhydrous sodium acetate. During the addition, the temperature must be maintained between 20 and 30 °C to assure that the reaction proceeds in a controlled fashion. Failure to do so resulted in low yields and numerous intermittant exotherms. After the addition was completed, the mixture was stirred for 1 h between 20 and 30 °C and then poured into 1 L of ice water. This mixture was stirred until the ice had melted and then filtered to yield a crude white solid. This solid was taken up in 200 mL of methylene chloride and shaken with 100 mL of 10% aqueous sodium sulfite, 200 mL of 10% aqueous sodium carbonate, and finally 50 mL of saturated aqueous sodium chloride. Drying ($MgSO_4$) and concentration in vacuo afforded 113.4 g (93%) of **51a** as a white powder, mp 81–82 °C, whose spectral data were identical with that obtained by method A.

Oxidations by method A or B were conveniently followed by TLC using 10% ethyl acetate in chloroform as eluent, the intermediate sulfoxides showing a substantially higher polarity than the starting sulfide and the sulfone being only slightly more polar than the starting sulfide.

Preparation of *trans*-2-Chloro-1-cyclohexyl Phenyl Sulfone (51b). Oxidation of 1.13 g (5.0 mmol) of *trans*-2-chloro-1-cyclohexyl phenyl sulfide (**11b**) by method A gave 1.28 g (99%) of a colorless oil, **51b:** NMR δ 7.8–8.0 (m, 2 H), 7.5–7.8 (m, 3 H), 4.2–4.5 (m, 1 H), 3.1–3.5 (m, 1 H), 1.2–2.5 (m, 8 H). M^+ Calcd for $C_{12}H_{15}ClO_2S$: 258.048. Found: 258.050.

Oxidation of 113.4 g (0.500 mol) of *trans*-2-chloro-1-cyclohexyl phenyl sulfide (**11b**) by method B afforded 110.0 g (85%) of **51b** as a crude white solid, mp 66–70 °C, whose spectral data were identical to that obtained by method A.

Preparation of *trans*-2-Chloro-1-cycloheptyl Phenyl Sulfone (51c). Oxidation of 1.20 g (5.0 mmol) of *trans*-2-chloro-1-cycloheptyl phenyl sulfide (**11c**) by method A yielded 1.34 g (99%) of **51c** as a white solid: mp 67–69 °C; NMR δ 7.8–8.1 (m, 2 H), 7.5–7.8 (m, 3 H), 4.6–4.9 (m, 1 H), 3.4–3.8 (m, 1 H), 1.1–2.5 (m, 10 H). M^+ Calcd for $C_{13}H_{17}ClO_2S$: 272.064. Found: 272.063.

Oxidation of 120.4 g (0.500 mol) of *trans*-2-chloro-1-cycloheptyl phenyl sulfide (**11c**) by method B provided 121.9 g (90%) of white solid **51c** whose spectral data were identical to that obtained by method A.

Preparation of *endo*-3-Chloro-*exo*-2-bicyclo[2.2.1]heptyl Phenyl Sulfone (53). Oxidation of 4.78 g (20 mmol) of *endo*-3-chloro-*exo*-2-bicyclo[2.2.1]heptyl phenyl sulfide (**14**) by method A furnished 5.35 g (99%) of **53** as a white solid: mp 82–84.5 °C; NMR δ 7.8–8.0 (m, 2 H), 7.5–7.8 (m, 3 H), 4.4 (dd, J = 5 and 5 Hz, 1 H), 2.9 (dd, J = 5 and 2 Hz, 1 H), 2.8–3.1 (m, 1 H), 2.3–2.7 (m, 1 H), 1.2–2.2 (m, 6 H). M^+ Calcd for $C_{13}H_{15}ClO_2S$: 270.048. Found: 270.053.

Preparation of *trans*-2-Chloro-3-cyclohexen-1-yl Phenyl Sulfone (55). Oxidation of 1.12 g (10.0 mmol) of *trans*-2-chloro-3-cyclohexen-1-yl phenyl sulfide (**18**) by method A furnished 1.275 g (99%) of **55** as an oil which was precipitated as a solid, mp 56–57.5 °C, by adding hexane to a solution of the oil in ether: NMR δ 7.8–8.0 (m, 2 H), 7.5–7.8 (m, 3 H), 5.6–6.1 (m, 2 H), 4.8–5.0 (m, 1 H), 3.4–3.7 (m, 1 H), 1.7–2.6 (m, 4 H). M^+ Calcd for $C_{12}H_{13}ClO_2S$: 256.032. Found: None. $M^+ - HCl$ Calcd for $C_{12}H_{12}O_2S$: 220.056. Found: 220.056.

Preparation of 3α-Phenylsulfonyl-2β-chlorocholestane (57).[18] Oxidation of 0.515 g (1.0 mmol) of 3α-phenylthio-2β-chlorocholestane (**20**) by method A afforded 0.526 g (96%) of **57** as a white solid: mp 163–165; NMR δ 7.5–8.0 (m, 5 H), 4.8 (m, 1 H), 3.6 (m, 1 H), 0.7–2.3 (m, 44 H). M^+ Calcd for $C_{33}H_{51}ClO_2S$: 546.330. Found: 546.328.

Preparation of 2-Chloro-2-methyl-1-cyclohexyl Phenyl Sulfone (59). Oxidation of 2.41 g (10.0 mmol) of a 90:10 mixture of **24a** and **24b,** respectively, by method A gave 2.7 g (99%) of a white solid, a 90:10 mixture of **59,** and 2-chloro-1-methyl-1-cyclohexyl phenyl sulfone by NMR. Recrystallization from 60 mL of hexane afforded 1.55 g (63% based on **59** in the mixture) of pure **59:** mp 102.5–105 °C; NMR δ 7.8–8.0 (m, 2 H), 7.5–7.7 (m, 3 H), 3.5 (dd, J = 5 and 7 Hz, 1 H), 1.1–2.4 (m, 8 H), 1.9 (s, 3 H). M^+ Calcd for $C_{13}H_{17}ClO_2S$: 272.064. Found: 272.065.

Preparation of 1-Cyclopenten-1-yl Phenyl Sulfone (52a). To 97.9 g (0.400 mol) of *trans*-2-chloro-1-cyclopentyl phenyl sulfone (**51a**) in 200 mL of methylene chloride at 0 °C in a dry ice/2-propanol bath was added 62.3 g (0.410 mol) of DBU[34] at a rate which maintained the temperature between −5 and 0 °C. The total addition was made over a 0.5-h period. The mixture was allowed to warm to room temperature and poured into 500 mL of ether. The organic phase was extracted with 100 mL of 2% aqueous hydrochloric acid, 100 mL of water, and 100 mL of saturated aqueous sodium chloride, and dried ($MgSO_4$). Concentration in vacuo gave 83.0 g (100%) of crude solid which was recrystallized from 600 ml of 1:1 (v/v) ether/hexane to yield 72.0 g (86%) of a white solid, **52a,** mp 64.5–65 °C. A second crop was obtained by concentration of the filtrate in vacuo and dissolution of the residue in 40 mL of ether. Cooling to −78 °C afforded an additional 4.5 g of white solid for a total recrystallized yield of 92%: NMR δ 7.8–8.0 (m, 2 H), 7.5–7.8 (m, 3 H), 6.75 (br s, 1 H), 2.3–2.8 (m, 4 H), 1.7–2.3 (m, 2 H). M^+ Calcd for $C_{11}H_{12}O_2S$: 208.056. Found: 208.058.

Eliminations were conveniently followed by TLC using 4:1 (v/v) ether/hexane as eluent, the vinyl sulfone product being slightly more polar than the starting β-chloro sulfone.

Preparation of 1-Cyclohexen-1-yl Phenyl Sulfone (52b). Substitution of 103.5 g (0.400 mol) of *trans*-2-chloro-1-cyclohexyl phenyl sulfone (**51b**) for *trans*-2-chloro-1-cyclopentyl phenyl sulfone (**51a**) afforded 86.9 g (98%) of a crude oil. Recrystallization from 4 L of hexane gave 64.7 g (73%) of **52b** as a white solid, mp 42.5–43.5 °C; a second crop was obtained by concentration of the filtrate in vacuo, dissolution of the residue in 125 mL of ether, and cooling to −78 °C. This produced an additional 7.7 g of white solid, for a total recrystallized yield of 81%: NMR δ 7.8–8.0 (m, 2 H), 7.5–7.8 (m, 3 H), 7.0–7.2 (m, 1 H), 2.0–2.5 (m, 4 H), 1.5–2.0 (m, 4 H). M^+ Calcd for $C_{12}H_{14}O_2S$: 222.071. Found: 222.071.

Preparation of 1-Cyclohepten-1-yl Phenyl Sulfone (52c). Substitution of 109.1 g (0.400 mol) of *trans*-2-chloro-1-cycloheptyl phenyl sulfone (**51d**) for *trans*-2-chloro-1-cyclopentyl phenyl sulfone (**51a**) in the preparation of **52a** resulted in 93.3 g (99%) of a crude brown oil, which was recrystallized from 350 mL of 4:1)v/v) ether/hexane to yield 70 g (84%) of **52c** as a white solid: mp 32–35 °C; NMR δ 7.7–8.0 (m, 2 H), 7.4–7.7 (m, 3 H), 7.3 (t, J = 6 Hz, 1 H), 2.1–2.5 (m, 4 H), 1.2–1.8 (m, 6 H). M^+ Calcd for $C_{13}H_{16}O_2S$: 236.087 Found: 236.087.

Preparation of Bicyclo[2.2.1]hept-2-en-2-yl Phenyl Sulfone (54). To a solution of 6.77 g (25 mmol) of *endo*-3-chloro-*exo*-2-bicyclo[2.2.1]heptyl phenyl sulfone (**53**) in 12.5 mL of chloroform heated under reflux was added via syringe 4.56 g (30 mmol) of DBU.[34] Heating was continued for 15 min, and then the mixture was allowed to cool to room temperature and poured into 50 mL of 2% aqueous hydrochloric acid. Fifty milliliters of ether was added to the acidic solution; the combined organic phase was then washed with 25 mL of saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to afford 5.68 g (97%) of crude oil. The oil was taken up in 120 mL of ether and cooled to −78 °C to afford 2.6 g (44%) of **54** as a white solid, mp 47.5–48.5 °C. Concentration of the filtrate in vacuo to a total volume of 20 mL and again cooling to −78 °C produced a second crop of 1.4 g (24%), for a total yield of 68%: NMR δ 7.8–8.0 (m, 2 H), 7.5–7.7 (m, 3 H), 6.9 (dm, J = 3 Hz, 1 H), 3.0–3.3 (m, 2 H), 1.0–2.0 (m, 6 H). M^+ Calcd for $C_{13}H_{14}O_2S$: 234.071. Found: 234.074.

Preparation of 1,3-Cyclohexadien-1-yl Phenyl Sulfone (56).[10c] A solution of 2.56 g (10.0 mmol) of *trans*-2-chloro-3-cyclohexen-1-yl phenyl sulfone (**55**) in 50 mL of methylene chloride was cooled to 0 °C in an ice bath and 1.82 g (12.0 mmol) of DBU[39] was added via syringe. When the addition was complete, the cooling bath was removed and the mixture was stirred for 15 min at room temperature. The mixture was poured into 25 mL of 2% aqueous hydrochloric acid and 100 mL of ether was added. The organic layer was washed with 25 mL of saturated aqueous sodium chloride and dried ($MgSO_4$). Concentration in vacuo afforded 2.15 g (98%) of a colorless oil which was recrystallized from 95% ethanol to afford 1.83 g (83%) of **56** as a white solid: mp 92–93 °C; NMR δ 7.8–8.0 (m, 2 H), 7.5–7.8 (m, 3 H), 7.0–7.1 (m, 1 H), 6.0–6.2 (m, 2 H), 2.2–2.4 (m, 4 H). M^+ Calcd for $C_{12}H_{12}O_2S$: 220.056. Found: 226.056.

Preparation of 3-Phenylsulfonyl-Δ²-cholestene (58). To a solution of 0.407 g (0.74 mmol) of 3α-phenylsulfonyl-2β-chlorocholestane (**57**) in 5 mL of methylene chloride was added 0.225 g (1.5 mmol) of DBU,[34] and the mixture was stirred for 1 h at room temperature. The mixture was poured into 25 mL of 2% aqueous hydrochloric acid, and 50 mL of ether was added. The organic layer was washed with 25 mL of saturated aqueous sodium chloride and dried ($MgSO_4$). Concentration in vacuo afforded an oil which was recrystallized from ethanol to yield a first crop of 0.195 g of **58** as white crystals, mp 174–175 °C; a second crop of 0.157 g was collected by cooling the filtrate to 0 °C, for a combined yield of 93%; NMR δ 7.4–8.0 (m, 5 H), 7.0 (m, 1 H), 0.7–2.3 (m, 44 H). M^+ Calcd for $C_{33}H_{50}O_2S$: 510.353. Found: 510. 355.

Preparation of 2-Methyl-1-cyclohexen-1-yl Phenyl Sulfone (60). To a solution of 1.36 g (5.0 mmol) of 2-chloro-2-methyl-1-cyclohexyl phenyl sulfone (**59**) in 25 mL of methylene chloride heated under reflux was added via syringe 1.52 g (10.0 mmol) of DBU.[34] Heating was continued for 1.5 h, and then the mixture was allowed to cool to room temperature and poured into 25 mL of 2% aqueous hydrochloric acid. Fifty milliliters of ether was added, and the solution

was washed with 25 mL of saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to afford 1.17 g (99%) of **60** as a colorless oil which defied all attempts at recrystallization: NMR δ 7.8–8.0 (m, 2 H), 7.5–7.7 (m, 3 H), 1.9–2.5 (m, 7 H), 1.4–1.8 (m, 4 H). M^+ Calcd for $C_{13}H_{16}O_2S$: 236.087. Found: 236.089.

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Registry No.—**27a,** 771-98-2; **27b,** 825-54-7; **27c,** 64740-95-0; **30a,** 64740-96-1; **30b,** 64740-97-2; **30c,** 64740-98-3; **31a,** 52178-91-3; **31b,** 4242-13-1; **32a,** 64740-99-4; **32b,** 64741-00-0; **38,** 1822-73-7; dihydrocholesterol, 80-97-7; methanesulfonyl chloride, 124-63-0; dihydrocholesterol mesylate, 3381-51-9; 6-methoxy-1-tetralone, 1078-19-9; 6-methoxy-1,2,3,4-tetrahydro-1-naphthol, 1682-32-2; 3-phenylthio-4,5-dihydrothiophene 1,1-dioxide, 20583-25-9; *m*-chloroperoxybenzoic acid, 64741-01-1; peracetic acid, 79-21-0.

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Intramolecular Cyclizations of Diphenyl Ether, Benzophenone, and Related 2-Sulfonylnitrenes[1a]

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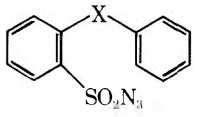
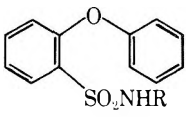
Thermolysis of 2-phenoxybenzenesulfonyl azide gave 6*H*-dibenzo[*b*,*f*][1,4,5]oxathiazepine 5,5-oxide (**4**) (the first seven-membered ring compound formed by intramolecular aromatic cyclization of a sulfonylnitrene) and other nitrene-derived products. On the other hand, diphenyl sulfide 2-sulfonyl azide (**1b**) gave some 3-phenylbenzo[1,3,2]-dithiazolium ylide 1,1-dioxide (**10**), but no seven-membered ring compound. Thermolysis of diphenyl sulfone 2-sulfonyl azide gave only small amounts of products derived from the aryl radical **16**, but no nitrene-derived compounds. Decomposition of 2-azidosulfonylbenzophenones gave the desired seven-membered sultams without rearrangement, together with an array of other products. Some of these are formed from the sulfonylnitrene, while it is proposed that the others result from ring–chain tautomerization of some undecomposed sulfonyl azide to 3-aryl-3-azidobenzo[*d*][2,1]oxathioles (**34**). Decomposition of the latter to the alkylnitrene and 1,2-aryl shifts would account for the products observed.

In earlier papers, the intramolecular cyclization of 2-biarylsulfonyl azides[2] and the intramolecular insertion of arylsulfonylnitrenes into aliphatic side chains[3] were described. A variety of five- and six-membered sultams was obtained and a number of important side reactions were noted and discussed. The present paper describes work aimed at synthesizing seven-membered sultams by intramolecular cyclization of appropriate ortho-substituted arylsulfonylnitrenes and discusses the scope and limitations of some of these reactions. At the time this work was initiated direct intramolecular cyclization of a nitrene to a seven-membered ring was unprecedented. Since then a number of examples (rings formed indirectly, however) have been recorded.[4]

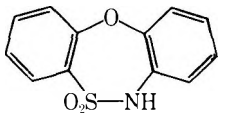
A. Decomposition of 2-Phenoxybenzenesulfonyl Azide (1a). The azide was thermolyzed in *n*-dodecane at 130–135 °C to give *N*-dodecyl-2-phenoxybenzenesulfonamide (**2**) (1%;



1a, X = O
b, X = S
c, X = SO_2
d, X = $NCOCH_3$; 4,4′-Me_2
e, X = CO



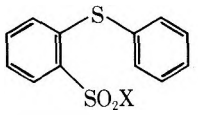
2, R = $C_{12}H_{25}$
3, R = H



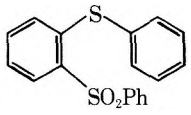
4

a mixture of isomers resulting from insertion of the nitrene into the solvent) and the hydrogen-abstraction product **3** (4%), together with the desired cyclization products 6*H*-dibenzo[*b*,*f*][1,4,5]oxathiazepine 5,5-dioxide (**4**) (15%). A better yield of **4** was obtained (38%) by carrying out the thermolysis in the absence of solvent.

B. Decomposition of Diphenyl sulfide 2-Sulfonyl Azide (1b). This azide was prepared as usual from the corresponding sulfonyl chloride **5**. When benzene was used as the solvent in the synthesis of **5** from the primary amine and the reaction mixture was warmed to 40 °C instead of being kept at room temperature, acylation of the solvent occurred and 2-phenyl thiodiphenyl sulfone (**6**) was isolated. No seven-membered ring product was isolated on thermolysis of **1b** in *n*-dodecane at 150 °C. Instead there were obtained the solvent insertion (**7**) and hydrogen-abstraction (**8**) products, together with some



5, X = Cl
7, X = $NHC_{12}H_{25}$
8, X = NH_2



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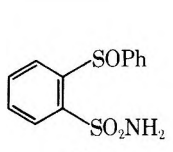
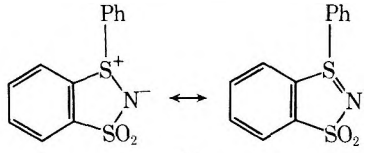
(4%) diphenyl sulfoxide 2-sulfonamide (**9**) and 3-phenylbenzo[1,3,2]dithiazolium ylide 1,1-dioxide (**10**) (10%). Again,

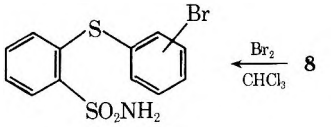


9

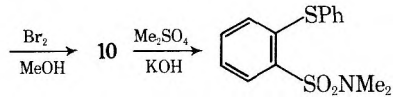


10

a better yield (28%) of **10** was obtained when the reaction was carried out in the absence of solvent. The sulfoxide **9** undoubtedly arises by hydrolysis of **10** during workup and, indeed, chromatography of **10** on neutral alumina gave **9**, as did basic hydrolysis of **10**. Authentic **10** could be prepared from **8** and bromine in aqueous methanol, with or without added base. On the other hand, bromination of **8** in chloroform at room temperature gave a mixture of 2- and 4-bromodiphenyl sulfide 2′-sulfonamide (**11**). Treatment of **10** with dimethyl sulfate and KOH gave diphenyl sulfide 2-*N*,*N*-dimethylsulfonamide (**12**), also obtained by the methylation of **8**.



11



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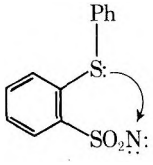
In view of the fact that both C–H insertion and hydrogen-abstraction products were obtained, indicating the intermediacy of a free sulfonylnitrene in these reactions, it seems likely that **10** is formed by nucleophilic trapping of the sul-



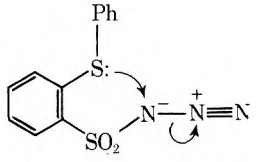


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Table I. Thermolysis Products of 1a–d

Registry no.	Compd	Temp, °C	Time, h	Solvent	Yield of products (%)
40182-15-8	**1a**	130–135	30	*n*-Dodecane	**2** (11%), **3** (4%), **4** (15%)
	1a	165	12		**3** (59.9%), **4** (37.9%)
64939-38-4	**1b**	150	61	*n*-Dodecane	**7** (8.8%), **8** (19%), **9** (4%), **10** (10%)
	1b	160–170	3		**9** (26%), **10** (27%)
64939-39-5	**1c**	150	16	*n*-Dodecane	**13** (27%), **14** (9%)
	1c	150	16	*n*-Dodecane/S_8	**13** (19%), **14** (19%)
	1c	160	18	Freon E-4	**14** (1.9%), **15** (2.6%)

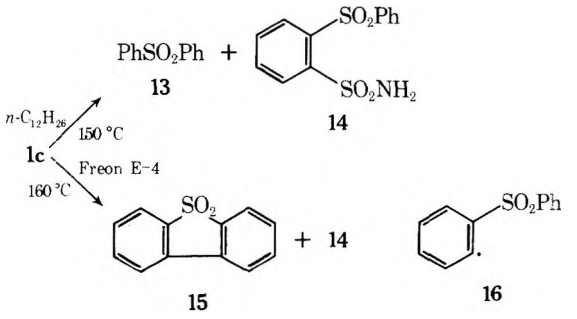
Table II. Thermolysis Products of Benzophenone-2-Sulfonyl Azides

					% yield of Products[a]								
Registry no.	Compd	Temp, C°	Time, h	Solvent	Starting azide	**17**	**18**	**19**	**20**	**21**	**25**	**26**	**27**
63113-42-8	**1e**	100	120	Freon 113	35	3.5	15	1	1	1			
	1e	140	48	Freon 113		3		2	1				
	1e	150	48	C_6H_5Cl		7		2		4			
	1e	100	120	EtOH	40	3		20					
63113-43-9	**23**	100	120	Freon 113	43	5	35	2	3	2			26
	23	140	10	Freon 113	15	6		4	4	trace	33		
63113-44-0	**24**	140	18	Freon 113		6				1		40	

[a] Corrected for recovered azide.

fonylnitrene by the sulfur atom rather than by participation of the latter in the nitrogen elimination.[5]

C. Decomposition of Diphenyl Sulfone 2-Sulfonyl Azide (1c). In order to prevent this nucleophilic attack by sulfur on nitrogen, the decomposition of **1c** was studied. In this case, again no seven-membered ring product was detected. Thermolysis in *n*-dodecane at 150 °C gave diphenyl sulfone (**13**) (27%) and diphenyl sulfone 2-sulfonamide (**14**) (9%), both identical with authentic samples. Decomposition in Freon E-4 at 160 °C gave dibenzothiophene 5,5-dioxide (**15**) and **14**, both in very low yields. Much tar was formed. While the hydrogen-abstraction product (**14**) probably arises from the triplet nitrene we propose that both **13** and **15** are formed from the corresponding aryl radical **16**. Evidence for the formation of



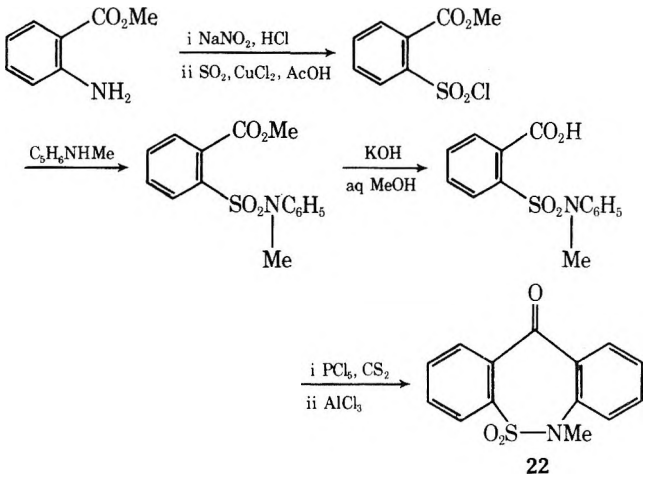
alkyl and aryl radicals in the thermolysis of some sulfonyl azides has been summarized.[6] For example, it has been shown that a small amount of *n*-pentane was formed in the decomposition of *n*-pentanesulfonyl azide in mineral oil and that aromatic sulfonyl azides can undergo free-radical thermal decomposition if a source of radicals is provided.[2,5,7] Diphenyl sulfone (**13**) would result from **16** by hydrogen abstraction from solvent, while in Freon E-4 where hydrogen atoms are not available Pschorr-type cyclization occurs to give **15**. That no seven-membered ring product is formed from **1c** might be due to a rapid intersystem crossing of singlet to triplet nitrene in this instance, or to an unfavorable geometry imposed by the relatively large SO_2 bridging group. The ease of Pschorr-type cyclizations in related systems has similarly been attributed to the internuclear separation between the rings involved as determined by the nature of the bridging group.[8]

A similar attempt to effect the cyclization of *N*-acetyldi-*p*-tolylamine 2-sulfonyl azide (**1d**) in dodecane did not yield any of the desired product; only the thermally unstable solvent insertion products were isolated. The results of the thermolyses of azides **1a–d** are summarized in Table I.

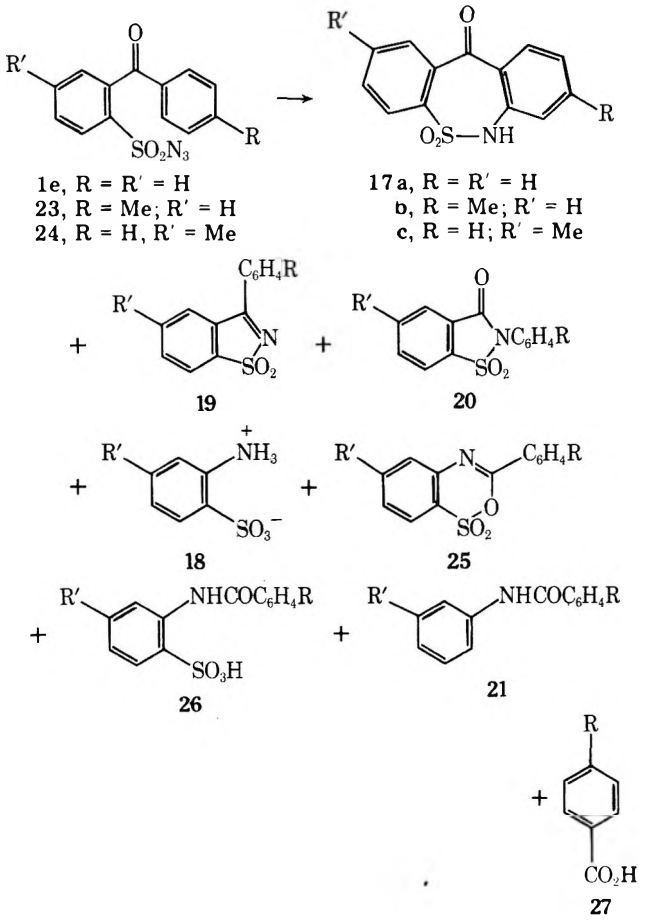
D. Decomposition of 2-Azidosulfonylbenzophenones. The decomposition of 2-azidosulfonylbenzophenone (**1e**) was much more productive. A low yield of the desired sultam **17a** was obtained (3.5%) together with some orthanilic acid (**18a**) (15%) and small amounts of 3-phenylbenzisothiazole 1,1-dioxide (**19a**), 2-phenylbenzisothiazolin-3-one 1,1-dioxide (**20a**), and benzanilide (**21**). The structure of the sultam **17a** was supported by its infrared spectrum (ν_{NH} 3200, $\nu_{C=O}$ 1640, ν_{SO_2} 1350, 1180 cm^{-1}) and by the synthesis of an authentic sample of its *N*-methyl derivative **22** from methyl anthranilate (Scheme I). Sultam **22** was identical with the product obtained on methylation of **17a** with sodium hydride and dimethyl sulfate. The benzisothiazole **19a** was identical with an authentic sample.[9] The isothiazolinone **20a** [IR 1730 (CO), 1335, 1185 cm^{-1} (SO_2)] could be synthesized from the *N*,2-dilithio derivative of benzenesulfonanilide by carbonation.[10]

In order to determine whether or not any rearrangements via a spiro intermediate[11] had occurred and to throw light on the formation of **21a**, the decompositions of 4′-methylbenzophenone-2-sulfonyl azide (**23**) and 5-methylbenzophenone-2-sulfonyl azide (**24**) were investigated. The results are summarized in Table II, and the nature of the products obtained is outlined in Scheme II. The sultam **17b** from the decomposition of **23** was *N*-ethylated to give **28**. If a rearrangement via a spiro intermediate in the cyclization step had occurred (Scheme III) then sultam **29** could have resulted. The *N*-ethyl derivative of the latter was prepared as described in Scheme I except that *N*-ethyl-*p*-toluidine was used in lieu of *N*-methylaniline. The product obtained was different from

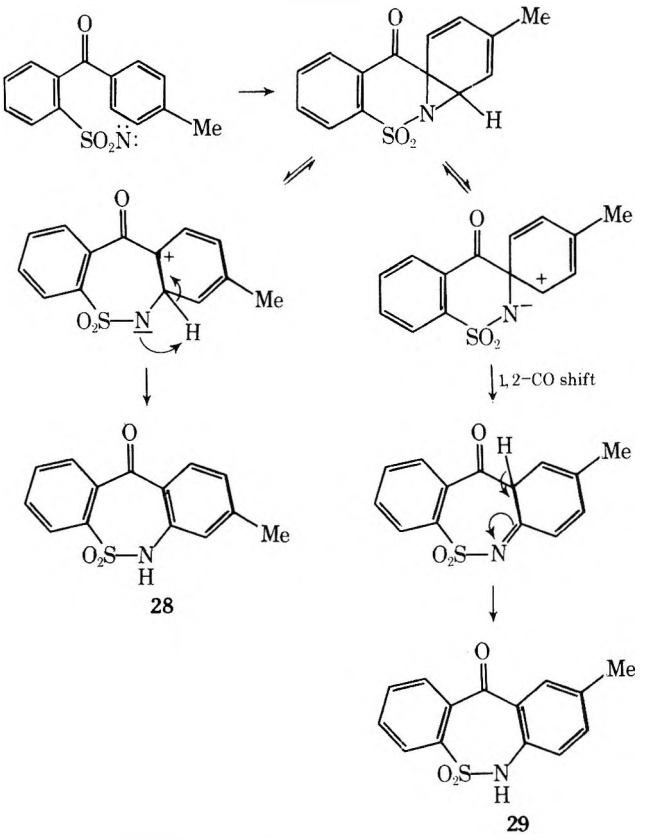
Scheme I



Scheme II



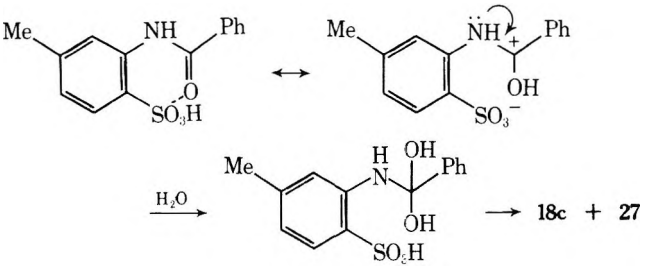
Scheme III



that formed on *N*-ethylation of **23**, showing that no rearrangement had occurred.

3-*p*-Tolylbenzisothiazole 1,1-dioxide (**19b**) was prepared either from saccharin and *p*-tolylmagnesium bromide[9] or from ammonium 4′-methylbenzophenone-2-sulfonic acid (synthesized from *o*-sulfobenzoic anhydride and toluene with aluminum chloride; only one product isolated) and $SOCl_2$ or PCl_5, and was identical with the product obtained from the azide. Authentic **20b** was prepared from *o*-sulfobenzoic anhydride and *p*-toluidine and then $SOCl_2$ as described,[12] while **20c** was made analogously to **20a**.

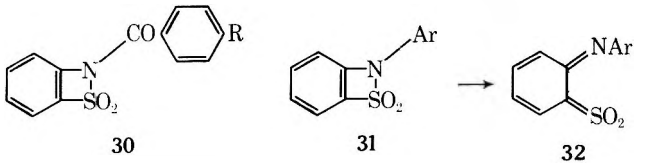
The thermolysis of 5-methylbenzophenone-2-sulfonyl azide (**24**) was studied to determine the origin of **18**, **21**, and **26**. It gave some 2-benzamido-4-methylbenzenesulfonic acid (**26**) as the major product, identical with an authentic sample. This underwent hydrolysis with remarkable ease: for example, attempted recrystallization from 95% ethanol gave 4-methylorthanilic acid (**18c**). Thus, the orthanilic acids obtained in those reactions arise from **26**. This ease of hydrolysis is to be contrasted, say, with the hydrolysis of *N*,*N*-dicyclohexylbenzanilide-2-carboxamide in 1 M sulfuric acid at 80 °C for 6 h, which gave 2-benzamidobenzoic acid,[13] indicating the stability of the latter *o*-carboxyamide under these much more drastic conditions. It seems likely that intramolecular acid catalysis is responsible for the facile hydrolysis of **26c**. Support for this comes from the observation of a broad carbonyl stretching band at 1615 cm^{-1}, indicating strong hydrogen bonding between the sulfonic acid and the ortho amide group.



A small amount of *N*-benzoyl-*m*-toluidide (**21**, R = H; R′ = Me) was also isolated in the thermolyses. Formation of these products indicates that the amino group occupies the position originally bearing the carbonyl group ortho to the sulfonyl azide function. The usual small yield (6%) of seven-membered sultam **17c** was also obtained.

In the thermolysis of 4′-methylbenzophenone-2-sulfonyl azide (**23**) at 140 °C in Freon 113, the main product (33%) obtained on careful workup was 3-(*p*-tolyl)benzo[c][2,1,4]-oxathiazine 1,1-dioxide (**25**, R′ = H). It exhibited a band at 1633 cm^{-1} consistent with an imidate C=N group,[14] and bands at 1360 and 1190 cm^{-1} (SO_2). It underwent solvolysis

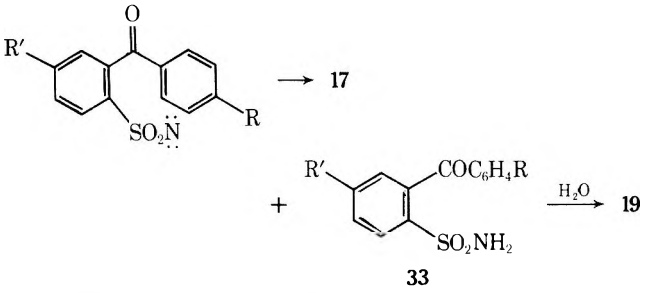
in ethanol readily to give orthanilic acid and ethyl *p*-methylbenzoate. An alternate structure considered for this product could be that of a β-sultam (**30**, R = CH_3). Some β-sultams (**31**) similar to **30** have been postulated, but only one has been



30 **31** **32**

characterized.[15] They are reported to cleave easily to the sulfene **32** and only when Ar is bulky can **31** be isolated. If, therefore, **30** were initially formed it would most likely rearrange to **25** (R′ = H) via the sulfene corresponding to **32**. Formation of **30** would, however, probably require insertion of a sulfonylnitrene into a position ortho to it and this has never been observed. Also, the frequency of the band observed at 1633 cm^{-1} is somewhat lower than that observed for a tertiary aromatic amide, particularly when it is considered that the electron-withdrawing SO_2 group on nitrogen is expected to raise the C=O stretching frequency by destabilizing the contributing structure $-SO_2N^+=C(-O^-)Ar$.

Assuming then that the compound has structure **25**, it is possible to explain the array of products formed in these reactions by postulating two competing processes. Thermolysis with loss of nitrogen to give the sulfonylnitrene would account for the intramolecular cyclization products **17** and the 3-arylbenzisothiazole 1,1-dioxides (**19**); the latter arising by dehydration of the hydrogen abstraction products (**33**).[10] It is



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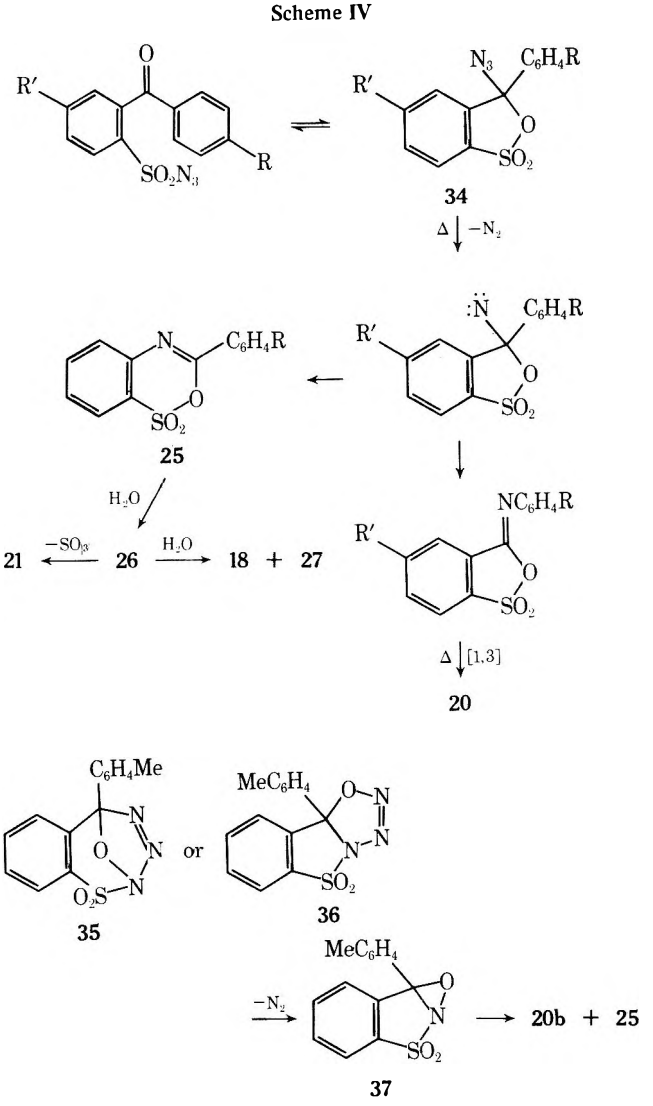
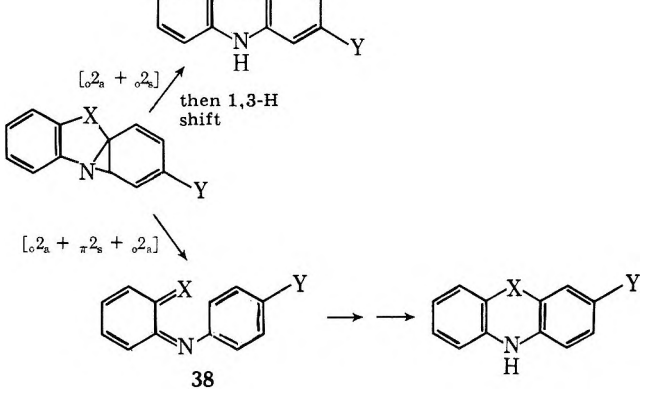
suggested that the other products arise by ring–chain tautomerization of some undecomposed sulfonyl azide (**1c**, **23**, **24**) to 3-aryl-3-azidobenzo[*d*][2,1]oxathioles (**34**). Decomposition of the latter to the alkylnitrene and 1,2-aryl shifts would give the observed products (Scheme IV), though a concerted nitrogen elimination aryl shift cannot be discounted.[16] Other mechanisms for the formation of the products are possible (e.g., 1,3-dipolar cycloaddition of the azide to the carbonyl group[17,18] to give **35** or **36** which, following cheletropic nitrogen elimination, would yield the oxaziridine **36** and thence on to the observed product[19]), but are considered less likely since they would predict the product ratios to be inverted.

Ring–chain tautomerism analogous to that proposed in Scheme IV has been reported often. Some examples include the tautomerization of *o*-benzoylbenzamide to aminophenylbenzo[*c*]oxoline,[20] of *o*-formylbenzoyl chloride to 3-chlorophthalide,[21] of *o*-formylbenzenesulfonyl chloride to 3-chlorobenzoxathiazoline,[22] of *o*-formylbenzenesulfonic acid to 3-hydroxybenzoxathiole,[23] and of benzophenone-2-sulfonamides to 3-hydroxy-3-phenyl-2,3-dihydrobenzisothiazole 1,1-dioxide.[24]

The fact that no rearrangement was observed in the intramolecular cyclization here or in that of 4′-bromobiphenyl-2-sulfonyl azide[2] deserves some comment. Had spiro intermediates been involved in the formation of the final sultams then one might have expected to observe at least some rearranged products, which was not the case. If a spiro intermediate is indeed formed, then it is necessary to postulate that reversal to aziridine or [1,2] shift of nitrogen followed by a prototropic shift with aromatization is faster than the [1,2] shift of a carbonyl or aryl group. On the other hand, if the rearrangements observed by Cadogan and others with arylnitrenes involve first a concerted $[{}_{\sigma}2_a + {}_{\pi}2_s + {}_{\sigma}2_a]$ shift to give an *o*-quinoid structure **38** (postulated[11] to explain the formation of other products) followed by a Cope-type cyclization, then the absence of rearrangements in the cases now under consideration is understandable, since concerted electrocyclic ring opening to an *o*-quinoid system is not possible in **39** and **40**, and the only option available is ring opening to the unrearranged products.

Scheme IV





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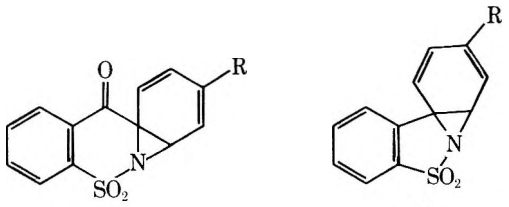

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Experimental Section

2-Phenoxybenzenesulfonyl Azide (1a). Sodium azide (3.25 g) in water (25 mL) was added to a stirred solution of 2-phenoxybenzenesulfonyl chloride (13.4 g) in acetone (125 mL) and the solution was stirred at room temperature for a further 27 h. It was evaporated in vacuo to about one-third of its volume and water (500 mL) was added. The precipitate (10.9 g, 79%) was filtered, washed with water (2 × 30 mL), and dried and had: mp 79–79.5 °C (from aqueous EtOH); IR (KBr) 2130, 1360, 1168 cm^{-1}.

Anal. Calcd for $C_{12}H_9N_3O_3S$: C, 52.35; H, 3.30; N, 15.26. Found: C, 52.26; H, 3.46; N, 15.41.

Thermolysis of 2-Phenoxybenzenesulfonyl Azide. A. In *n*-Dodecane. A suspension of the azide (4.125 g) in *n*-dodecane (25 mL) was heated with stirring at 130–135 °C for 30 h. The mixture was cooled to room temperature, the dodecane solution was decanted onto a column of neutral alumina (150 g) and the black tarry residue was extracted with boiling methanol (4 × 25 mL), and the extracts were evaporated, concentrated to 2 mL, and added to the alumina column. Elution with light petroleum gave *n*-dodecane. Elution with ether gave an almost colorless gum (0.972 g) which was distilled (some decomposition) to give slightly impure ***N*-dodecyl-2-phenoxybenzenesulfonamide (2)** as a yellow viscous liquid (0.696 g, 11%): bp 208 °C (0.2 mm); IR 3300, 1340, 1165 cm^{-1}; NMR (CCl_4) δ 7.90–6.66 (m, ArH), 4.88 (d, 1, NH, exchangeable), 3.20 (m, 1, CH), 1.40–0.70 (m, 24); mass spectrum *m/e* 417 ($M^{+\cdot}$) (calcd for $C_{24}H_{35}NO_3S$: $M^{+\cdot}$ 417). Elution with ether–methanol (95:5 v/v) gave **2-phenoxybenzenesulfonamide (3)** (0.134 g, 4%) [mp 113–114 °C (from benzene–light petroleum); IR (KBr) 3340, 3240, 1335, 1165 cm^{-1}] identical with an authentic sample prepared (76%) from sulfonyl chloride and ammonium hydroxide at room temperature.

Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.84; H, 4.42; N, 5.62. Found: C, 57.72; H, 4.40; N, 5.59.

Elution with methanol gave a brown gum which, on crystallization from benzene, gave **6*H*-dibenzo[*b,f*][1,4,5]oxathiazepine 5,5-dioxide (4)** (0.571 g, 15%): mp 142–144 °C (aqueous EtOH); λ_{max} 279 mm; IR (KBr) 3180, 1335, 1172 cm^{-1}; mass spectrum *m/e* 247 ($M^{+\cdot}$).

Anal. Calcd for $C_{12}H_9NO_3S$: C, 58.29; H, 3.67; N, 5.67. Found: C, 58.32; H, 3.66; N, 5.75.

B. In Absence of Solvent. The azide (0.70 g) was heated at 165 °C for 12 h. The tarry products were chromatographed on a column of neutral alumina (30 g). Elution with light petroleum (bp 40–60 °C) gave 2-phenoxybenzenesulfonamide (0.19 g, 59.5% based on 2 mol of azide/mol of amide): mp 113–114 °C. Elution with methanol gave 6*H*-dibenzo[*b,f*][1,4,5]oxathiazepine 5,5-dioxide (0.24 g, 37.9%): mp 136–139 °C.

Diphenyl Sulfide 2-Sulfonyl Chloride (5). To a solution of 2-aminodiphenyl sulfide (20.1 g) in glacial acetic acid (140 mL) and concentrated HCl (44 mL) at 0 °C was added a solution of sodium nitrite (8.0 g) in water (20 mL) at 0 °C. The diazonium salt solution of SO_2 in glacial acetic acid (61 mL), ether (61 mL), and cupric chloride (5.0 g) was stirred at room temperature for 22 h. The solution was poured into ice-cold water (1500 mL) and the resulting yellow-orange solid was collected, washed with ice cold water (3 × 60 mL), and dried to give the sulfonyl chloride (17.4 g, 61%): mp 54–54 °C (lit.[25] mp 53–55 °C).

If benzene was used in the above reaction instead of ether and the reaction mixture was warmed at 40 °C for 30 h instead of being kept at room temperature for 22 h an oil mixed with needle-shaped crystals was obtained on pouring the mixture into water. The crystals (6 g) could be separated by taking advantage of their slight solubility in acetone. Recrystallization from benzene–methanol (1:1 v/v) gave **2-phenyl thiodiphenyl sulfone (6):** mp 123.5–125.5 °C; IR (KBr) 1445 (s), 1075 cm^{-1} (m); mass spectrum *m/e* 326 ($M^{+\cdot}$).

Anal. Calcd for $C_{18}H_{14}O_2S_2$: C, 66.27; H, 4.29. Found: C, 66.50; H, 4.42.

Diphenyl Sulfide 2-Sulfonyl Azide (1b). Sodium azide (0.65 g) in water (5.0 mL) was added to a stirred solution of diphenyl sulfide 2-sulfonyl chloride (2.85 g) in acetone (25 mL) at room temperature and stirring was continued for 46 h. The mixture was concentrated with ether (3 × 25 mL), the combined extracts were dried (Na_2SO_4), and the solvent was evaporated to give the azide (2.91 g, 100%) which, on attempted distillation, decomposed; IR (film) 2130 (s) (N_3), 1360, 1165 (s) cm^{-1} (SO_2).

Thermolysis of Diphenyl Sulfide 2-Sulfonyl Azide. A. In *n*-Dodecane. An emulsion of the azide (2.91 g) in *n*-dodecane (25 mL) was heated with stirring at 150 °C for 61 h. The mixture was cooled, the dodecane was decanted onto a column of neutral alumina (140 g), and the residual black tar was extracted with boiling MeOH (4 × 25 mL). The combined extracts were concentrated to 2 mL and added to the above alumina column. Elution with light petroleum gave *n*-dodecane. Elution with ether–light petroleum (1:1 v/v) gave a mixture of ***N*-dodecyldiphenyl sulfide 2-sulfonamides (7)** (0.387 g) as a yellow gum: IR (film) 3300, 3060, 2950, 2920, 2850, 1320, 1175 cm^{-1}; NMR ($CDCl_3$) δ 8–6.90 (m, 9, ArH), 5.55 (m, 1, exchangeable, NH), 3.18 (m, 1, CH), 1.40–0.7 (m, 24); mass spectrum *m/e* 483 ($M^{+\cdot}$). Elution with ether–methanol (19:1 v/v) gave a yellow gum (0.875 g) which crystallized from ethanol–light petroleum to give **diphenyl sulfide 2-sulfonamide** (8) (0.504 g, 19%) [mp 111–112 °C; IR (KBr) 3380, 3270, 1340, 1170 cm^{-1}] identical with a sample prepared (76% yield) from the sulfonyl chloride and ammonia.

Anal. Calcd for $C_{12}H_{11}NO_2S_2$: C, 54.34; H, 4.15. Found: C, 54.60; H, 4.20.

Further elution with the same solvent gave a yellow gum (0.176 g) which crystallized from ethanol to give **diphenyl sulfoxide 2-sulfonamide (9)** (0.101 g, 4%): mp 155.5–156.5 °C; IR (KBr) 3310, 3170, 1360, 1184 cm^{-1}.

Anal. Calcd for $C_{12}H_{11}NO_3S_2$: C, 51.25; H, 3.91. Found: C, 51.10; H, 4.00.

Continued elution with ether–methanol gave a yellow gum (0.558 g) which crystallized from ethanol to give **3-phenylbenzo[1,3,2]-dithiazolium ylide 1,1-dioxide (10)** (0.274 g, 10%): mp 191–193 °C; IR (KBr) 1293 (s), 1160 cm^{-1} (s); λ_{max} (95% EtOH) 277.5, 270, 265, 230 nm (ε 4632, 3242, 3367, 14690); mass spectrum *m/e* 263 ($M^{+\cdot}$).

Anal. Calcd for $C_{12}H_9NO_2S_2$: C, 54.71; H, 3.45. Found: C, 54.79; H, 3.78.

B. In the Absence of Solvent. The azide (3.0 g) was heated under dry nitrogen at 160–170 °C for 3 h. The dark product was chromatographed on a column of neutral alumina (90 g). Elution with benzene gave 3-phenylbenzo[1,3,2]dithiazolium ylide 1,1-dioxide (0.75 g, 27%) (mp 191–193 °C) identical with the sample obtained above and with an authentic sample (vide infra). Elution with methanol gave diphenyl sulfide 2-sulfonamide (0.36 g, 26%), identical with the product obtained above.

3-Phenylbenzo[1,3,2]dithiazolium Ylide 1,1-Dioxide (10). A. To a stirred solution of diphenyl sulfide 2-sulfonamide (1.325 g) in methanol (6 mL) and water (2 mL) was slowly added a solution of bromine (0.80 g) in methanol (2 mL) at room temperature. The solution was stirred for a further 20 min and poured into water (75 mL). The precipitated solid was filtered, washed with water, dried, and recrystallized from ethanol to give the ylide (1.034 g, 79%): mp 189–192 °C, undepressed on admixture with the above sample. The same product was obtained (69%; mp 191–192 °C) when the sulfonamide in 5 N NaOH was treated at 0 °C with a solution of bromine in methanol.

B. Bromine (0.80 g) in $CHCl_3$ (5 mL) was added slowly to a stirred solution of the sulfonamide (1.325 g) in $CHCl_3$ (15 mL) and the mixture was stirred at room temperature for 75 h. The solution was washed with water (2 × 20 mL), dried (Na_2SO_4), and evaporated to give an orange-red gum (1.71 g) which was chromatographed on a column of neutral alumina. Elution with ether gave a colorless gum (1.58 g) which crystallized from benzene to give what appears to be a mixture of 2- and 4-bromodiphenyl sulfide 2′-sulfonamide (11) [mp 91–94 °C; IR (KBr) 3420, 3360, 3290, 3250, 1330, 1175, 1170 cm^{-1}; mass spectrum *m/e* ($M^{+\cdot}$, ^{81}Br), 343 ($M^{+\cdot}$, ^{79}Br)] which could not be resolved.

Diphenyl Sulfoxide 2-Sulfonamide (9). A. 3-Phenylbenzo[1,3,2]dithiazolium ylide 1,1-dioxide (0.526 g) in ethanol (25 mL) and 20% aqueous NaOH (25 mL) was boiled under reflux for 13 h. The mixture was cooled, water (100 mL) was added, and the solution was acidified with concentrated HCl and kept at room temperature overnight. The solid was collected, washed with water (3 × 15 mL), dried, and recrystallized from ethanol to give the sulfoxide (0.313 g, 56%) (mp 155–157 °C) identical with the product obtained from the sulfonyl azide thermolysis.

B. The ylide (0.526 g) in the minimum volume of $CHCl_3$ was chromatographed on a column of neutral alumina (150 g). The column was eluted with light petroleum and then allowed to stand for 3 days. Elution with ether–methanol (19:1 v/v) gave unchanged ylide (0.266

g): mp 191.5–193 °C. Elution with MeOH gave the sulfoxide (0.139 g, 26%) [mp 155–156 °C (EtOH)], identical with the above sample.

Diphenyl Sulfone 2-Sulfonamide (14). Diphenyl sulfoxide 2-sulfonamide (**9**) (0.281 g) in glacial acetic acid (2.0 mL) and 30% hydrogen peroxide (1.0 mL) was heated at 100 °C for 21 h. The cooled solution was poured into water (50 mL) and the solid which precipitated was recrystallized from ethanol to give **diphenyl sulfone 2-sulfonamide** (0.151 g, 51%) (mp 162–163 °C) identical with a sample prepared from the sulfonyl chloride (see below) and ammonia: IR (KBr) 3360, 3270, 1345, 1145 cm^{-1}.

Anal. Calcd for $C_{12}H_{11}NO_4S_2$: C, 48.48; H, 3.70. Found: C, 48.61; H, 3.82.

Diphenyl Sulfide 2-*N,N*-Dimethylsulfonamide (12). A. 3-Phenylbenzo[1,3,2]dithiazolium ylide 1,1-dioxide (**10**) (0.5 g) in absolute ethanol (5 mL) containing saturated aqueous KOH (15 mL) was stirred at 60 °C as dimethyl sulfate (6 mL) was added dropwise. The mixture was then boiled under reflux for 6 h, cooled, and diluted with water until the white precipitate formed initially almost completely dissolved. The mixture was kept overnight and the **diphenyl sulfide 2-*N,N*-dimethylsulfonamide** which separated was recrystallized from a benzene–hexane mixture (1:4 v/v) (0.48 g, 81.7%): mp 118–119 °C; mass spectrum *m/e* 309 ($M^{+\cdot}$).

Anal. Calcd for $C_{14}H_{15}NO_2S_2$: C, 54.33; H, 4.89; N, 4.53. Found: C, 54.38; H, 4.70; N, 4.47.

B. To a solution of diphenyl sulfide 2-sulfonamide (0.56 g) in EtOH (5 mL) containing 20% aqueous NaOH (15 mL) was added slowly with shaking dimethyl sulfate (6 mL) and the solution was boiled under reflux for 13 h. Workup as above gave the *N,N*-dimethyl derivative (0.34 g, 55%): mp 121–122 °C.

Diphenyl Sulfone 2-*N,N*-Dimethylsulfonamide. The sulfoxide (0.31 g) in glacial acetic acid (2.0 mL) and 30% H_2O_2 (1.0 mL) was heated at 100 °C for 17.5 h. The mixture was cooled and poured into water (50 mL). The precipitated solid was filtered, washed with water (3 × 10 mL), and recrystallized from benzene–light petroleum to give the sulfone (0.20 g, 63%) [mp 148–149 °C (EtOH)] identical with a sample prepared (55%) from the sulfonyl chloride and dimethylamine: IR (KBr) 1320, 1310, 1170, 1160 cm^{-1}.

Anal. Calcd for $C_{14}H_{15}NO_4S_2$: C, 51.69; H, 4.62. Found: C, 15.91; H, 4.61.

Diphenyl Sulfone 2-Sulfonyl Chloride. A solution of 2-aminodiphenyl sulfone[26] (2.33 g) in glacial acetic acid (7.0 mL) and concentrated HCl (2.2 mL) at 0 °C was treated with sodium nitrite (0.8 g) in water (2.0 mL). The diazonium salt solution was poured into an ice cold mixture of a saturated solution of SO_2 in glacial acetic acid (6.1 mL), benzene (6.1 mL), and cupric chloride (0.5 g), and the mixture was stirred at room temperature for 16 h. It was poured into water and the yellow solid which precipitated was filtered, washed with water, dried, and recrystallized from ethyl acetate–light petroleum to give the sulfonyl chloride (2.68 g, 85%): mp 137–138 °C; IR (KBr) 1370, 1310, 1150 cm^{-1}.

Anal. Calcd for $C_{12}H_9ClO_4S_2$: C, 45.50; H, 2.84. Found: C, 45.81; H, 2.90.

Diphenyl Sulfone 2-Sulfonyl Azide (1c). Sodium azide (1.30 g) in water (10 mL) was added to a stirred solution of diphenyl sulfone 2-sulfonyl chloride (8.31 g) in acetone (50 mL) at room temperature and stirring was continued for 16 h. The solution was concentrated in vacuo down to 15 mL to give the azide as an oil which solidified (6.34 g, 85%): mp 99.5–100 °C (ethanol–light petroleum); IR (KBr) 2150, 1340, 1205, 1180 cm^{-1}.

Anal. Calcd for $C_{12}H_9N_3O_4S_2$: C, 44.56; H, 2.79. Found: C, 44.62; H, 2.91.

Thermolysis of Diphenyl Sulfone 2-Sulfonyl Azide. A. In *n*-Dodecane. A suspension of diphenyl sulfone 2-sulfonyl azide (1.615 g) in *n*-dodecane (25 mL) was heated with stirring at 150 °C for 16 h. The reaction mixture was cooled and worked up as in the above cases. Elution of the alumina column with light petroleum gave first *n*-dodecane and then diphenyl sulfone (**13**) (0.297 g, 27%) (mp 125 °C) identical (mixture melting point and infrared spectrum) with an authentic sample. Elution with MeOH gave a dark brown gum (0.381 g) which was extracted with benzene (10 mL), filtered, and concentrated down to ~1 mL to give diphenyl sulfone 2-sulfonamide (**14**) (0.138 g, 9%) (mp 159–160 °C) identical with an authentic sample.

When this thermolysis was repeated but in the presence of sulfur (0.128 g), diphenyl sulfone (0.203 g, 19%) and diphenyl sulfone 2-sulfonamide (0.287 g, 19%) were isolated.

B. In Freon E-4. A suspension of the azide (0.969 g) in Freon E-4 (15 mL) was heated with stirring at 160 °C for 18 h. The cooled mixture was worked up as usual. Elution of the column with ether gave a brown gum (0.062 g) which gave dibenzothiophene *S,S*-dioxide (**15**) as colorless needles (0.002 g) [mp 232–233 °C from EtOH; IR (KBr) 1295, 1170, 1160 cm^{-1}] identical with an authentic sample.[27] Elution with methanol gave diphenyl sulfone 2-sulfonamide (**14**) (0.002 g), identical with an authentic sample.

***N*-Acetyldi-*p*-tolylamine 2-Sulfonyl Chloride.** *N*-Acetyldi-*p*-tolylamine (1 g) (mp 84–85 °C) was dissolved in $CHCl_3$ (5 mL) and the solution cooled in ice. Chlorosulfonic acid (5 mL) was added dropwise with stirring and the solution was kept at room temperature for 1 h. It was then poured onto crushed ice and the $CHCl_3$ layer was separated, washed with cold water, dried ($MgSO_4$), and evaporated to give the sulfonyl chloride (1.09 g, 77.2%): mp 133.5–134.5 °C (from light petroleum containing a few drops of $CHCl_3$); IR (KBr) 1665 (s), 1365 (s), 1170 cm^{-1} (s).

Anal. Calcd for $C_{16}H_{16}ClNO_3S$: C, 56.85; H, 4.78. Found: C, 56.43; H, 4.84.

***N*-Acetyldi-*p*-tolylamine 2-Sulfonyl Azide (1d).** The sulfonyl chloride (0.14 g) in acetone (20 mL) was treated at 0 °C with a solution of sodium azide (0.5 g) in the minimum amount of water. After stirring the solution at 0 °C for 1 h it was diluted with water (200 mL) and the precipitated azide (0.13 g, 91.1%) was recrystallized from *n*-hexane to give colorless crystals: mp 94–95 °C; IR (KBr) 2118 (s), 1670 (s), 1170 cm^{-1} (s).

Anal. Calcd for $C_{16}H_{16}N_4O_3S$: C, 55.77; H, 4.69. Found: C, 55.79; H, 4.93.

Thermolysis of *N*-Acetyldi-*p*-tolylamine 2-Sulfonyl Azide in *n*-Dodecane. The azide (1.0 g) in degassed *n*-dodecane (10 mL) was heated at 160–170 °C for 6 h with stirring. Workup as usual and chromatography on neutral alumina gave, on elution with light petroleum (bp 40–60 °C), a mixture of the ***N*-acetyldi-*p*-tolylamine *N'*-dodecyl-2-sulfonamides** as a brown oil (0.3 g) which could not be crystallized or distilled without decomposition: IR (film) 3280 (NH), 1650 (CO), 1315, 1150 cm^{-1} (SO_2); mass spectrum *m/e* (rel intensity) 486 ($M^{+\cdot}$, 8), 239 ($M^{+\cdot} - SO_2NHC_{12}H_{25}$, 36), 197 ($C_{14}H_{15}N^+$, 100).

Benzophenone-2-sulfonyl Azide (1e). This was prepared (0.4 g, 70%) from the sulfonyl chloride[28] (0.6 g) in acetone (25 mL) with sodium azide (1 g) in water (6 mL): mp 120–121 °C (hexane); IR (KBr) 2140, 1660, 1375, 1190 cm^{-1}.

Anal. Calcd for $C_{13}H_9N_3O_3S$: C, 54.35; H, 3.16; N, 14.63. Found: C, 54.28; H, 3.32; N, 14.89.

Thermolysis of Benzophenone-2-sulfonyl Azide. A. In Chlorobenzene. The azide (1 g) in chlorobenzene (50 mL) was heated at 150 °C for 2 days. The black residue on evaporation of the solvent was resolved by preparative TLC (silica gel, benzene developer) to give: (i) 3-phenylbenzoisothiazole 1,1-dioxide (**19**, R = R' = H) (19 mg, 2%) [mp 167 °C, mass spectrum *m/e* 243 ($M^{+\cdot}$)] identical (mmp and IR) with an authentic sample;[9] (ii) benzanilide (**21**, R = R' = H) (30 mg, 4%) (mp 160–161 °C) identical with an authentic sample; (iii) **11-oxo-6*H*-dibenzo[*c,f*][1,2]thiazepine 5,5-dioxide (17a)** (60 mg, 7%) [mp 214–215 °C; IR (KBr) 3200, 1635, 1345, 1290, 1180 cm^{-1}; mass spectrum *m/e* 259 ($M^{+\cdot}$)].

Anal. Calcd for $C_{13}H_9NO_3S$: C, 60.22; H, 3.50. Found: C, 60.12; H, 3.50.

This (20 mg) was treated with sodium hydride (10 mg) in THF (1 mL) and dimethyl sulfate (0.3 mL) was added. After 12 h at room temperature the mixture was filtered and the solvent was evaporated to give 6-methyl-11-oxo-6*H*-dibenzo[*c,f*][1,2]thiazepine 5,5-dioxide (**22**) (20 mg, 90%) [mp 159–160 °C (absolute EtOH)] identical with authentic material (vide infra).

B. In Freon 133 at 100 °C. The azide (1.0 g) in Freon 113 (50 mL) was heated for 5 days at 100 °C in a sealed tube. The solvent was evaporated and ethanol (10 mL) was added to precipitate orthanilic acid (60 mg, 15%) (mp > 250 °C dec), identical (IR) with authentic material. The ethanol was evaporated and the residue was resolved by preparative TLC (silica gel, benzene developer) to give: (i) recovered azide (332 mg, 35%); (ii) 2-phenylbenzoisothiazolin-3-one 1,1-dioxide (4 mg, 1%) [mp 186–187 °C (EtOH); IR (KBr) 1735, 1725, 1340, 1300, 1185 cm^{-1}; mass spectrum *m/e* 259 ($M^{+\cdot}$)] identical with an authentic sample;[10] (iii) 3-phenylbenzoisothiazole 1,1-dioxide (5 mg, 1%) (mp 165–167 °C) identical with an authentic sample; (iv) 11-oxo-6*H*-dibenzo[*c,f*][1,2]thiazepine 5,5-dioxide (32 mg, 3.5%) (mp 213–214 °C) (v) benzanilide (7 mg, 1%) (mp 160°161 °C).

C. In Freon 113 at 140 °C. Thermolysis of the azide (2.0 g) in Freon 113 at 140 °C for 2 days gave: (i) 2-phenylbenzoisothiazolin-3-one 1,1-dioxide (**20**) (14 mg, 1%); (ii) 3-phenylbenzoisothiazole 1,1-dioxide (40 mg, 2%); (iii) 11-oxo-6*H*-dibenzo[*c,f*][1,2]thiazepine 5,5-dioxide (54 mg, 3%).

D. In Absolute Ethanol. The azide (0.8 g) in absolute ethanol (50 mL) was heated at 100 °C for 5 days to give recovered azide (0.39 g, 40%), 3-phenylbenzoisothiazole 1,1-dioxide (82 mg, 20%), and 11-oxo-6*H*-dibenzo[*c,f*][1,2]thiazepine 5,5-dioxide (17 mg, 3%).

Methyl Benzoate 2-*N*-Methylsulfonanilide. Methyl benzoate 2-sulfonyl chloride[29] (11 g) and *N*-methylaniline (5 mL) in pyridine (16 mL) were kept at room temperature for 30 min and water (50 mL) was then added. The precipitate was filtered and washed with 3% HCl (50 mL) and then with water (3 × 50 mL) to give the anilide (12.2 g, 90%): mp 93–94 °C (MeOH); IR (KBr) 1720, 1340, 1170 cm^{-1}; NMR ($CDCl_3$) δ 7.3 (m, 9), 3.8 (s, 3, OCH_3), 3.3 (s, 3, NCH_3); mass spectrum *m/e* 305 ($M^{+\cdot}$).

Anal. Calcd for $C_{15}H_{15}NO_4S$: C, 59.00; H, 4.95. Found: C, 58.98; H, 4.95.

6-Methyl-11-oxo-6*H*-dibenzo[*c,f*][1,2]thiazepine 5,5-Dioxide (22). The above anilide (12.1 g) was saponified with 30% aqueous methanolic (130 mL) KOH (4.6 g). After 3 h at 40 °C the mixture became homogeneous. Concentration afforded a white solid, a portion (6.2 g) of which was treated with PCl_5 (5 g) in carbon disulfide (200 mL) at 50 °C for 1 h, and then with anhydrous aluminum chloride (3.5 g) in nitromethane (6 mL). Heating was continued for 1 h, the CS_2 was decanted, and the red residue was treated with ice water (50 mL). The organic material was extracted with methylene chloride (100 mL), washed with 5% aqueous KOH (2 × 25 mL) and water (2 × 25 mL), and dried ($MgSO_4$). Evaporation of the solvent gave the 6-methyl compound (2 g, 30%): mp 158–159 °C (absolute EtOH); IR (KBr) 1630, 1350, 1180 cm^{-1}; NMR ($CDCl_3$) δ 8.25 (m, 1, ortho to SO_2), 7.65 (m, 7), 3.36 (s, 3, CH_3); mass spectrum *m/e* 273 ($M^{+\cdot}$).

Anal. Calcd for $C_{14}H_{11}NO_3S$: C, 61.52; H, 4.06. Found: C, 61.53; H, 4.07.

4-Methylbenzophenone-2-sulfonic Acid. A. 2-Amino-4′-methylbenzophenone[30] (7.2 g) in acetic acid (20 mL) and concentrated HCl (10 mL) was treated with sodium nitrite (2.8 g) at 0 °C and the diazonium salt solution poured all at once into a cold saturated solution of SO_2 in acetic acid (30 mL) and benzene (70 mL) containing copper(II) chloride dihydrate (3 g). After 25 min at 25–30 °C (negative β-naphthol test) the dark green solution was poured into ice water (280 mL). The benzene layer was separated, the aqueous layer was extracted with ether (2 × 50 mL), and the combined organic layers were washed with water (3 × 50 mL), dried ($MgSO_4$), and concentrated to give an orange oil (10.1 g). This was treated with KOH (4 g) in water (100 mL) at 60 °C for 1 h. The aqueous phase was decanted and extracted with toluene (20 mL). Acidification and concentration of the water layer gave a semisolid which was treated with ethanol. The potassium chloride was filtered and the ethanol concentrated to give 4′-methylbenzophenone-2-sulfonic acid (5 g, 53%) as an oil: NMR (D_2O) δ 8.2 (dd, 1, ortho to SO_2), 7.5 (m, 7), 2.4 (s, 3, CH_3). The acid was treated with KOH (5 g) in water (20 mL) to give potassium 4′-methylbenzophenone-2-sulfonate (4 g, 50%): mp 249–253 °C (lit.[31] mp 248 °C).

The alkali insoluble residue from the above reaction (3.9 g) was triturated with EtOH to give **bis(4′-methyl-2-benzophenone) disulfide** (1.6 g, 21%): mp 160–162 °C (from CH_3CN); IR (KBr) 1640 cm^{-1}; mass spectrum *m/e* 227 ($M^{+\cdot}$/2); NMR ($CDCl_3$) δ 8.2 (m, 8), 2.4 (s, 3).

Anal. Calcd for $C_{28}H_{22}O_2S_2$: C, 73.97; H, 4.88. Found: C, 73.77; H, 4.95.

The ethanol filtrate gave **bis(4′-methyl-2-benzophenone) disulfide *S,S*-dioxide** (0.25 g, 3%): mp 115–116 °C (toluene); IR (KBr) 1650, 1320, 1280, 1265, 1145 cm^{-1}; NMR ($CDCl_3$) δ 7.5 (m, 17), 2.3 (d, 6, 2 CH_3).

Anal. Calcd for $C_{28}H_{22}O_6S_2$: C, 69.11; H, 4.55. Found: C, 69.18; H, 4.46.

B. Aluminum chloride (43 g) in nitromethane (43 mL) was added at room temperature to *o*-sulfobenzoic anhydride[32] (30 g) in toluene (500 mL). A precipitate formed immediately. After 2 h the supernatent liquid was decanted, cold ammonium hydroxide (100 mL) was added to the solid, and the mixture was filtered. The solid was washed with EtOH, the combined filtrates were evaporated, and the residual syrup was treated with KOH (30 g) in water (250 mL) at 40 °C for 1 h. On cooling, potassium 4′-methylbenzophenone-2-sulfonate separated as brownish crystals. Recrystallization from water (70 mL) gave pure sulfonate (30 g, 59%): mp 245–250 °C.

3-*p*-Tolylbenzoisothiazole 1,1-Dioxide (19, R = *p*-Me; R′ = H). A. Ammonium 4′-methylbenzophenone-2-sulfonate (5 g), prepared (syrup) as under B above, was heated with thionyl chloride (15 mL) in toluene (15 mL) at 100 °C for 7 h. Concentration of the solution afforded **3-*p*-tolylbenzoisothiazole 1,1-dioxide** (3.9 g, 61%): mp 179–180 °C (EtOH); IR (KBr) 1335, 1175 cm^{-1}; NMR (CF_3CO_2H) δ 7.9 (m, 6), 7.45 (d, 2, *J* = 8 Hz, half of an A_2B_2 quartet), 2.5 (s, 3, CH_3); mass spectrum *m/e* 257 ($M^{+\cdot}$).

Anal. Calcd for $C_{14}H_{11}NO_2S$: C, 65.34; H, 4.31. Found C, 65.24; H, 4.32.

B. To saccharin (1.8 g) in dry THF (200 mL) was added dropwise a THF solution of *p*-tolylmagnesium bromide [from *p*-bromotoluene (6.5 g) and magnesium (1.1 g) in THF (20 mL)]. After 2 days the solvent was evaporated and water was added to the residue. The mixture was filtered and solid was washed with water (25 mL) and then with ethanol–chloroform (1:1 v/v; 3 × 25 mL). Concentration of the organic filtrates gave the product (1 g, 50%): mp 179–180 °C (CH_3CO_2H).

C. 4′-Methylbenzophenone-2-sulfonyl chloride (2 g) in methanol (20 mL) was treated with ammonia for 2 h at room temperature. Evaporation of the methanol, washing the residue with water, and recrystallization from acetic acid gave the desired product (1 g, 60%): mp 179–180 °C.

4′-Methylbenzophenone-2-sulfonyl Azide (23). Potassium 4′-methylbenzophenone-2-sulfonate (33 g) and phosphorus pentachloride (28 g) were heated for 3 h at 100 °C, ice water was added, and the mixture was extracted with methylene chloride (50 mL). The organic layer was washed with water (2 × 20 mL), dried ($MgSO_4$), and treated with tetramethylguanidinium azide (19 g). After 6 h the solution was washed with water (2 × 20 mL), dried ($MgSO_4$), and evaporated to give an orange oil (23 g). This was chromatographed on a column of silica gel (25 × 250 mm) and eluted with toluene (400 mL) to give the azide as an oil which crystallized from ethanol (8.1 g, 25%): mp 72–73 °C; IR (KBr) 2140, 1665, 1360, 1170 cm^{-1}; NMR (CH_3OD) δ 8.1 (m, 1, ortho to SO_2), 7.7 (m, 7), 2.4 (s, CH_3); mass spectrum *m/e* 301 ($M^{+\cdot}$).

Anal. Calcd for $C_{14}H_{11}N_3O_3S$: C, 55.80; H, 3.68; N, 13.94. Found: C, 56.05; H, 3.78; N, 13.50.

Methyl Benzoate 2-[*N*-Ethyl-*N*-(*p*-tolyl)]sulfonamide. Triethylamine (7.4 g) and *N*-ethyltoluidine (10 g) were added to an ether (200 mL) solution of methyl benzoate 2-sulfonyl chloride (17.0 g). After 12 h, triethylamine hydrochloride (9.8 g, 95%) was filtered. The ether was evaporated and the residue was recrystallized at low temperature from MeOH to give the amide (18 g, 75%): mp 54–56 °C; IR (KBr) 1730, 1330, 1290, 1170, 1150 cm^{-1}; NMR ($CDCl_3$) δ 7.4 (br, s, 4), 7.06 (s, 4), 3.90 (s, 3, OCH_3), 3.74 (q, 2, *J* = 7 Hz, NCH_2), 2.33 (s, 3, CH_3), 1.08 (t, 3, *J* = 7 Hz, NCH_2CH_3); mass spectrum *m/e* 333 ($M^{+\cdot}$).

Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74. Found: C, 61.27; H, 5.74.

***N*-Ethyl-*N*-*p*-tolylbenzenesulfonamide-2-carboxylic Acid.** The ester (4.8 g) in MeOH (10 mL) was saponified with NaOH (3.2 g) in water (171 mL) at 60 °C for 3 h. The solution was made just acidic with concentrated HCl and the oil which separated was extracted with $CHCl_3$. Evaporation gave the acid (3.0 g, 65%): mp 119–120 °C (CCl_4); IR (KBr) 2600 (br), 1720 (m), 1630 (br s), 1345 (s), 1150 cm^{-1} (s); NMR ($CDCl_3$) δ 11 (br s, 1, CO_2H), 7.5 (m, 4), 7.1 (s, 4), 3.7 (q, 2, *J* = 7 Hz, CH_2), 2.3 (s, 3, CH_3), 1.1 (t, 3, *J* = 7 Hz, CH_2CCH_3); mass spectrum *m/e* 319 ($M^{+\cdot}$).

Anal. Calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.36. Found: C, 60.20; H, 5.33.

6-Ethyl-9-methyl-11-oxo-6*H*-dibenzo[*c,f*][1,2]thiazepine 5,5-Dioxide. The above acid (1.0 g) and phosphorus pentachloride (0.91 g) in CS_2 (20 mL) were boiled under reflux for 1 h, and then anhydrous aluminum chloride (0.3 g) was added. After heating for 1 h more, the solvent was evaporated and concentrated HCl (1 mL) and water (30 mL) were added. The oil was extracted with methylene chloride (60 mL) and the extract was washed with water (2 × 20 mL), dried ($MgSO_4$), and evaporated to give an oil which, on treatment with methanol, gave the thiazepine dioxide (0.30 g, 32%): mp 154–155 °C (MeOH); IR (KBr) 1645, 1345, 1180 cm^{-1}; NMR ($CDCl_3$) δ 7.7 (m, 7), 3.7 (q, 2, *J* = 7 Hz, NCH_2), 2.3 (s, 3, CH_3), 0.99 (t, 3, *J* = 7 Hz, CH_2CH_3); mass spectrum *m/e* 301 ($M^{+\cdot}$).

Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.75; H, 5.02. Found C, 63.78; H, 5.02.

Evaporation of the methanol mother liquors gave methyl benzoate 2-[*N*-ethyl-*N*-(*p*-tolyl)]sulfonamide (0.50 g, 48%).

Thermolysis of 4′-Methylbenzophenone-2-sulfonyl Azide (23). A. In Freon 113 at 100 °C. The azide (0.643 g) in Freon 113 (40 mL) was heated for 5 days at 100 °C in a sealed tube. The Freon was evaporated and chloroform was added to the black residue to precipitate orthanilic acid (73 mg, 35%) (mp >250 °C) identical (IR) with an authentic sample. The chloroform solution was added to the black residue to precipitate orthanilic acid (73 mg, 35%) (mp >250 °C) identical (IR) with an authentic sample. The chloroform solution was evaporated and the residual mixture was resolved by preparative TLC (silica gel, toluene developer) to give: (i) starting azide (0.278 g, 43%); (ii) 2-(*p*-tolyl)benzoisothiazolin-3-one 1,1-dioxide (**20**, R = *p*-Me; R′ = H) (10 mg, 3%) [mp 198–199 °C; IR (KBr) 1730, 1335, 1305, 1180; mass spectrum *m/e* 273 ($M^{+\cdot}$)] identical with an authentic sample;[12] (iii) 3-*p*-tolylbenzoisothiazole 1,1-dioxide (**19**) (7.5 mg, 2%) (mp 177–179 °C) identical with the sample prepared above; (iv) 4-

methylbenzanilide (**21**, R = Me; R′ = H) (3 mg, 2%) [mp 145 °C; IR (KBr) 3280, 1635 cm^{-1}; mass spectrum *m/e* 211 ($M^{+}\cdot$)] identical with an authentic sample; (v) **8-methyl-11-oxo-6*H*-dibenzo[*c,f*][1,2]-thiazepine 5,5-dioxide (17b)** (19 mg, 5%) [mp 235–236 °C (toluene); IR (KBr) 3190, 1630, 1340, 1290, 1185, 1175 cm^{-1}; NMR (acetone-d_6) δ 7.95 (d, 1, ortho to SO_2), 7.75 (m, 5), 7.08 (m, 2), 4.7 (br s, 1, exchanges with D_2O. NH), 2.36 (s, 3, CH_3); mass spectrum *m/e* 273 ($M^{+}\cdot$)].

Anal. Calcd for $C_{14}H_{11}NO_3S$: C, 61.52; H, 4.06. Found: C, 61.53; H, 4.08.

The above sultam (25 g) in THF (1 mL) was treated with sodium hydride (10 mg) and then with diethyl sulfate (30 μL). After 12 h at room temperature the solution was filtered and evaporated to give **6-ethyl-8-methyl-11-oxo-6*H*-dibenzo[*c,f*][1,2]thiazepine 5,5-dioxide** (21 mg, 90%) [mp 118–119 °C (toluene–hexane); IR (KBr) 1640, 1355, 1285, 1243, 1178 cm^{-1}; NMR ($CDCl_3$) δ 7.90 (m, 5), 7.24 (m, 2), 3.84 (q, 2, J = 7 Hz), 2.45 (s, 3, CH_3), 0.93 (t, 3, J = 7 Hz)]; this compound was different from the 6-ethyl-9-methyl derivative prepared above.

Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.75; H, 5.02. Found: C, 63.79; H, 5.02.

(vi) *p*-Toluic acid (**27**, R = Me) (40 mg, 26%) (mp 176–178 °C) identical with an authentic sample.

B. In Freon 113 at 140 °C. Thermolysis of the azide (1.67 g) in Freon 113 (40 mL) at 140 °C for 10 h gave a precipitate of 3-(*p*-tolyl)benzo[*c*][2,1,4]oxathiazine 1,1-dioxide (**25**, R = Me; R′ = H) (0.430 g, 33%): mp 144–146 °C (from hexane); IR (KBr) 1633, 1360, 1190; mass spectrum *m/e* 273 ($M^{+}\cdot$).

Anal. Calcd for $C_{14}H_{11}NO_3S$: C, 61.52; H, 4.06. Found: C, 61.28; H, 4.21.

Treatment of this compound with ethanol gave orthanilic acid (**18**, R′ = H), identical with an authentic sample, and ethyl *p*-methylbenzoate [the latter was detected in the alcohol mother liquors by GLC on a column of 15% SE 30 on Chromosorb W at 152 °C, and identified by its infrared spectrum (identical with that of an authentic sample)].

The Freon filtrate was evaporated and resolved by TLC (silica gel; toluene developer) to give: (i) recovered sulfonyl azide (0.256 g, 15%); (ii) 2-*p*-tolylbenzoisothiazolin-3-one 1,1-dioxide (45 mg, 4%); (iii) 3-*p*-tolylbenzoisothiazole 1,1-dioxide (44 mg, 4%); (iv) 8-methyl-11-oxo-6*H*-dibenzo[*c,f*][1,2]thiazepine 5,5-dioxide (80 mg, 6%); (v) a trace of 4-methylbenzanilide.

Rechromatography of the material that had remained on the baseline using $CHCl_3$ as eluent gave an unidentified compound (40 mg): mp 182–183 °C (EtOH); IR (KBr) 3240, 1650, 1340, 1180 cm^{-1}; NMR ($CDCl_3$) δ 7.9 (m, 6), 7.3 (m, 2), 2.7 (s, 3); mass spectrum *m/e* 345 ($M^{+}\cdot$ + 4 for ^{35}Cl), 343 ($M^{+}\cdot$ + 2), 341 ($M^{+}\cdot$, ^{35}Cl) (in the abundance ratio 1.7:6.1:9.0; calcd for 2 Cl 1.0:6.0:9.0), 309, 307 (abundance ratio 1.2:3.0; calcd for 1 Cl 1.0:3.0).

Anal. Found: C, 55.54; H, 3.67.

2-Benzamido-4-methylbenzenesulfonic Acid. Sodium 2-amino-4-methylbenzenesulfonate [from 2-amino-4-methylbenzenesulfonic acid[33] (0.5 g) and an equivalent amount of aqueous NaOH followed by evaporation of the water] and benzoyl chloride (2 mL) were heated for 3 h at 100 °C and then for 30 min under reflux. The excess benzoyl chloride was distilled and the residue was extracted with hot acetonitrile. On cooling the benzamido derivative separated: mp 180–183 °C (from CH_3CN); IR (KBr) 1620, 1325, 1190, 1175 cm^{-1}; mass spectrum *m/e* 273 ($M^{+}\cdot$ − 18).

Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.71; H, 4.50. Found: C, 57.57; H, 4.49.

5-Methylbenzophenone-2-sulfonyl Chloride. 2-Amino-5-methylbenzophenone hydrochloride[34] (19 g) in acetic acid (30 mL) and concentrated HCl (25 mL) was diazotized with sodium nitrite (7 g) in water (10 mL) and then added to a cold saturated solution of SO_2 in benzene (90 mL) and acetic acid (90 mL) containing $CuCl_2$ (5 g). After 5 h at room temperature, the organic layer was separated, washed with water (5 × 50 mL), dried ($MgSO_4$), and evaporated to yield an oil (10.8 g). This was treated with acetic acid (100 mL), concentrated HCl (20 mL), and potassium chlorate (5.8 g) in water (50 mL).[35] After 3 h at room temperature the solvent was evaporated, ethanol was added to the residual oil, and KCl (3.2 g, 91%) was separated. Concentration of the ethanol filtrate give **5-methylbenzophenone-2-sulfonic acid** (7.7 g, 36%) as a lime-colored syrup. The crude sulfonic acid (7.7 g) was heated under reflux with thionyl chloride (20 mL) and DMF (0.5 mL) for 3 h and poured over ice (100 g) to give **5-methylbenzophenone-2-sulfonyl chloride** (6 g, 73%): mp 118–120 °C (EtOH); IR (KBr) 1670, 1360, 1170 cm^{-1}; NMR ($CDCl_3$) δ 8.05 (d, 1, J = 8 Hz, ortho to sulfonyl), 7.75 (dd, 2, J = 8, 2 Hz, H_3 and H_4), 7.4 (m, 5, Ph), 2.5 (s, 3, CH_3); mass spectrum *m/e* 296 ($M^{+}\cdot$, ^{37}Cl), 294 ($M^{+}\cdot$, ^{35}Cl).

Anal. Calcd For $C_{14}H_{11}ClO_3S$: C, 57.04; H, 3.76. Found: C, 56.91; H, 3.73.

5-Methylbenzophenone-2-sulfonyl Azide (24). This was prepared from the sulfonyl chloride (1.5 g) and tetramethylguanidinium azide (2 g) in $CHCl_3$ (30 mL) at room temperature for 12 h. The azide (0.52 g, 34%) had: mp 97.5–99 °C (from toluene); IR (KBr) 2130, 1675, 1360, 1175 cm^{-1}; NMR ($CDCl_3$) δ 7.95 (d, 1, J = 8 Hz, ortho to SO_2), 7.65 (dd, 2, J = 8, 2 Hz, H_3 and H_4), 7.4 (m, 5, Ph), 2.45 (s, 3, CH_3); mass spectrum *m/e* 301 ($M^{+}\cdot$).

Anal. Calcd for $C_{14}H_{11}N_3O_3S$: C, 55.80; H, 3.68. Found: C, 55.82; H, 3.69.

Thermolysis of 5-Methylbenzophenone-2-sulfonyl Azide. The azide (1.17 g) in Freon 113 (60 mL) was heated for 18 h at 140 °C in a sealed tube. The mixture was filtered from 2-benzamido-5-methylbenzenesulfonic acid (**26**, R = H; R′ = Me) (0.42 g, 40%) [mp 183 °C (toluene or CH_3CN)] identical with the authentic sample prepared above. This, on treatment with ethanol, gave 2-amino-5-methylbenzenesulfonic acid (**18**, R′ = Me) identical with authentic material.

The Freon filtrate was resolved by preparative TLC (silica gel, $CHCl_3$ eluent) to give: (i) benz-*m*-toluidide (**21**, R = H; R′ = Me) (20 mg, 1%) (mp 125–126 °C) identical with an authentic sample; (This was shown to be a single isomer under conditions—microslide TLC, silica gel, methylene chloride development—suitable for the resolution of the *m*- and *p*-toluidides.) (ii) **2-methyl-11-oxo-6*H*-dibenzo[*c,f*][1,2]thiazepine 5,5-dioxide (17c)** (64 mg, 6%): mp 203–204 °C (toluene); IR (KBr) 3200, 1640, 1350, 1300, 1180, 1140 cm^{-1}; mass spectrum *m/e* 273 ($M^{+}\cdot$).

Anal. Calcd for $C_{14}H_{11}NO_3S$: C, 61.52; H, 4.06. Found: C, 61.43; H, 4.11.

Treatment of this sultam (21 mg) in THF (1 mL) with sodium hydride (5 mg) and diethyl sulfate (50 μL) in THF (1 mL) for 2 h at 80 °C gave **6-ethyl-2-methyl-11-oxo-6*H*-dibenzo[*c,f*][1,2]thiazepine 5,5-dioxide** (20 mg, 90%): mp 140–142 °C (MeOH); IR (KBr) 1655, 1345, 1175 cm^{-1}.

Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.75; H, 5.02. Found: C, 63.71; H, 5.02.

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Registry No.—**1d**, 64939-40-8; **2**, 64939-41-9; **3**, 23393-41-1; **4**, 22172-69-6; **5**, 2688-87-1; **6**, 64939-42-0; **7**, 64939-43-1; **8**, 22172-72-1; **9**, 64939-44-2; **10**, 22172-71-0; **11** (2-Br), 64939-45-3; **11** (4-Bu), 64939-46-4; **12**, 22172-73-2; **13**, 127-63-9; **14**, 6462-14-2; **14** *N,N*-dimethyl, 64939-47-5; **17a**, 63113-45-1; **17b**, 63113-46-2; **17** (R = *p*-Me; R′ = H), 38938-54-4; **20** (R, R′ = H), 15449-00-0; **21** (R, R′ = H), 93-98-1; **22**, 26638-46-0; **25**, (12 = *p*-Me; R′ = H), 63113-48-4; sodium azide, 26628-22-8; 2-phenoxybenzenesulfonyl chloride, 2688-85-9; diphenyl sulfone 2-sulfonyl chloride, 6462-15-3; 2-aminodiphenyl sulfone, 4273-98-7; *N*-acetyldi-*p*-tolylamine, 32047-89-5; chlorosulfonic acid, 7790-94-5; *N*-acetyldi-*p*-tolylamine 2-sulfonyl chloride, 64939-29-3; *N*-acetyldi-*p*-tolylamine *N*′-dodecyl-2-sulfonamide, 64939-30-6; dodecane, 112-40-3; benzophenone-2-sulfonyl chloride, 54075-06-8; methyl benzoate 2-*N*-methylsulfonanilide, 26638-44-8; methyl benzoate 2-sulfonyl chloride, 26638-43-7; *N*-methyaniline, 100-61-8; 2-amino-4′-methylbenzophenone, 36192-63-9; 4′-methylbenzophenone-2-sulfonic acid, 64939-31-7; potassium 4′-methylbenzophenone-2-sulfonate, 64939-32-8; bis(4′-methyl-2-benzophenone) disulfide, 64939-33-9; bis(4′-methyl-2-benzophenone) disulfide *S,S*-dioxide, 64939-34-0; o-sulfobenzoic anhydride, 64975-68-4; ammonium 4′-methylbenzophenone-2-sulfonate, 64939-35-1; *p*-bromotoluene, 106-38-7; 4′-methylbenzophenone-2-sulfonyl chloride, 64939-36-2; tetramethylguanidinium azide, 64939-37-3; methyl benzoate 2-[*N*-ethyl-*N*-(*p*-tolyl)sulfonamide, 64939-24-8; *N*-ethyltoluidine, 622-57-1; *N*-ethyl-*N*-*p*-tolylbenzenesulfonamide-2-carboxylic acid, 63113-54-2; 6-ethyl-9-methyl-11-oxo-6*H*-dibenzo[*c,f*]-[1,2]thiazepine 5,5-dioxide, 63113-52-0; diethyl sulfate, 64-67-5; 6-ethyl-8-methyl-11-oxo-6*H*-dibenzo[*c,f*][1,2[thiazepine 5,5-dioxide, 63113-53-1; 2-benzamido-4-methylbenzenesulfonic acid, 63113-51-9; sodium 2-amino-4-methylbenzenesulfonate, 42876-65-3; benzoyl chloride, 98-88-4; 2-amino-5-methylbenzophenone HCl, 64939-25-9; 5-methylbenzophenone-2-sulfonic acid, 64939-26-0; 5-methylbenzophenone-2-sulfonyl chloride, 64939-27-1; 6-ethyl-2-methyl-11-oxo-6*H*-dibenzo[*c,f*][1,2]thiozepine 5,5-dioxide, 64939-28-2.

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(5) If sulfur participation were involved the thermolysis would be expected to take place at a temperature below that (~130–150 °C) at which unassisted decomposition takes place. The nitrene would be by-passed and hence, also, formation of **7** and **8**, unless assisted and unassisted decompositions are delicately balanced. Formation of **10** rather than the sulfur analogue of **4** can be explained by the superior nucleophilicity of sulfur compared with the benzene ring toward the electrophilic singlet sulfonylnitrene.
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Addition and Annulation Reactions between Indoles and α,β-Unsaturated Ketones

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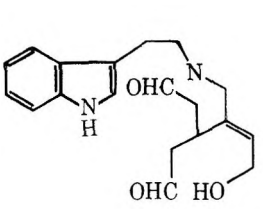
The structure of the addition product formed by acid-catalyzed reaction between 1,3-dimethylindole and mesityl oxide is shown to be **12**. Analogous products are formed with methyl vinyl ketone and benzalacetone as annulating agents. The reactions between methyl vinyl ketone and indole, 1,2-dimethylindole, and 3-methylindole are compared with these and with cyclization steps in the syntheses of the alkaloids villalstonine and vindorosine.

In a planned synthesis of strychnine Robinson and Saxton envisaged[1] the conversion of the dialdehyde **1** by a combination of Mannich and aldol-type condensations into the Wieland–Gumlich aldehyde **2**, already known to be convertible into strychnine. The conversion **1** → **2** would have exemplified the concept of annulation utilizing electrophilic addition reactions of indoles. Subsequently, this concept has been realized in Büchi's synthesis of vindorosine,[2] in which a key step is the cyclization of the *N*-acetylenone **3** with boron trifluoride etherate into the indoline **4**, and by our biomimetic synthesis of villalstonine (**5**) from macroline (**6**) and pleio-



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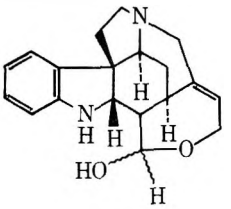

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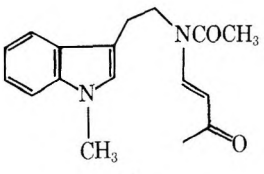

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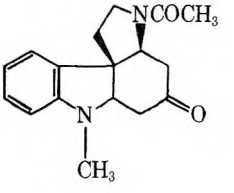

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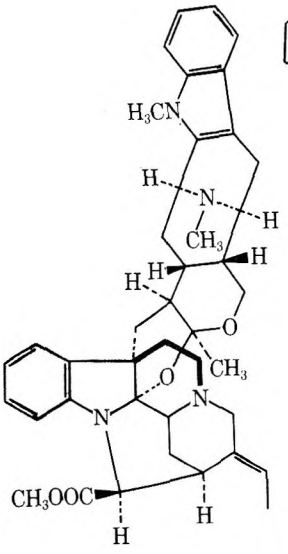

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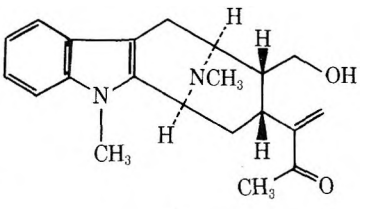

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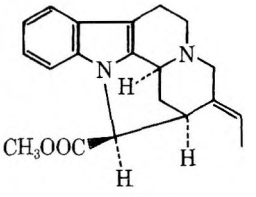

7

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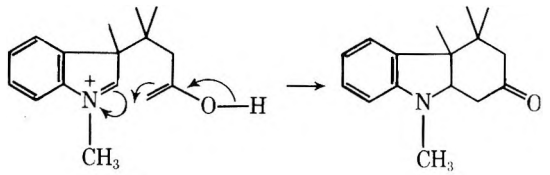
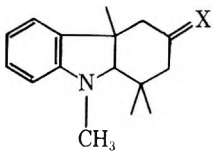
carpamine (7) with 0.2 N aqueous hydrochloric acid.[3] In these examples, a carbocyclic and two heterocyclic rings, respectively, are generated. In view of a surprising lack of general information on the scope and limitations of these potentially useful annulation reactions of indoles, and to compare them with the villalstonine synthesis, we have studied model reactions between indoles and enones.

Cockerill, Robinson, and Saxton[4] had reported that 1,3-dimethylindole reacts with mesityl oxide in aqueous ethanolic hydrogen chloride to give the adduct $C_{10}H_{21}NO$. On the basis of color tests and reasoning by analogy they assigned structure **9** to this compound. This would presumably arise by cycliza-

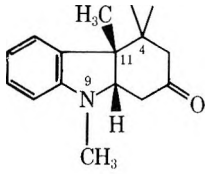


8 **9**

tion of an intermediate **8**, which would be analogous to that involved in the vindorosine annulation **3** → **4**.[2] In 1958 Noland and D. N. Robinson proposed structure **10** for this adduct,[5]



10, X = O
11, X = H_2

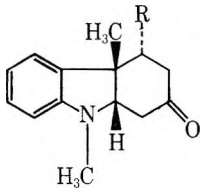


12

but this proposal was refuted in 1960 by B. Robinson and Smith,[6] who established the nonidentity of the deoxydihydro derivative of the adduct with compound **11** synthesized independently. We have, therefore, first reinvestigated this reaction and have established the validity of Cockerill, Robinson, and Saxton's original structure proposal.[4] Further, the stereochemistry shown in **12** has been determined. In the NMR spectrum, 3 H singlets at δ 0.82, 1.06, 1.46, and 2.64 are assigned to the two 4-methyl, the 11-methyl, and the 9-methyl groups, respectively. The aromatic protons give a 4 H multiplet centered at δ 6.9. The ring junction methine proton gives rise to a triplet-like doublet of doublets at δ 3.36 (J, $J \sim 4$ Hz), split by the two adjacent methylene protons, whose absorption is partly obscured by that of the N-methyl group, but appears like a doublet (J = 4 Hz). The remaining isolated pair of methylene hydrogens gives rise to an AB pattern centered at δ 2.26 (J_{AB} = 15 Hz, $\Delta\nu$ = 8 Hz).

These spectral data clearly establish the gross structure **12** for this adduct, whose mode of formation is analogous to that of **4** from **3**.[2] Because **4** is a β,β′-diamino ketone, two of the three chiral centers generated are epimerizable and the stereoisomer obtained is the thermodynamically most stable one. One chiral center in **12** is similarly epimerizable, and the stereochemistry in this less constrained compound was therefore of interest. If the aliphatic rings were trans fused, models would suggest one possible pseudo-chair and two pseudo-boat conformations for the cyclohexanone ring. These would be expected to lead to ABX (J_{AB} ca. 15 Hz, $J_{AX} = J_{BX}$) patterns from the ring junction methine and adjacent methylene protons. These possibilities are clearly ruled out by the data given above, which are in accord with a cis fusion. Similar inferences have been made for other comparably generated ring systems by Stevens and his co-workers.[7] A preliminary x-ray crystallographic investigation of **12** is in accord with these stereochemical assignments, although the crystal structure has not yielded to satisfactory refinement below R = 0.14.[8]

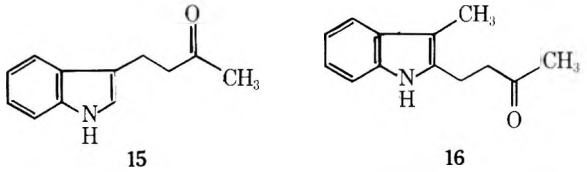
The reaction can be extended to other α,β-unsaturated ketones; methyl vinyl ketone and benzalacetone with 1,3-dimethylindole give, respectively, adducts **13** and **14** as pre-



13, R = H
14, R = C_6H_5

dominant reaction products. The structures are assigned on the basis of the closely analogous IR and NMR spectra to those of **12** (see Experimental Section). The pseudoequatorial configuration for the phenyl group in **14** is also assigned on the basis of NMR evidence. First, two of the aromatic protons are markedly shielded, in particular the 5 proton of the dihydroindole ring, which gives rise to a signal at ca. δ 5.8. This arises from mutual shielding of the two aromatic rings, possible only if the phenyl substituent is pseudoequatorial. The ring junction methine hydrogen gives rise to a triplet-like doublet of doublets at δ 3.52 (both J = 3 Hz). The proton adjacent to the phenyl ring gives rise to a clear doublet of doublets (J = 13, 4 Hz) centered at δ 3.28, which shows the phenyl ring to be pseudoequatorial; if it were pseudoaxial the pseudoequatorial hydrogen would, from Dreiding models, have approximately equal dihedral angles of ca. 45° with each neighboring methylene proton and would be expected to give rise to a second triplet-like doublet of doublets having J values of ca. 3 Hz.

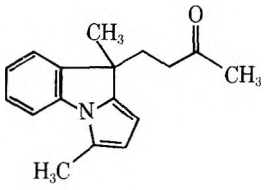
These reactions can be compared with some described by Szmuszkovicz.[9] Indole was reported to react with methyl vinyl ketone in acetic acid with or without added acetic anhydride to give the 3-substituted adduct **15**, but skatole (3-methylin-



15 **16**

dole) with methyl vinyl ketone in acetic acid–acetic anhydride was said to give the 2-substituted adduct **16**;[9] no tetrahydrocarbazole analogous to **12** was obtained. Since the analytical and spectral data quoted in support of structure **16** are equivocal, we repeated the condensation. We obtained, as well as much recovered skatole, an oil having the same infrared spectral characteristics as reported by Szmuszkovicz,[9] but TLC of this substance showed it to contain at least seven compounds. The major product, isolated by preparative TLC, was an oily ketone, $C_{17}H_{19}NO$. A methyl ketone was inferred from the infrared (ν_{max} 1715 cm^{-1}) and NMR (δ 2.33, 3 H, s) spectra. The low-field NMR spectrum showed, as well as the four indolic protons, two coupled 1 H doublets at δ 6.60 and 6.10 (J = 6 Hz each). The spectrum also showed two other methyl group signals at δ 1.83 and 1.53. The base peak ion in the mass spectrum had formula $C_{13}H_{12}N$ and is believed to arise from the molecular ion by loss of C_4H_7O. These data taken together are consonant with structures **17** or **18** for this compound, although a distinction between the two is certainly not possible from the data at hand. The ultraviolet spectrum [λ_{max} 215 nm (ε 9200), 232 sh (8100), 252 sh (3500), 315 (3700)] is not easily correlated with spectra of model compounds (cf. ref 10); the rigid planar structures of **17** and **18** and the sub-

stitution patterns of the chromophoric groups prevent empirical comparison with other systems known to us. The compound must arise from 1 mol of skatole and 2 of the enone; various pathways can be envisaged for generating structures **17** and **18**.



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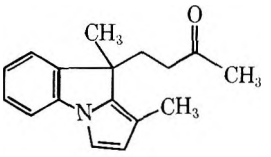

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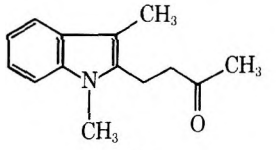
When 1,3-dimethylindole was treated with methyl vinyl ketone in acetic acid–acetic anhydride, one product, in addition to recovered starting material, was obtained. This compound, mp 72 °C, had molecular formula $C_{14}H_{17}NO$ and from examination of its spectra could be assigned structure **19**. The



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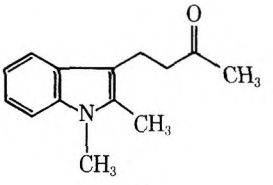

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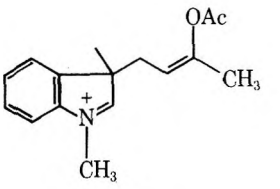
infrared spectrum shows a nonconjugated carbonyl group (ν_{max} 1715 cm^{-1}), which is assigned to a methyl ketone function from the 3 H methyl singlet at δ 2.10 in the NMR spectrum. The indolic *N*-methyl signal falls at δ 3.61 and the 3-methyl group at δ 2.25. The four methylene protons give a complex, extensive, and almost symmetrical multiplet centered at δ 2.8. These data are comparable with, but distinct from, those reported[11] for the isomer **20**; this compound was prepared in high yield from 1,2-dimethylindole and methyl vinyl ketone in acetic acid–acetic anhydride.[11] These results show that the thermodynamically most stable stereoisomers of hexahydrocarbazoles can readily be prepared from 1,3-disubstituted indoles and enones under acidic conditions in the absence of acylating agents such as acetic anhydride.

The reactions considered in this work can be interpreted together as follows. The annulation reactions, which take place in acidic alcohol solutions, involve intermediates such as **8**. In these reactions the initial electrophilic attack at C-3 of the indole is followed by ketonization, re-enolization, and ring closure (**8** → **9**). The reaction of 1,3-dimethylindole and methyl vinyl ketone in acetic acid–acetic anhydride presumably involves the acylation of an intermediate enol to give **21**, which may either revert to starting material or else undergo rearrangement by migration of an alkyl substituent from the indolic 3 position; in **21** migration of the allylic ester chain would preempt that of the methyl group (see ref 12). We may assume that in the former case (annulation in acidic alcohol solution) tautomerization of the initially produced enol to the isomeric enol which cyclizes is fast compared to alkyl group shift, and in the latter case (2 substitution in acetic acid–acetic anhydride) alkyl group migration is the faster process. The villalstonine annulation may be seen in this light; the initially produced iminium ion **22** is trapped by the hemiacetal OH group faster than alkyl group migration can take place. Note that 1,2-dimethylindole, however,[11] reacts with methyl vinyl ketone in acetic acid–acetic anhydride to give the simple 3-alkylated indole; here, the initial ion resulting from electrophilic attack at the unsubstituted 3 position loses the 3 proton and re-aromatizes with great rapidity, excluding alternative pathways. Skatole, a 3-substituted but N-unalkylated indole, undergoes complex reactions involving both N- and C-alkyl-



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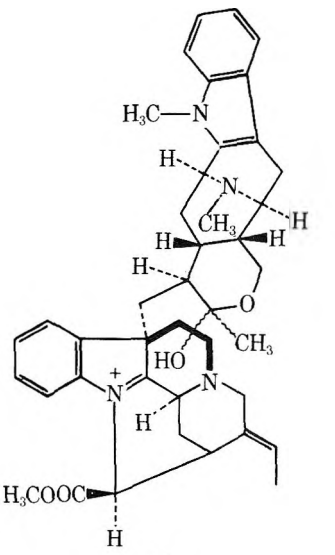

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ation by the enone. In the cases of the simpler indoles, it appears that the reactions with enones, analyzed by modern separation techniques, may be much more diverse than has been recognized hitherto and would repay further investigation as a means of entry to novel indolic and other heterocyclic systems.

Experimental Section

Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points were taken in a Thomas-Hoover capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian T-60 spectrometer. Infrared spectra were taken on a Perkin-Elmer 567 instrument. Analytical TLC plates used were Eastman UV-active 2-mm and 0.5-mm silica gel on glass. The indicator was a saturated solution of cerium(IV) sulfate in 50% aqueous sulfuric acid.

Condensation of 1,3-Dimethylindole and Mesityl Oxide. A mixture of 1,3-dimethylindole (0.40 g, 2.81 mmol), ethanol (1.65 mL), and water (0.35 mL) was stirred while concentrated sulfuric acid (1.0 mL) was added quickly. The temperature rose to 70 °C. More sulfuric acid (0.5 mL) was added, followed immediately by mesityl oxide (0.50 g, 5.1 mmol). After stirring for 5 min, the mixture was heated to 93 °C, and stirring was continued a further 5 min. The reaction mixture was made alkaline with concentrated ammonia and evaporated to dryness under reduced pressure. The residue was taken up in dichloromethane, the insoluble inorganic salts were filtered off by suction, and the dichloromethane solution was reduced in volume under reduced pressure. Preparative TLC (silica gel, benzene) of the residue gave two components. A faster moving minor component degraded rapidly on exposure to air, but the slower moving major component slowly crystallized to greenish-white needles on evaporation of the extracting solvent (ethanol). The product was purified by sublimation (80 °C, 0.03 mm), giving 0.421 g (61%) of off-white needles, mp 90 °C. Recrystallization from cyclohexane gave white rectangular prisms of 1,2,3,4,10,11-hexahydro-4,4,9,11-tetramethyl-2-oxocarbazole (**12**): mp 92–95 °C (lit.[4] 96–97 °C); NMR δ ($CDCl_3$) 0.82 (s, 3 H), 1.06 (s, 3 H), 1.46 (s, 3 H), 2.26 (dd, J = 14, 16 Hz, 2 H), 2.64 (s, 3 H), 2.72 (d, J = 4 Hz, 2 H), 3.36 (t, J = 4 Hz, 1 H), 7.32–6.46 (m, 4 H); IR (KBr) ν 2980, 2940, 2900, 2865, 2840, 2810, weak overtones at 1920 and 1882, 1705, 1591, 1481, 1450, with strongest bands below 1400 at 1350, 1292, 1020, 790, 744 cm^{-1}.

The product was also prepared several times by using a saturated HCl solution to catalyze the reaction, as recommended by Cockerill, Robinson, and Saxton.[4] The highest yield obtained was 30% of theory.

An attempt to catalyze the reaction with BF_3·Et_2O was unsuccessful.

Condensation of 1,3-Dimethylindole and Methyl Vinyl Ketone. To a solution of 1,3-dimethylindole (0.40 g, 2.81 mmol) in 83% aqueous ethanol (2 mL) was added quickly concentrated sulfuric acid (1.5 mL, temperature reached 70 °C) followed immediately by 3-buten-2-one (0.36 g, 5.1 mmol). The mixture was stirred 5 min without further heating and then made basic with concentrated ammonia. The mixture was concentrated to dryness under reduced pressure, and the product was taken up in dichloromethane. This solution was dried

(Na_2CO_3) and filtered. TLC (silica gel, benzene) showed nearly complete disappearance of 1,3-dimethylindole (R_f 0.58) and formation of two new compounds, the major component having an R_f of 0.37 (color with cerium(IV) reagent, red). Preparative TLC (silica gel, benzene) allowed separation of the desired product, pure by TLC, as a golden oil: NMR δ ($CDCl_3$) 1.42 (s, 3 H), 1.70–2.23 (complex, 4 H), 2.64 (d, J = 3 Hz, 2 H), 3.34 (t, J = 3 Hz, 1 H), 7.22–6.26 (complex multiplet, 4 H); IR (neat) ν (major features) 3040, 3020, 2950, 2920, 2860, 2805, 1713, 1600, 1485, 1295, 1192, 1105, 1015, 948, 743 cm^{-1}. Kugelrohr distillation (twice at 1 mm, 120–130 °C) yielded 163 mg (27%) of analytically pure 1,2,3,4,10,11-hexahydro-9,11-dimethyl-2-oxocarbazole (**13**). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.12; H, 7.98; N, 6.42.

Condensation of 1,3-Dimethylindole with Benzalacetone. To 1,3-dimethylindole (0.81 g, 5.7 mmol) in ethanol (3.30 mL) and water (0.70 mL) was added concentrated sulfuric acid (ca. 2 mL, continuous stirring) followed immediately by benzalacetone (0.78 g, 5.3 mmol). After stirring for 10 min, the reaction mixture was made basic with concentrated aqueous ammonia and evaporated to dryness under reduced pressure, and the residue taken up in dichloromethane. Preparative TLC (silica gel, benzene) gave as the major component a brown oil. Purification by Kugelrohr distillation (1 mm, 140–160 °C) gave a highly viscous golden oil (452 mg, 29%). Preparative TLC (silica gel, benzene) of this showed three components: R_f 0.10 (color with Ce(IV), red), R_f 0.19 (colorless, turns grey on standing), and R_f 0.63 (1,3-dimethylindole; colorless, turns gray on standing). Extraction of the band at R_f 0.10 gave 302 mg of a crystalline material, still contaminated owing to overlap with the band at R_f 0.19. Recrystallization from cyclohexane[9] gave **14** as a white crystalline material, nearly pure (TLC): mp 125–139 °C; R_f 0.17; NMR δ ($CDCl_3$) 1.45 (s, 3 H), 2.66 (s, 3 H), 2.00–3.40 (complex, 5 H), 3.52 (dd, J = 3 Hz, 1 H), 5.70–5.84 (complex, 1 H), 6.34–7.34 (complex, 8 H). Two small absorptions at δ 1.32 and 2.74, much larger in the crude substance, are apparent singlets associated with the major impurity and were seen to decrease in intensity at each successive stage of purification. Final purification by sublimation (0.10 mm, 109–111 °C) gave white crystals, mp 122–134 °C, pure by TLC; IR (film) ν (major features) 3020, 2950, 2859, 2800, 1713, 1600, 1480, 1450, 1293, 1020, 750, 700 cm^{-1}. Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.41; H, 7.19; N, 4.77.

Reaction of 3-Methylindole with Methyl Vinyl Ketone in Acetic Acid–Acetic Anhydride. 3-Methylindole (655 mg, 5 mmol) was dissolved in a solution of glacial acetic acid (9.2 mL) containing acetic anhydride (3.1 mL). To this solution was added methyl vinyl ketone (700 mg, 10 mmol), and the reaction mixture was heated on the steam bath for 0.5 h. Water (50 mL) was then added and the solution heated for an additional 0.5 h. The reaction mixture was then neutralized with saturated sodium carbonate solution and extracted with chloroform (3 × 10 mL). The chloroform extracts were dried over anhydrous sodium carbonate, concentrated to a small volume under reduced pressure, and distilled. The major products were unreacted 3-methylindole and a small amount of a new product (75 mg), bp 170–200 °C (0.1 mm). This product was chromatographed on a silica gel preparative plate (0.25 mm, benzene) to yield 50 mg of an oil (pure by TLC) which had the following properties: UV (EtOH) λ_{max} 215 nm (ε 9200), 232 sh (8100), 252 sh (3500), 315 (3750); IR (neat) 3030, 2920, 1715 broad, 1455, 1345, 750 cm^{-1}; NMR ($CDCl_3$) δ 7.6–6.95 (4 H, m, aromatic protons), 6.60–6.10 (2 H, dd, J = 6 Hz), 2.33 (3 H, s), 1.83 (3 H, s, CH_3), 1.58 (3 H, s, CH_3); mass spectrum, m/e 253 (M^+), 182 (100); high-resolution mass spectrum, M^+ 253.147 (calcd for $C_{17}H_{19}NO$, 253.146), 182.097 (calcd for $C_{13}H_{12}N$, 182.096).

Preparation of 1,3-Dimethyl-2-(3′-oxobutyl)indole (19). 1,3-Dimethylindole (5 g, 35 mmol) was dissolved in a solution of glacial acetic acid (23 mL) containing acetic anhydride (8 mL). To this solution was added methyl vinyl ketone (7 g, 0.1 mmol). The solution was heated on the steam bath for 0.5 h, water (100 mL) added, and the solution heated for an additional 0.5 h. The reaction mixture was then neutralized with saturated sodium carbonate solution and extracted with chloroform (3 × 50 mL). The chloroform solution was dried over anhydrous sodium carbonate and concentrated to a small volume under reduced pressure. Distillation of the residue at 170 °C (0.01 mm) produced a yellow oil (1.2 g) slightly contaminated with impurities. Chromatography of this oil on silica gel preparative plates (0.5 mm, benzene) followed by excision of the major band produced 1 g of a yellow oil, substantially pure. Kugelrohr distillation at 140 °C (0.25 mm) produced a yellow oil which recrystallized on standing: mp 72 °C; IR (film) 2920, 1715, 1475, 1370, 1170, 1015, 745 cm^{-1}; NMR ($CDCl_3$) δ 7.5–6.90 (4 H, m, aromatic protons), 3.61 (3 H, s, NCH_3), 3.2–2.2 (4 H, m, $-CH_2CH_2$), 2.25 (3 H, s, indole 3-CH_3), 2.10 (3 H, s, $COCH_3$). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.95; N, 6.50. Found: C, 78.06; H, 8.04; N, 6.53.

Acknowledgment. We thank Dr. James Evans for mass spectral measurements and a referee for valuable comments.

Registry No.—**12**, 64884-70-4; **13**, 64884-71-5; **14**, 64884-72-6; **17/18**, 64885-16-1; **19**, 64884-73-7; 1,3-dimethylindole, 875-30-9; mesityl oxide, 141-79-7; 3-buten-2-one, 78-94-4; benzalacetone, 122-57-6; 3-methylindole, 83-34-1.

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Anodic Oxidation of 2,3-Diphenylindole

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The anodic (oxidative) electrochemical behavior of 2,3-diphenylindole (1) has been investigated with a view toward elucidating the decomposition pathway(s) of the initially generated cation radical. In acetonitrile with tetraethylammonium perchlorate as supporting electrolyte, the one-electron transfer step at platinum is followed by a rapid coupling of two 1 cation radicals to give the dimeric species 2. From the various spectral data, primarily ^{13}C NMR, of 2 it appears that 2 is an indole–indolenine dimer, the dimeric bond being formed between the 3 position in the indolenine moiety and, most probably, the 5 position in the indole portion of the dimer. This is in contrast to the analogous coupling patterns for various carbazole derivatives, whose cation radicals form simple carbazole–carbazole dimers.

The indole nucleus, with its widespread occurrence in natural systems,[1] has been the object of much chemical investigation. In this communication we wish to report the results of an anodic (oxidative) electrochemical study of 2,3-diphenylindole (1). The anodic electrochemical behavior of indole and its derivatives has only briefly been investigated, but these studies indicate that reactivity may be centered both in the benzene ring[2] and in the pyrrole ring.[3] Electrochemical studies of the structurally similar carbazole system in acetonitrile have revealed dimerization as the dominant process upon anodic oxidation.[4] The present study was directed toward determining which of these possibilities might pertain to the indole system under investigation.

Previous studies on indole itself[3] had shown that the electrochemistry was quite involved, but was concerned mainly with reactivity centered in the area of the 2,3 double bond. It was anticipated that protection of the double bond with phenyl groups might lead to less complicated behavior and that useful information on indole itself could be inferred from the "model" behavior of this compound; the results of this study are presented herein.

Results and Discussion

Initial information about the 2,3-diphenylindole system was obtained from a cyclic voltammetric study. The cyclic voltammogram (Figure 1) shows two waves; the first of these corresponds to the initial oxidation of 1, while the further anodic wave apparently is due to the oxidation of a product formed from the initially generated species. From a comparison of the cyclic voltammograms of 1 and its electrolysis product, it may be seen that the oxidation wave for this product corresponds fairly closely with the further anodic wave in the cyclic voltammogram of 1, there being an approximately 70 mV cathodic shift of the former with respect to the latter. This shift is most probably due to the presence of protons in the unreduced electrolysis mixture. In a study of the peak potential shift as a function of scan rate, an anodic shift of 20 mV per decade scan rate increase was found. A shift of this magnitude corresponds theoretically to a reversible (fast) electron transfer followed by a rapid second-order reaction.[5] The parameter $i_p/v^{1/2}C$ should also remain constant with scan rate;[6] a decrease of only 1% in this value over the range 0.5–60 V/min was observed. Previous work on various substituted carbazoles has indicated that the initial formation of a cation radical upon anodic oxidation is a reversible one-electron process.[7] Thus, it seems reasonable to suppose that the initial oxidation of 1 also produces the cation radical, which then undergoes a rapid dimerization (i.e., a subsequent second-order reaction). A coulometrically determined n value for this oxidation lends additional support for this one-electron process, the n value found being 1.05 (corrected for background current).

An approximate value for the rate constant of the dimerization reaction was determined by the method of Olmstead et al.[5] This method involves correlating the shift in peak potential from the standard potential $E°$ of the system (as a function of scan rate) with the kinetic parameter (i.e., the rate constant) of the system, thus requiring a value for $E°$. This value, a characteristic of the one-electron cation radical system in the absence of any kinetic complications, was obtained by scanning at a high rate (250 V/min) using oscilloscopic recording. The cyclic voltammogram obtained was that of a reversible system, having equal anodic and cathodic peak currents with no evidence of the second anodic wave; the $E°$ value was +1.08 V. A value of 2×10^6 M^{-1} s^{-1} for the rate constant was obtained from extrapolation of the working curve given by Olmstead et al.[5]

This value must be regarded as approximate because of possible errors in relating oscilloscopically recorded traces to conventionally recorded values of potential and because of the difficulty of obtaining an extremely accurate value from the oscilloscope abscissa. Nevertheless, the results serve to indicate that the following reaction is very rapid, an aspect also observed in the structually similar carbazole systems.[4]

The nature of the species finally formed in the electrochemical reaction was determined by spectral characterization of the mass electrolysis product. In general, as evidenced by the data in the Experimental Section, the spectral properties of 1 and of its electrolysis product are quite similar, suggesting similar structures for the two compounds. From the mass spectral data (peak at m/e 536), it appears that the compound is indeed a dimer of 1, with two hydrogens lost in the coupling reaction. The composition $C_{40}H_{28}N_2$ indicates that the electrolysis product is a simple dimer; in other words, apparently no further oxidation or gross structural changes in the basic indole nucleus have occurred. The infrared spectral data also support this conclusion, there being no bands present in the carbonyl region (1650–1800 cm^{-1}).

Especially useful in characterizing the dimer was its ^{13}C NMR spectrum. The spectral data for the dimer are presented in Table I, along with data for 1 and for 2,3,3-trimethylindolenine,[8] a model compound for the proposed dimer structure (cf. 2, Figure 2c). The assignments for 1 were made on the basis of those for 2- and 3-phenylindole[9] as well as for various methylated indole derivatives.[10] It should be noted that there is some ambiguity regarding the assignments for both the 4 and 6 carbons and the 2 and 9 carbons, the reverse assignments also being possible. The corresponding 2 and 9 carbons, as well as the 4, 6, and 7′ carbons, in the dimer also cannot be given with great certainty because several resonances in the 133–136-ppm and 120–122-ppm regions, respectively, were present in the dimer spectrum. The same situation holds for the 8 position in both 1 and 2 since this resonance usually occurs at approximately 126 ppm[10] and there are several

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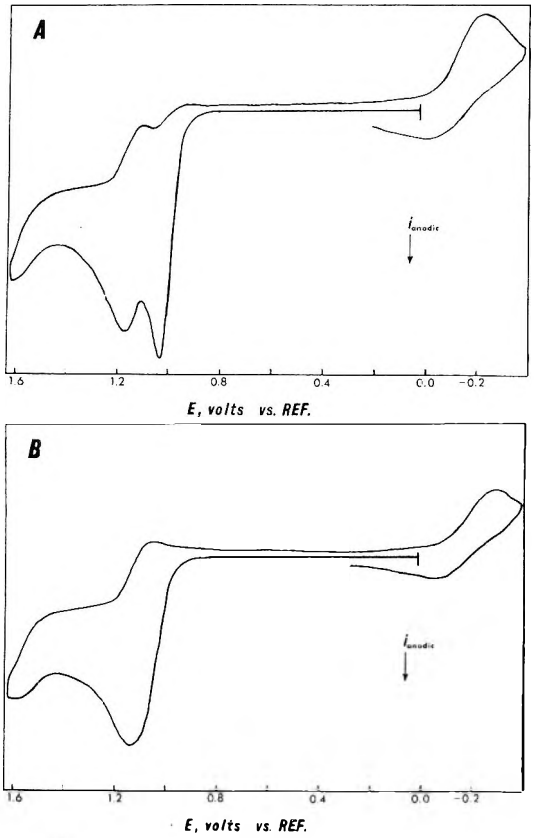

Figure 1. (A) Cyclic voltammogram of 2,3-diphenylindole (1.0×10^{-3} M) in MeCN/TEAP at platinum, sweep rate = 100 mV/s. (B) Cyclic voltammogram of the isolated electrolysis product under the same conditions.

closely spaced resonances in this region of the spectra. Tabular values given only to the nearest integral number imply the existence of several resonances in close proximity to one another near the value indicated.

As seen from the data in Table I, the spectrum of the dimer contained many of the peaks present in **1** as well as several other peaks corresponding to carbon atoms in widely different environments from those in **1**. Thus, the dimer is obviously unsymmetrical, one half of it consisting of an apparently intact **1** moiety. The furthest peaks downfield (181.9 ppm) and upfield (72.1 ppm) suggest a change in structure in the other half of the dimer in which one carbon is now doubly bonded to either an oxygen or a nitrogen atom while another carbon now becomes saturated. Since evidence has already been presented against the presence of a carbonyl group, it appears that the most likely explanation for the ^{13}C NMR spectral data is a shift of the double bond in the pyrrole ring from the 2,3 position to the 1,2 position, thus forming an indolenine. A comparison of the resonances of 2,3,3-trimethylindolenine with those in the nonindole half of the dimer supports the characterization of this portion of the dimer as having an indolenine structure since the two sets of resonances can be seen to consist of rather similar values. The assignments for the resonances in the indolenine half of the dimer were then made on the basis of those given for the model compound.

The formation of the indole–indolenine dimer may be visualized (Figure 2) as the coupling of two **1** cation radicals, the resonance structures indicating positions of high reactivity, to form the dimer **2** with elimination of two protons. The reaction at the C-3 position of the cation radical is supported not only by the creation of an apparently aliphatic carbon atom (appearance of upfield peak at 72.1 ppm) but also by the fact that in many cases the reactivity of indoles is centered at the 3 position.[11]

Table I. ^{13}C NMR Spectral Data of 2,3-Diphenylindole (1) and Its Electrolysis Product (2)

Carbon assignments	Chemical shifts, ppm from Me_4Si		
	1[d]	2[a]	2,3,3-Trimethylindolenine[b]
2	135.7	135.8	189.0
3	114.9	114.6 s	—
4	120.3	121 d[c]	123.4
5	122.5	—	129.2
6	119.5	119.6 d	126.8
7	110.8	110.8 d	121.2
8	—	—	147.9
9	134.9	134.8	155.6
2′		181.9 s	
3′		72.1 s	
4′		123.8 d	
5′		129	
6′		126–127 d[c]	
7′		121 d[c]	
8′		148.9 s	
9′		153.6 s	

[a] For numbering scheme of dimer see Figure 2. Registry no.: **2**, 64728-25-2. [b] In Me_2SO; original data converted using $\delta_c^{CS_2}$ 192.8. [c] All of the peaks in each of the regions indicated appeared to be doublets under SFORD conditions. [d] Registry no.: **1**, 3469-20-3.

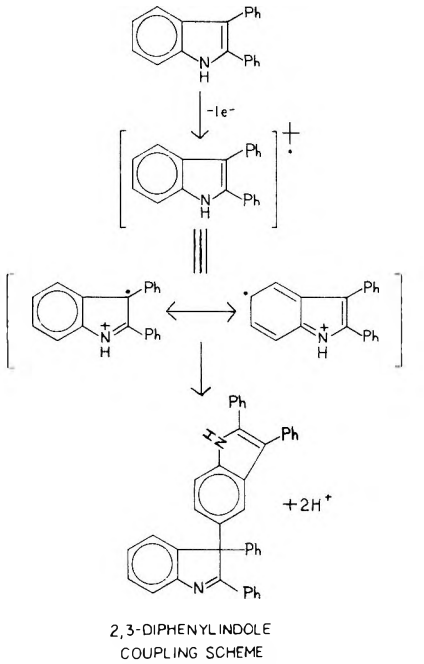

Figure 2. Proposed coupling scheme for the formation of the indole–indolenine dimer (**2**).

That the position of substitution in the indole nucleus is in the benzene ring of the molecule was inferred from the fact that a resonance corresponding to the 3 position was still present in the ^{13}C NMR spectrum of **2**, suggesting that the pyrrole ring in this half of the dimer remained unaltered. Further, based on considerations of greatest electron density (from HMO calculations) in the indole ring at the 1, 3, 5, and 7 positions,[3] the 5 and 7 positions now seemed to be most likely positions for substitution. A single-frequency off-resonance ^1H-decoupled (SFORD) ^{13}C NMR study of **2** indicated that the 4, 6, and 7 positions were unsubstituted, the resonances corresponding to these positions being split into doublets in the SFORD study, as indicated in Table I. Thus, these positions apparently are not those at which coupling occurs, leaving the

5 position as the only remaining possibility. Indeed, the ^{13}C NMR spectrum of **2** contained no resonances within ±1 ppm of 122.5 (C-5 in **1**), again suggesting that coupling involves the 5 position since this process should shift the resonance considerably downfield. The exact value of this shift is rather uncertain since there still remain unassigned resonances in the spectrum of **2** both at 140.3 ppm and (one resonance) in the 135-ppm region. To make a meaningful choice between these two values, a model compound involving a similarly substituted indole would be necessary.

The infrared data also support the structure assignment since the diminished intensity of the N–H band (3400 cm^{-1}) in the product spectrum suggests that only one of the dimer components contains the N–H functionality. The band at 1520 cm^{-1} (6.58 μm), assigned to the imine stretching vibration of the indolenine nucleus, falls somewhat outside the usual range for this vibration (6.10–6.30 μm), but shifts to longer wavelengths have been noted when the double bond is further conjugated.[12]

The UV spectra of **1** and its dimer **2** are, as stated before, quite similar. However, the molar absorptivities of the two compounds at approximately 310 nm are quite different, that for the dimer **2** being almost twice that for **1**. This would seem to be evidence for a dimeric structure consisting of two coupled indole rings until one considers that the UV spectrum for 3,3-dimethyl-2-phenylindolenine, which should be very similar to that for the indolenine in the proposed dimer **2**, also exhibits an absorbance at 306 nm ($\log a = 4.177$).[13] Thus, due to the similarity of absorbance characteristics, both in wavelength and in strength, of the indole and indolenine chromophores in this instance, it is not possible to ascertain whether the electrolysis product of **1** is an indole–indole or an indole–indolenine dimer on the basis of the UV spectral data.

Finally, the mass spectrum of the dimer may now be explained as arising from the loss of a phenyl substituent to give a fragment at *m/e* 459, followed by loss from this fragment of either benzonitrile or HCN to give fragments at *m/e* 356 or *m/e* 432, respectively, these latter eliminations probably depending upon which phenyl (2 or 3) substituent is lost in the first elimination. Fragments resulting from the loss of these entities have been previously noted in the mass spectrum of **1**.[14] The peak at *m/e* 268 would, of course, correspond to cleavage of the dimeric bond.

Experimental Section

Melting points are uncorrected. The IR spectra were taken with a Perkin-Elmer Model 621 grating infrared spectrophotometer. The ^{13}C NMR spectra were recorded in $CDCl_3$ on a JEOL JNM-PS-100 instrument. A Hitachi Perkin-Elmer RMU-6 mass spectrometer was used to obtain a mass spectrum of **1**, while the spectrum of the electrolysis product of **1** was recorded with a Hewlett-Packard 5930A mass spectrometer. With both instruments, a direct solid probe was used for sample introduction, the ionization energy being 70 eV. UV spectra were taken with a Cary 15 spectrometer.

1 was prepared by the Bischler indole synthesis, as outlined by Szmuszkovicz et al.,[15] and was purified by column chromatography on Fisher activated alumina followed by recrystallization first from ethanol and then from ether–hexane to give colorless crystals, mp 122–123 °C (lit.[16] 123 °C); IR (KBr) 3400 s (NH), 1599 cm^{-1} m (C=C); UV max (MeOH) 308 nm ($\log \epsilon$ 4.24), 250 (4.42); mass spectrum, *m/e* 269 (M^+, base peak). These spectral data were in good agreement with the published spectral data.[14,17]

The electrochemical instrumentation used to obtain cyclic voltammetric and chronoamperometric data has been described previously.[4] A Hewlett-Packard 7045A X-Y recorder was used with this instrument.

Mass electrolyses and coulometric determinations were carried out at controlled potential using a Wenking Model 68 FR 0.5 potentiostat. Electrolyses were at a platinum gauze working electrode in acetonitrile with 0.1 M tetraethylammonium perchlorate (TEAP) as supporting electrolyte, using a SCE (NaCl) reference electrode. The same medium was used for obtaining the cyclic voltammetric data. The purification of acetonitrile and TEAP have been described previously.[18] Two types of electrolysis cells were used in this study; one was a standard "H-type" two-compartment Sargent cell and the other was a 500-mL beaker with the auxiliary electrode compartment separated from the working electrode compartment by a porous ceramic cup. These cells gave equivalent results. The current passed during the electrolysis was integrated by voltage–frequency conversion of the *IR* drop across a standard resistor in the auxiliary electrode circuit, followed by counting of the frequency pulses.

Preparative Electrolysis of 2,3-Diphenylindole (1). An approximately 9 mM solution of **1** in acetonitrile was electrolyzed at a potential about 100 mV anodic of the primary oxidation wave in the cyclic voltammogram of **1**, the electrolysis being continued until 1 equiv of electricity had been passed through the cell ($n = 1$). After oxidation the solution was reduced to a potential of −0.6 V in order to reduce any protons formed in the oxidation and to take any electrolysis products back to the neutral form.

The electrolysis product was obtained as a benzene solution by either extracting the evaporated electrolysis mixture (leaving as residue the product and TEAP) or partitioning the electrolysis mixture between benzene and deionized water. Evaporation of the benzene solution yielded the same crude product in either case. Chromatography of this product on activated alumina (Matheson Coleman and Bell) showed the presence of only one component, the purified yield being 90–95%. Recrystallization from ethanol–ether yielded small light yellow crystals, mp 225–226 °C; IR (KBr) 3400 m (NH), 1595 m (C=C), 1520 cm^{-1} m–w (C=N); UV_{max} (MeOH) 314 nm ($\log \epsilon$ 4.49), 257 (4.67); mass spectrum, *m/e* 536 (M^+, 100), 459 (14), 432 (21), 356 (25), 268 (14). Anal. Calcd for $C_{40}H_{28}N_2$: C, 89.52; H, 5.26; N, 5.22. Found: C, 89.33; H, 5.29; N, 5.18.

Acknowledgment. We would like to acknowledge the helpful assistance of Mr. Courtney Pape and Dr. Richard Cox in obtaining and interpreting the ^{13}C NMR spectra. Special thanks are due to Dr. R. N. Adams and Dr. D. E. Smith for their support and encouragement.

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3-Methyl-2,1-benzisoxazolium, Benzisothiazolium, and Indazolium Salts as New Active-Methyl Compounds

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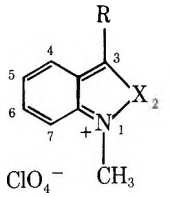
The 3-CH_3 group of the title salts has been shown to be quite reactive (nucleophilic) by condensing with aldehydes, ketones, orthoesters, and diazonium salts, forming new styryl, cyanine, and azo dyes, respectively. The 3 position of the title salts has also been found to be electrophilic, and the consequence of this bifunctionality (adjacent nucleophilic and electrophilic centers) has been utilized in the syntheses of potential thermochromic materials.

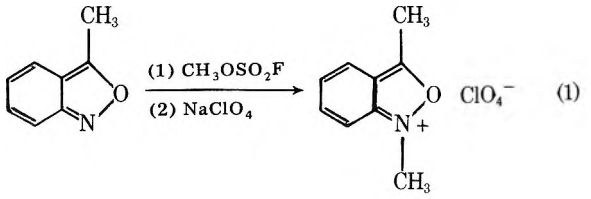
Recently both Olofson and Nakagawa have utilized the exceptionally low electron density at the carbon atom in the 3 position of *N*-alkyl-2,1-benzisoxazolium salts 1 as a synthon



1a, R = H; X = O
b, R = CH_3; X = O
c, R = CH_3; X = S
d, R = CH_3; X = NCH_3

for both the highly strained benzoazetinone and the well-known tranquilizer Valium.[1,2] Olofson utilized the high acidity of the C-3 proton for his synthesis and Nakagawa the electrophilic behavior of the C-3 carbon itself toward attack by nucleophiles. We report now the activation of the methyl group attached to the 3 position of 1,3-dimethyl-2,1-benzisoxazolium salt **1b** and its utility as a *nucleophile* in dye-forming reactions. Similarly, we also report and compare the reactivity of the corresponding 3-methyl-2,1-benzisothiazolium and indazolium salts (**1c, 1d**).

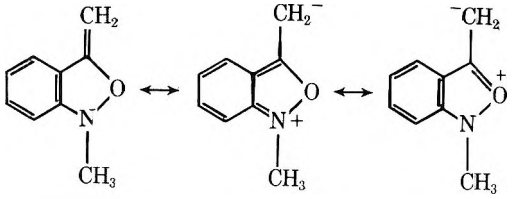
1,3-Dimethyl-2,1-benzisoxazolium perchlorate (**1b**) was prepared according to eq 1 in the expectation that it would



(1)

1b

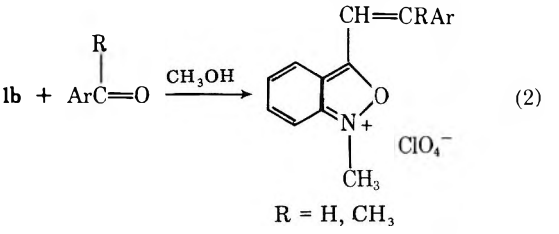
react as a nucleophile (high electron density) at the C-3 methyl carbon atom and an electrophile (low electron density) at the C-3 ring carbon atom. In fact, resonance contributors 2 and



anhydro base 2 3

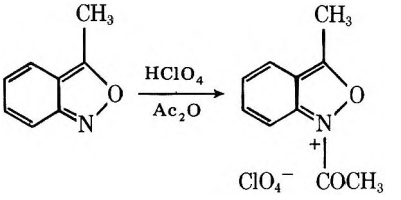
3 of the anhydro base of **1b** show that the exocyclic carbon atom at C-3 is not only the terminal atom of a vinylogous enamine but of a vinyl ether as well; therefore, considerable negative charge should be located at this site as shown by resonance form **2.**

We have found that both 3-methyl-2,1-benzisoxazole and 1,3-dimethyl-2,1-benzisoxazolium perchlorate (**1b**) condense with aromatic aldehydes and ketones to form highly colored styryl derivatives as shown in eq 2 and 3. The condensation

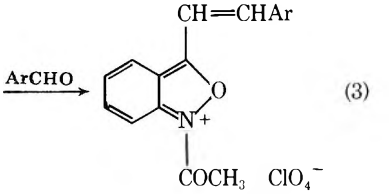


(2)

R = H, CH_3



4



(3)

of **1b** proceeds in the absence of added base, whereas 3-methyl-2,1-benzisoxazole condenses with aromatic aldehydes in a strong acid medium such as $HClO_4$–Ac_2O, probably via the *N*-acetyl derivative **4** (eq 3).

The mechanism for the formation of the styryl compounds shown in Table I probably involves the anhydro base, which is in rapid equilibrium with the protonated form (**1b**). In methanol–D_2O the hydrogen–deuterium exchange of the C-3 methyl protons of **1b** is complete within 15 min. This rapid rate of exchange with deuterium oxide as well as the rates of reaction of **1b** with aromatic aldehydes is noteworthy when compared with the much slower reaction rates of the corresponding benzthiazole and indazole derivatives which will be discussed later.

1,3-Dimethyl-2,1-benzisoxazolium perchlorate (**1b**) also reacts as a nucleophile via the C-3 methyl group with diazonium salts (eq 4). The product **5,** formally the *p*-nitrophenylhydrazone of 1-methyl-3-formyl-2,1-benzisoxazolium perchlorate, deprotonates easily in basic medium yielding the azo derivative **6.**

Cyanine dyes **7** and **8** were also synthesized from **1b** to illustrate its utility as a dye-forming reagent. With triethyl orthoformate the symmetrical cyanine dye **7** is readily formed, whereas **1b** and Fischer's aldehyde readily yield the unsymmetrical cyanine **8.**

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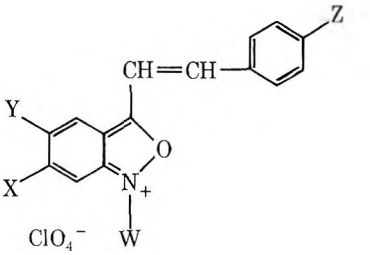
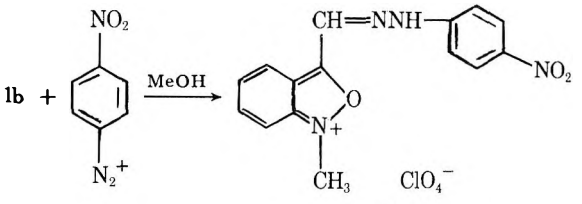
Table I. 3-Styryl-2,1-benzisoxazolium Salts

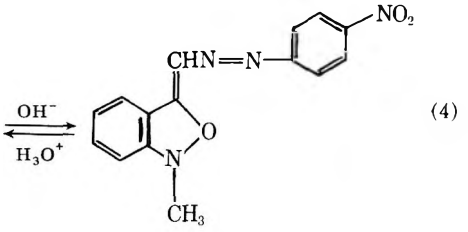


Compd	Registry no.	W	X	Y	Z	λ_{max} (CH_3CN), nm	(log ε)	Yield, %	Mp, °C
20	64872-09-9	CH_3	H	H	H	414			
21	64872-11-3	CH_3	H	H	OH	465	(4.49)	86	210 dec
22	64872-13-5	CH_3	H	H	$N(CH_3)_2$	584	(4.77)	100	173-174 dec
23	64872-15-7	CH_3	H	NO_2	$N(CH_3)_2$	635	(4.82)	62	177-178 dec
24	64872-17-9	CH_3	OCH_2	O	$N(CH_3)_2$	530	(4.52)	80	192 dec
25	64872-19-1	$COCH_3$	H	H	$N(CH_3)_2$	650	(4.45)	19	174 dec
26	64872-21-5	$C(CH_3)_3$	H	H	$N(CH_3)_2$	590	(4.99)	95	130-131 dec



5

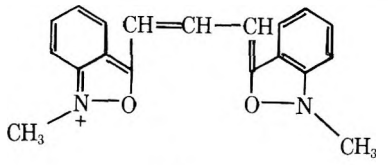
λ_{max} (CH_3CN) 485 nm



6

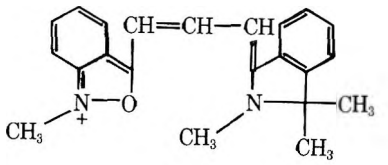
λ_{max} (CH_3CN) 555 nm

Reaction of dimethyl salt **1b** with base (Et_3N) instantaneously gives dimer **9**; further addition of base deprotonates



7

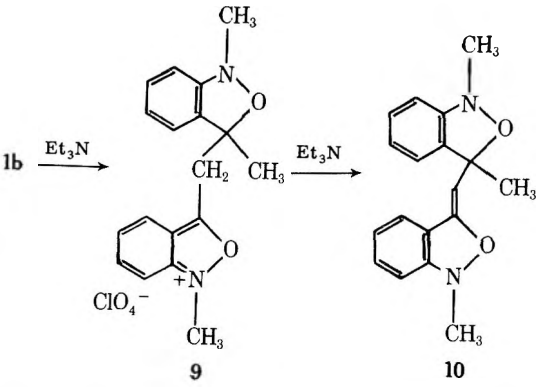
λ_{max} (CH_3CN) 617 nm



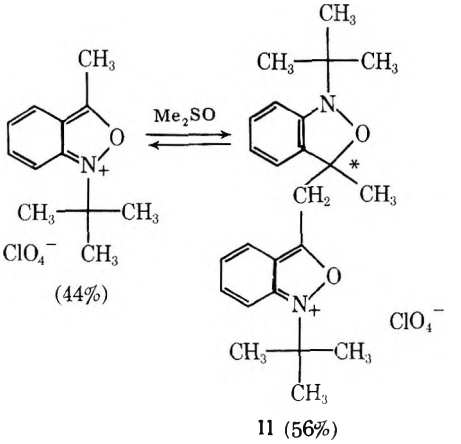
8

λ_{max} (CH_3CN) 557 nm

the dimer yielding anhydro base **10**, itself a dye-forming agent. The entire reaction sequence can be followed conveniently by NMR. Dimer formation is best accomplished simply by dissolving **1b** in Me_2SO (rather than treating with Et_3N) followed by precipitation with water. Structure **9** for the dimer is supported by spectral evidence and microanalysis. However, we were concerned that the diastereotopic methylene protons in **9** appeared only as a broadened singlet rather than an AB quartet in the NMR spectrum. Examination by NMR of dimer **11** formed from the *N-tert*-butyl analogue of **1b** in Me_2SO-d_6 shows that a facile equilibrium is formed between monomer and dimer, but more importantly, the methylene



9 10



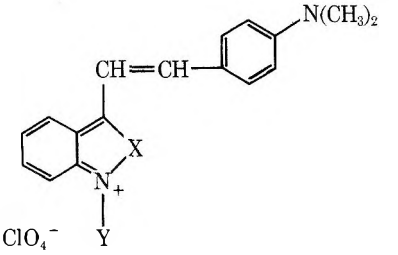
(44%)

11 (56%)

group of the dimer (**11**) appears as an AB quartet. Apparently the broadened singlet found for the methylene protons in **9** is fortuitous.

For comparison purposes, we prepared 3-methyl-2,1-benzisothiazolium and indazolium salts **1c** and **1d** to ascertain whether they are similar in reactivity to **1b**. A priori, based only on simple electronegativity differences, one would predict an increase in electron density at the C-3 carbon atom if oxygen is replaced with sulfur or nitrogen. Thus, the reactivity

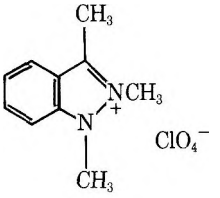
Table II. Effect of Heteroatom and N-Substituent on Styryl-2,1-benzisoxazolium Dyes



Compd	Registry no.	X	Y	λ_{max} (CH_3CN), nm	(log ϵ)	Mp, °C	Yield, %
20		O	CH_3	585	(4.77)	173-174 dec	100
27	64872-23-7	S	CH_3	592	(4.58)	255-256 dec	92
28	64872-25-9	NCH_3	CH_3	428	(4.55)	245-247 dec	40
25		O	$COCH_3$	650[a]	(4.45)	174 dec	19
29	64872-27-1	S	$COCH_3$	705[a]	(4.74)	212-213 dec	60

[a] In CH_2Cl_2 as solvent.

of the C-3 carbon atom (electrophilic site) and its bonded methyl group (nucleophilic site) should be less in **1c** and **1d** compared to **1b**. Furthermore, **1d** should be less reactive than **1c** since it has a more energetically favorable resonance form, **12**. In **12** the benzenoid character of one ring has been restored,

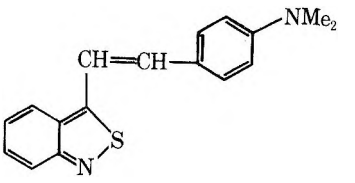


12

while **1c** still possesses an orthoquinoid electronic structure. In fact, **1d**'s reactivity should be similar to that of a methylated indoxazene.

Although the reaction rates are much slower, the isothiazolium and indazolium salts **1c** and **1d** undergo nucleophilic addition with aromatic aldehydes in a manner analogous to the behavior of **1b** (eq 2). For example, with *p*-*N*,*N*-dimethylaminobenzaldehyde, **1b** gave styryl dye **22** in 99% yield in less than 1 min at room temperature, benzisothiazolium **1c** gave a 92% yield of **27** after 30 min at reflux, and indazolium **1d** gave a 40% yield of **28** only after 24 h at reflux temperature (methanol). Also, **1c** shows no hydrogen–deuterium exchange at the C-3 methyl group after 72 h in MeOH–D_2O. A comparison of styryl dyes **22**, **27**, and **28** (Table II) shows the effect of heteroatom substitution on the long-wavelength absorption maxima. Exchange of oxygen by sulfur results in a small bathochromic shift, whereas substitution of nitrogen gives a large hypsochromic shift. Perhaps a resonance form such as **12** is becoming more important. Exchange of the *N*-methyl group for acetyl also produces a large bathochromic shift in absorption wavelength (Table II). In fact, the benzisothiazolium dye **29** shows a shift of 113 nm when the N substituent is changed from methyl to acetyl. Evidently, the chromophore has changed dramatically; however, treatment of the acetyl dyes with any base instantaneously yields merocyanine dyes such as **13**, indicating no gross structural differences among dyes from **1b**, **1c**, and 3-methyl-2,1-benzisoxazole.

As indicated earlier, the C-3 position of **1b** should be the site for nucleophilic attack. Several reports have appeared[1-3] which describe such chemistry; consequently, we will limit our discussion to new chemistry involving nucleophilic attack and subsequent reactions of **1b** and **1c**. 1,3-Dimethyl-2,1-benzisoxazolium perchlorate is unique in that the 3-methyl group



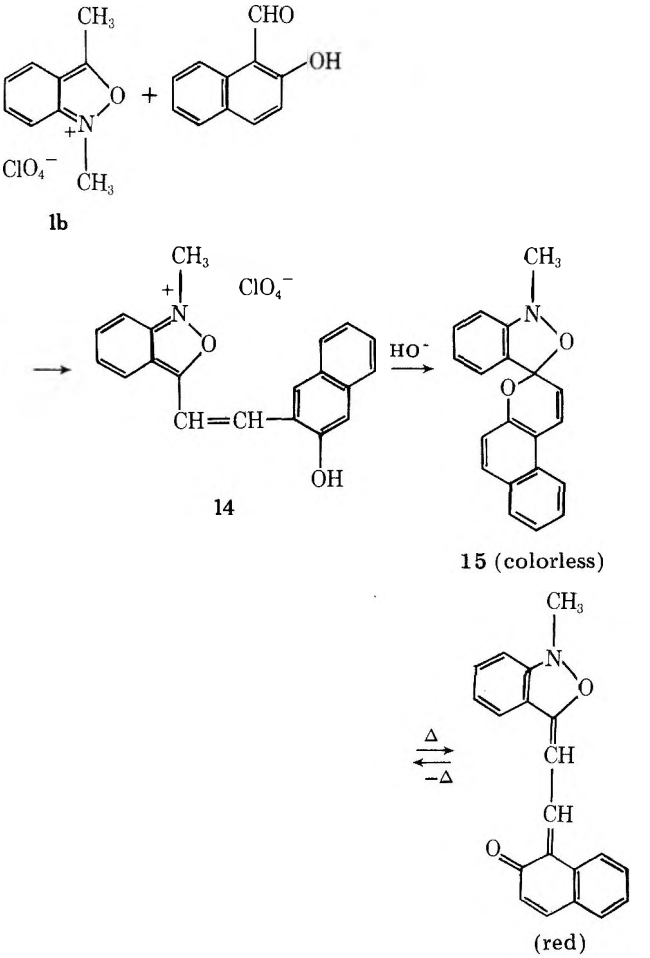
13

λ_{max} (CH_3CN) 435 nm

can serve as a nucleophile and the C-3 carbon as an electrophile in successive reactions.

An example of its bifunctionality is shown in Scheme I. The

Scheme I



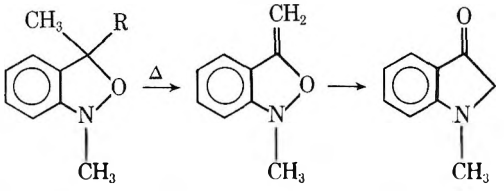
1b

14

15 (colorless)

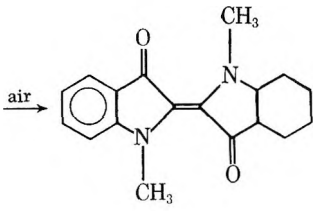
(red)

Scheme II



16 17

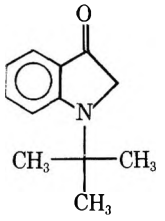
R = CN, N_3, OCH_3



18

styryl dye **14**, formed from 2-hydroxy-1-naphthaldehyde, cyclizes in base to the thermochromic spiropyran **15**. Dimerization of **1b** to dimer **9** is another example of the bifunctional behavior of **1b**.

Cyanide, azide, and methoxide ions react with **1b** to give 3-substituted benzisoxazolines (**16**, Scheme II). Similar reactions have been described by Olofson;[1] however, subsequent reactions of our resulting benzisoxazolines are quite different.Whereas Olofson's benzisoxazolines undergo thermal ring opening to o-acyl anilines, our derivatives (**16**) lose HCN, HN_3, or CH_3OH on heating (130 °C) to yield what is believed to be *N,N'*-dimethylindigo **18** (identical UV–vis spectrum).[4] We propose that the formation of indigo **18** arises via the mechanism outlined in Scheme II. Support for the mechanism is based on the following information: (1) the formation of HCN or HN_3 was observed spectroscopically, (2) *N-tert*-butyl-3-cyano-3-methyl-2,1-benzisoxazoline yielded *N-tert*-butylindoxyl **19** on heating to 130 °C, (3) pyrolysis of 3-cyano-



19

1,3-dimethyl-2,1-benzisoxazoline under a nitrogen atmosphere gave a compound whose NMR spectrum is consistent with *N*-methylindoxyl **17**, and (4) the oxidation of **17** to indigo **18** is a known reaction.[5]

Experimental Section

Melting points are uncorrected. IR spectra were obtained with a Perkin-Elmer 137 spectrophotometer and NMR spectra with a Varian T-60 spectrometer using Me_4Si as an internal standard. UV spectra were taken with a Cary 17 spectrophotometer. All compounds included in this paper gave satisfactory microanalyses and IR, NMR, UV–vis, and mass spectra consistent with the proposed structures.

***N*-Alkyl-2,1-benzisoxazolium Salts. Typical Procedures. 1,3-Dimethyl-2,1-benzisoxazolium Perchlorate (1b):** To a solution of 3-methyl-2,1-benzisoxazole (13.3 g) in diethyl ether (100 mL) was added methyl fluorosulfonate (12.0 g) in 1 portion. The reaction mixture was stirred for 1 h at room temperature. The precipitated white solid was collected, washed with diethyl ether, and then dissolved in a minimum amount of water. To this aqueous solution was added sodium perchlorate monohydrate (15.0 g) dissolved in water (20 mL). A white crystalline solid precipitated immediately and was collected and washed with cold water. Recrystallization from hot water gave 21.9 g (89%) of 1,3-dimethyl-2,1- benzisoxazolium perchlorate: mp 152–153 °C (explodes at 154 °C); NMR (CD_3CN) δ 7.8 (m, 4 H), 4.4 (s, 3 H), 3.0 (s, 3 H); IR (KBr) 1630, 1500, 1420, 1090, 755 cm^{-1}; UV λ_{max} (H_2O) 335 nm (log ϵ 3.54), 201 (4.40).

Anal. Calcd for $C_9H_{10}ClNO_5$: C, 43.7; H, 4.1; N, 5.7. Found: C, 44.1; H, 4.0; N, 5.9.

***N*-*tert*-Butyl-3-methyl-2,1- benzisoxazolium Perchlorate:** Nitromethane (20 mL) containing 3-methyl-2,1-benzisoxazole (13 g), *tert*-butyl alcohol (8 g), and 70% perchloric acid (16 g) was stirred at room temperature for 48 h. To the solution was added diethyl ether (200 mL), and the precipitated white solid was collected and washed with diethyl ether. Recrystallization from methanol gave *N-tert*-butyl-3-methyl-2,1- benzisoxazolium perchlorate (20 g): mp 183 °C dec; NMR (CD_3CN) δ 8.0 (m, 3 H), 7.4 (m, 1 H), 3.0 (s, 3 H), 1.9 (s, 9 H); IR (KBr) 1625, 1450, 1090, 760 cm^{-1}; UV λ_{max} (H_2O) 335 nm (log ϵ 3.72), 268 (3.68), 205 (4.43).

Anal. Calcd for $C_{12}H_{16}ClNO_5$: C, 49.7; H, 5.6; N, 4.8. Found: C, 49.4; H, 5.6; N, 5.1.

1,3-Dimethyl-2,1-benzisothiazolium Perchlorate (1c): 83%; mp 161–162 °C; NMR (CD_3CN) δ 3.2 (s, 3 H), 4.4 (s, 3 H), 8.0 (m, 4 H); UV λ_{max} (CH_3CN) 350 nm (log ϵ 3.69), 300 (4.09).

Anal. Calcd for $C_9H_{10}ClNO_4S$: C, 41.0; H, 3.8; N, 5.3; S, 12.2. Found: C, 40.9; H, 3.7; N, 5.5; S, 12.5.

1,2,3-Trimethylindazolium Perchlorate (1d): 75%; mp 219–220 °C; NMR (CD_3CN) δ 2.8 (s, 3 H), 4.2 (s, 6 H), 7.8 (m, 4 H).

Anal. Calcd for $C_{10}H_{13}ClN_2O_4$: C, 46.1; H, 5.0; N, 10.8. Found: C, 46.4; H, 5.1; N, 10.6.

Condensation of 1b–d with Aromatic Aldehydes, Ketones, Diazonium Salts, and Orthoesters. Typical Procedures. 3-(*p*-Dimethylaminostyryl)-1-methyl-2,1-benzisoxazolium Perchlorate (22): *p*-Dimethylaminobenzaldehyde (1.5 g, 0.01 mol) and **1b** (2.5 g, 0.01 mol) were dissolved in methanol (25 mL) and refluxed briefly. Cooling followed by filtration gave 3.7 g (100%) of blue crystals: mp 173–174 °C dec; NMR (CF_3CO_2H) δ 8.3–7.5 (m, 10 H), 4.5 (s, 3 H), 3.5 (s, 6 H).

Anal. Calcd for $C_{18}H_{19}ClN_2O_5$: C, 57.1; H, 5.1; N, 7.4. Found: C, 57.1; H, 4.8; N, 7.7.

1,3-Dimethyl-2,1-benzisothiazolium perchlorate (**1c**) and 1,2,3-trimethylindazolium perchlorate (**1d**) required 0.5 and 24 h reflux times, respectively.

3-(*p*-Dimethylamino-α-methylstyryl)-1-methyl-2,1-benzisoxazolium Perchlorate (eq 2, R = CH_3, Ar = C_6H_5): *p-N,N*-Dimethylaminoacetophenone (1.6 g, 0.01 mol) and **1b** (2.5 g, 0.01 mol) were dissolved in methanol (50 mL) and refluxed for 1 h. Cooling followed by filtration gave 3.6 g (92%) of blue crystals: mp 168–169 °C; NMR (CF_3CO_2H) δ 7.9–7.0 (m, 9 H), 4.2 (s, 3 H), 3.2 (s, 6 H), 2.5 (s, 3 H); UV–vis λ_{max} (CH_3CN) 574 nm (log ϵ 4.71), 305 (4.01).

Anal. Calcd for $C_{19}H_{21}ClN_2O_5$: C, 58.1; H, 5.4; N, 7.1. Found: C, 57.9; H, 5.4; N, 7.0.

3-Formyl-1-methyl-2,1-benzisoxazolium Perchlorate *p*-Nitrophenylhyrazone (5) and Its Conversion to 6: *p*-Nitrobenzenediazonium tetrafluoroborate (0.24 g, 1 mmol) and **1b** (0.25 g, 1 mmol) were dissolved in methanol (30 mL), and the solution was stirred at room temperature for 18 h. Filtration gave 0.27 g (68%) of red crystals: mp 216 °C dec; UV–vis λ_{max} (CH_3CN) 485 nm (log ϵ 4.48); IR (KBr) 3175 (NH), 1620 (C=N), 1090 cm^{-1} (ClO_4).

Anal. Calcd for $C_{15}H_{13}ClN_4O_7$: C, 45.4; H, 3.3; N, 14.1. Found: C, 45.2; H, 3.4; N, 14.0.

A solution of **5** (1.0 g) in methylene chloride (100 mL) was stirred overnight with 0.1 N NaOH (100 mL). Chromatography of the organic phase on silica gel eluting with EtOAc–benzene (25:75) gave **6** as a cherry-red solid (0.51 g, 68%): mp 250–252 °C; UV–vis λ_{max} (CH_3CN) 555 nm (log ϵ 4.06), 395 (4.15).

Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.8; H, 4.1; N, 18.9. Found: C, 60.4; H, 4.2; N, 18.9.

1-Methyl-2,1-benzisoxazolium Trimethinecyanine Perchlorate (7): **1b** (0.5 g, 0.02 mol) and triethyl orthoformate (15 mL) were heated on a steam bath for 1 h. The solution was cooled, and 0.3 g (75%) of blue crystalline solid was collected by filtration: mp 138 °C dec; UV–vis λ_{max} (CH_3CN) 615 nm (log ϵ 4.56).

Anal. Calcd for $C_{19}H_{17}ClN_2O_6$: C, 56.4; H, 4.2; N, 6.9. Found: C, 56.3; H, 4.0; N, 6.6.

***N*-Acetyl-3-(*p*-*N,N*-dimethylaminostyryl)-2,1-benzisothiazolium Perchlorate (29):** 3-Methyl-2,1-benzisothiazole (1.5 g, 0.01 mol) and acetic anhydride (15 mL) were cooled to −20 °C and treated dropwise with 70% perchloric acid (1.5 g, 0.11 mol). This procedure was followed by the addition of *p*-dimethylaminobenzaldehyde (1.5 g, 0.01 mol) at room temperature, and the resulting solution soon deposited metallic green crystals. Filtration yielded 2.5 g (60%) of material: mp 212–213 °C dec; UV–vis λ_{max} (CH_2Cl_2) 705 nm (log ϵ

4.74), 660 (4.47): IR (KBr) 1724 (C=O), 1613 (C=N), 1087 cm^{-1} (ClO_4); NMR (TFA) δ 8.4–7.4 (m, 10 H), 3.3 (s, 6 H), 2.9 (s, 3 H).

Anal. Calcd for $C_{19}H_{19}ClN_2O_5S$: C, 54.0; H, 4.5; N, 6.6; S, 7.6. Found: C, 53.7; H, 4.8; N, 6.8; S, 7.5.

***N*-Acetyl-3-(*p*-*N*,*N*-dimethylaminostyryl)-2,1-benzisoxazolium Perchlorate (25):** This was prepared as above from 3-methyl-2,1-benzisoxazole in 20% yield: mp 174 °C dec; UV–vis λ_{max} (CH_2Cl_2) 650 nm (log ε 4.45), 605 (4.20); IR (KBr) 1724 (C=O), 1081 cm^{-1} (ClO_4).

Anal. Calcd for $C_{19}H_{19}ClN_2O_6$: C, 56.1; H, 4.7; N, 6.9. Found: C, 55.8; H, 5.0; N, 7.0.

Dimerization of 1b with Me_2SO and Deprotonation with Triethylamine to 10: A solution of **1b** (1.0 g, 0.004 mol) in dimethyl sulfoxide (5 mL) was stirred for 15 min. Water (15 mL) was added, and the orange solid was collected by filtration and recrystallized from methanol, giving 0.7 g (44%) of **9**: mp 140 °C dec; IR (Nujol) 1640 (C=N), 1090 cm^{-1} (ClO_4); NMR (TFA) δ 8.4–7.5 (m, 8 H), 4.5 (s, 3 H), 4.3 (br s, 2 H), 3.8 (s, 3 H), 2.1 (s, 3 H).

Anal. Calcd for $C_{18}H_{19}ClN_2O_6$: C, 54.8; H, 4.9; N, 7.1. Found: C, 55.0; H, 5.1; N, 7.2.

The NMR spectrum of *N*-*tert*-butyl-3-methyl-2,1-benzisoxazolium perchlorate in Me_2SO-d_6 shows it is in a 44:56 (dimer) equilibrium with dimer **11**: NMR (Me_2SO-d_6) δ 8.3–6.8 (aromatic), 4.2 (d, J = 14 Hz, HCH dimer), 3.9 (d, J = 14 Hz, HCH dimer), 3.1 (s, $=CCH_3$ monomer), 1.9 (s, $N^+C(CH_3)_3$ monomer), 1.8 (s, CCH_3 dimer), 1.7 (s, $N^+C(CH_3)_3$ dimer), 1.0 (s, $NC(CH_3)_3$ dimer). Addition of D_2O results in a loss of resonance at δ 4.2, 3.9, 3.1, and 1.8, indicating the two species are in equilibrium.

Dimer **9** (1 g) was suspended in methylene chloride (25 mL), and triethylamine was added until the color was discharged. The resulting solution was extracted three times with water (25-mL portions), dried over anhydrous $MgSO_4$, filtered, and evaporated under vacuum. The residual pale yellow oil **10** (0.5 g) which slowly crystallized was analytically pure: NMR ($CDCl_3$) δ 7.2–6.6 (m, 8 H), 5.1 (s, 1H), 3.1 (s, 6 H), 1.9 (s, 3 H); IR (KBr) 1690 cm^{-1} (C=C).

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.4; H, 6.2; N, 9.5. Found: C, 73.2; H, 6.1; N, 9.4.

3-(*p*-Dimethylaminostyryl)-2,1-benzisothiazole (13): *N*-Acetyl-3-(*p*-dimethylaminostyryl)-2,1-benzisothiazolium perchlorate (1 g) was stirred for 6 h with triethylamine (10 mL), water (50 mL), and diethyl ether (100 mL). The organic phase was separated and dried ($MgSO_4$). Evaporation under vacuum yielded 0.6 g of **13**, a red yellow solid: mp 150–152 °C; UV–vis λ_{max} (CH_3CN) 435 nm (log ε 4.41), 308 (4.15); NMR ($CDCl_3$) δ 7.6–6.5 (m, 10 H), 3.0 (s, 6 H).

Anal. Calcd for $C_{17}H_{16}N_2S$: C, 72.8; H, 5.8; N, 10.0; S, 11.4. Found: C, 72.6; H, 5.8; N, 9.8; S, 11.3.

Cyclization of 14 to Spiropyran 15: 2-Hydroxy-1-naphthaldehyde (1.7 g, 0.01 mol) and **1b** (2.5 g, 0.01 mol) were dissolved in methanol (25 mL) and stirred for 2 h at 40 °C. Cooling followed by filtration yielded 3.5 g (87%) of red styryl dye **14**: mp 215–216 °C; IR (KBr) 3125 (OH), 1087 cm^{-1} (ClO_4); UV–vis λ_{max} (CH_3CN) 520 nm (log ε 4.52).

Anal. Calcd for $C_{20}H_{16}ClNO_6$: C, 59.8; H, 4.0; N, 3.5. Found: C, 59.5; H, 4.3; N, 3.2.

Styryl dye **14** (1.0 g) was stirred in diethyl ether (50 mL), ammonium hydroxide (10 mL), and water (20 mL) until all the solid had dissolved. The organic phase was separated, dried ($MgSO_4$), and evaporated under vacuum to yield 0.6 g (80%) of **15**, a white solid: mp 160–163 °C (turns red at 155 °C); NMR ($CDCl_3$) δ 8.2–6.8 (m, 11 H), 5.9 (d, J = 9 Hz, 1 H), 3.2 (s, 3 H).

Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.7; H, 5.0; N, 4.6. Found: C, 79.6; H, 4.9; N, 4.4.

General Procedure for Addition of Cyanide, Azide, Hydride, or Methoxide to 1b, Yielding 16. Sodium cyanide solution (0.5 g in 10 mL water) was added to **1b** (2.5 g, 0.01 mol) slurried in diethyl ether (50 mL). The mixture was stirred for 1 h and diluted with water (50 mL); the ether layer was separated, dried ($MgSO_4$), and evaporated under vacuum. Distillation of the residual yellow oil at 0.05 Torr gave 1.4 g (80%) of 3-cyano-1,3-dimethyl-2,1-benzisoxazoline: bp 50–54 °C; NMR ($CDCl_3$) δ 7.3–6.8 (m, 4 H), 3.1 (s, 3 H), 1.9 (s, 3 H).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.9; H, 5.8; N, 16.1. Found: C, 68.8; H, 5.9; N, 16.0.

3-Azido-1,3-dimethyl-2,1-benzisoxazoline from **1b** and NaN_3 (58% yield, yellow oil which was not distilled): IR (neat) 2083 cm^{-1} (N_3); NMR ($CDCl_3$) δ 7.6–6.8 (m, 4 H), 3.1 (s, 3 H), 1.9 (s, 3 H).

Anal. Calcd for $C_9H_{10}N_4O$: C, 56.8; H, 5.3; N, 29.5. Found: C, 56.4; H, 5.0; N, 28.9.

1,3-Dimethyl-2,1-benzisoxazoline from **1b** and $NaBH_4$ (ethanol was used as solvent instead of ether–water, 68%): bp 91–93 °C (18 Torr); NMR ($CDCl_3$) δ 7.2–6.4 (m, 4 H), 5.3 (q, J = 7 Hz, 1 H), 3.0 (s, 3 H), 1.5 (d, J = 7 Hz, 3 H).

Anal. Calcd for $C_9H_{11}NO$: C, 72.5; H, 7.4; N, 9.4. Found: C, 72.4; H, 7.4; N, 9.4.

1,3-Dimethyl-3-methoxy-2,1-benzisoxazoline from **1b** and methanol–triethylamine (methanol was used as solvent instead of ether–water, and 1 equiv of triethylamine was added, 54%): NMR ($CDCl_3$) δ 7.3–6.8 (m, 4 H), 3.1 (s, 6 H), 1.9 (s, 3 H).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 62.0; H, 7.3; N, 7.8. Found: C, 66.7; H, 7.0; N, 7.7.

Pyrolysis of 3-Cyano-1,3-dimethyl-2,1-benzisoxazoline (16, R = CN). 3-Cyano-1,3-dimethyl-2,1-benzisoxazoline (1 g) was heated at 130 °C for 3 min under N_2. NMR ($CDCl_3$) of the dark blue liquid showed a mixture of (1) starting material at δ 1.8 (s, CCH_3) and 3.10 (s, $N—CH_3$), (2) *N*-methylindoxyl **17** at δ 3.3 (s, CH_2) and 2.6 (s, $N—CH_3$), and (3) *N*,*N*′-dimethylindigo **18** at δ 2.9 (s, $N—CH_3$). The IR spectrum (neat) showed absorption at 3400 and 2250 cm^{-1} due to HCN and at 1715 and 1645 cm^{-1} due to *N*-methylindoxyl and dimethylindigo, respectively. The UV–vis spectrum showed a maximum absorption at 640 cm with a shoulder at 600 nm; the spectrum is identical to that of *N*,*N*′-dimethylindigo.[4]

N-*tert*-Butyl-3-cyano-3-methyl-2,1-benzisoxazoline when treated as above gave only *N*-*tert*-butylindoxyl **19**: NMR ($CDCl_3$) δ 7.5–6.5 (m, 4 H), 3.4 (s, 2 H), 1.1 (s, 9 H); IR (neat) 1715 (C=O), 3400 and 2250 cm^{-1} (HCN).

Registry No.—**1b**, 63609-41-6; **1c**, 64872-29-3; **1d**, 64872-31-7; **5**, 64872-33-9; **6**, 64872-34-0; **7**, 64871-88-1; **8**, 64872-07-7; **9**, 64871-90-5; **10**, 64871-91-6; **11**, 64871-93-8; **13**, 64871-94-9; **14**, 64871-96-1; **15**, 64871-97-2; **17**, 3260-62-6; **18**, 64871-98-3; **19**, 64871-99-4; 3-methyl-2,1-benzisoxazole, 4127-53-1; methyl fluorosulfonate, 421-20-5; sodium perchlorate, 7601-89-0; *tert*-butyl alcohol, 75-65-0; perchloric acid, 7601-90-3; *N*-*tert*-butyl-3-methyl-2,1-benzisoxazolium perchlorate, 63609-46-1; 3-methyl-2,1-benzisothiazole, 20712-09-8; 2,3-dimethylindazole, 50407-18-6; *p*-dimethylaminobenzaldehyde, 100-10-7; *p*-*N*,*N*-dimethylaminoacetophenone, 2124-31-4; *p*-nitrobenzenediazonium tetrafluoroborate, 456-27-9; triethyl orthoformate, 122-51-0; 2-hydroxy-1-naphthaldehyde, 708-06-5; sodium cyanide, 143-33-9; 3-cyano-1,3-dimethyl-2,1-benzisoxazoline, 64872-00-0; 3-azido-1,3-dimethyl-2,1-benzisoxazoline, 64872-01-1; sodium azide, 26628-22-8; 1,3-dimethyl-2,1-benzisoxazoline, 64872-02-2; 1,3-dimethyl-3-methoxy-2,1-benzisoxazoline, 64872-03-3; *N*-*tert*-butyl-3-cyano-3-methyl-2,1-benzisoxazoline, 64900-50-1; $NaBH_4$, 16940-66-2; 3-(*p*-dimethylamino-α-methylstyryl)-1-methyl-2,1-benzisoxazolium perchlorate, 64872-05-5.

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Reactions of Alkylaminonitroalkenes

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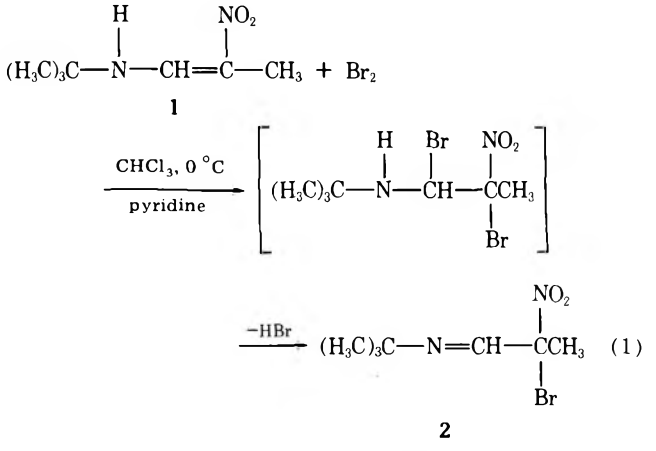
1-Alkylamino-2-nitro-1-alkenes react with bromine in the presence of amines to give α-bromo-α-nitroaldimines. In a novel and reversible amine interchange, secondary and primary amines react with secondary and tertiary aminonitroalkenes to give, respectively, tertiary and secondary aminonitroalkenes. These compounds are rapidly hydrolyzed by aqueous base to amines and nitroalkanes.

1-Alkylamino-2-nitro-1-alkenes have recently become available by the direct alkyl nitration of aldimines.[1] In this paper we are reporting on their reactions with bromine and amines.

Bromination. The reaction of bromine in chloroform with 1-(*tert*-butylamino)-2-nitro-1-propene (**1**) led to cleavage, as evidenced by the isolation of *tert*-butylammonium bromide. However, when the bromination of **1** was carried out in the presence of pyridine or diethylamine, *N*-(2-bromo-2-nitropropylidene)-*tert*-butylamine (**2**) was obtained in 77% yield. It is very likely that the intermediate in the formation of **2** is the dibromo compound which eliminates hydrogen bromide (eq 1).

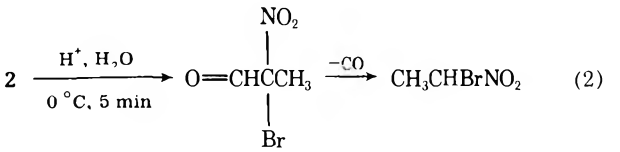


1

2

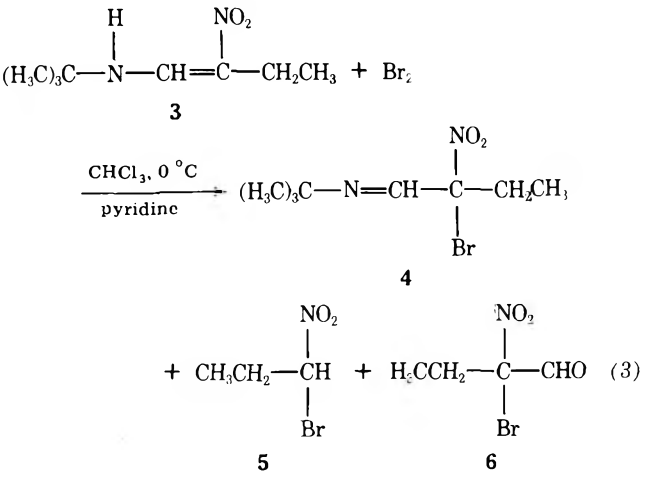
The structure of **2** was confirmed by its spectral data. The infrared spectrum showed absorptions at 1665 cm^{-1} (C=N) and at 1570 and 1339 cm^{-1} (NO_2). The position of the asymmetric NO_2 vibration frequency at 1570 cm^{-1} was particularly significant because it denoted the presence of an unconjugated NO_2 group.[2] The NMR spectrum of **2** was also consistent with the nitroimine structure, exhibiting singlet resonances for the *tert*-butyl, methyl, and azomethine protons at δ 1.22, 2.35, and 7.93, respectively.

Compound **2** was stable to brief neutral and alkaline washes but was rapidly hydrolyzed in dilute acid. Treatment of **2** with 1 equiv of 0.02 N hydrochloric acid at 0 °C for 5 min and distillation of the reaction mixture afforded 1-bromo-1-nitroethane (36%). 2-Bromo-2-nitropropanal was very likely an intermediate in the hydrolysis of **2**. Infrared analysis of the reaction mixture before distillation showed that the C=N band at 1665 cm^{-1} had disappeared and a new absorption at 1718 cm^{-1}, characteristic of the C=O group, was present (eq 2).



Compound **2** lost bromine when exposed to moisture and was reconverted to **1**.

Bromination of 1-(*tert*-butylamino)-2-nitro-1-butene (**3**) in the presence of pyridine gave a mixture which, based on NMR analysis, consisted of *N*-(2-bromo-2-nitrobutylidene)-*tert*-butylamine (**4**), 1-bromo-1-nitropropane (**5**), and a compound believed to be 2-bromo-2-nitrobutanal (**6**) (eq 3).



3

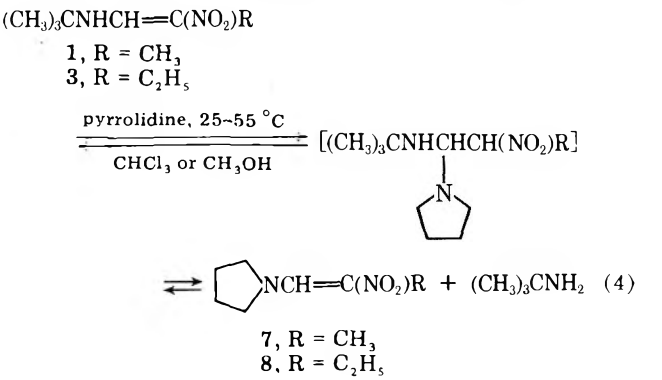
4

5 **6**

Distillation of the mixture in vacuo afforded fractions which contained all three components. The higher boiling fractions contained increasing amounts of **5** which might have been due to the thermal decomposition of **6**.

The presence of compounds **4** and **6** was established by their infrared absorptions at 1667 (CH=N) and 1748 cm^{-1} (C=O), respectively. In the NMR spectrum, **4** was identified by absorptions at δ 1.20 (*tert*-butyl) and 7.78 (CH=N), **5** by a triplet at δ 5.90 ($CHBrNO_2$), and **6** by a singlet at δ 9.40 (CHO).

Transamination. Upon treatment with pyrrolidine in either methanol or chloroform, the secondary aminonitroolefins **1** and **3** underwent amine interchange reactions to afford, respectively, 1-pyrrolidino-2-nitro-1-propene (**7**) and 1-pyrrolidino-2-nitro-1-butene (**8**) (eq 4). However, the reaction was



7, R = CH_3
8, R = C_2H_5

found to be of rather limited scope. For example, 1-cyclohexylamino-2-nitro-1-propene (**9**) failed to react with pyr-

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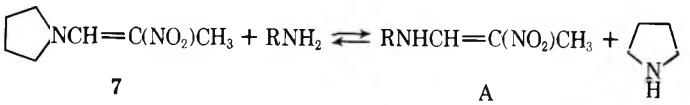
Table I. Reaction of 1-(Pyrrolidino)-2-nitro-1-propene (7) with Primary Amines



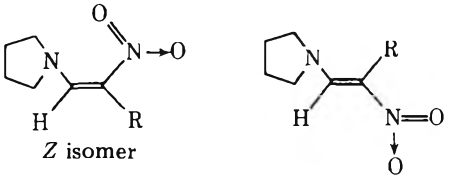
7 A

Amine, R	Registry no.	Amount, mol	Solvent	Temp, °C	Time, h	Yield of A, %	7 recovd, %
t-Bu	75-64-9	2.0	$CDCl_3$	40	22	74[a,b]	26[a,b]
		[c]	Neat	45	1.5	90	
i-Pr	75-31-0	2.2	$CHCl_3$	25	73	41[a]	41[a]
		[c]	Neat	45	1.0	42[d]	18[d]
n-Pr	107-10-8	1.1	$CHCl_3$	25	19	54[d]	11[d]
		1.1	MeOH	25	48	38[b]	14[b]

[a] Based on NMR analysis of the olefinic methyl singlets of compounds 7 and A. [b] Based on separation by preparative thin-layer chromatography. [c] The amine was used as the solvent. [d] Based on separation by column chromatography.

rolidine and was recovered in 76% yield. Furthermore, no reaction occurred when 1 was treated with piperidine, morpholine, diisopropylamine, or diethylamine. The failure of 1 to react with morpholine (pK_a 8.33), diethylamine (pK_a 11.04), and diisopropylamine (pK_a 11.13) may be attributed to the low nucleophilicity of the first and perhaps to steric hindrance in the latter two amines. The failure of 1 to react with piperidine was surprising since the pK_a values and steric requirements of both pyrrolidine (pK_a 11.27) and piperidine (pK_a 11.12) are similar.

Comparison of the NMR spectra of 7 and 8 with those of 3 revealed that the tertiary aminonitroolefins differed from the secondary aminonitroolefins in two important respects. Whereas the latter were shown to consist of a mixture of *Z* and *E* isomers, with the *Z* isomer predominating, the tertiary



R = CH_3 or C_2H_5

aminonitro compounds were found to consist solely of a single species. The positions of the olefinic proton resonances of 7 and 8 at δ 8.45 and 8.43, respectively, indicated that they were in the *E* rather than the *Z* configuration. The preference for the *E* configuration is believed to be a consequence of minimizing steric crowding. Molecular models show that the *E* isomers of 7 and 8 are less hindered than the *Z* isomers. In addition, the nonbonded p–p and p–π interactions between the amino and nitro groups are absent in the *E* isomer.

Additional evidence for the *E* configuration was obtained from the ultraviolet spectrum of 7, in which the long wavelength (K band) absorption [382 nm (log ε 4.17)] was displaced by 12 nm to longer wavelength, relative to the secondary aminonitroolefins 1 and 3. This bathochromic shift is not due to the loss of hydrogen-bonding ability in 7. Freeman and Emmons have shown that the disruption of intramolecular hydrogen bonding in aminonitroolefins leads to a hypsochromic shift of the K band absorption.[3] However, the observed bathochromic shift is consistent with the existence of the *E* isomer, for it is well-known that the less sterically hindered of two geometric isomers absorbs at the longer wavelength.[4,5]

The reversibility of the transamination reaction was established by reconversion of 7 to 1 upon treatment with *tert*-butylamine. The reaction was carried out in deuteriochloroform solution employing 2.0 molar equivalents of amine. Its progress was followed by the decrease of the olefinic methyl signal of 7 at δ 2.32 in the NMR spectrum and by the appearance of the olefinic methyl resonance of 1 at δ 2.08. The reaction progressed fairly rapidly, and after 20 min 50% of 1 was formed. The equilibrium was reached after 35 min when the amount of 1 had increased to 67%. After 22 h only a slight increase of 7 was indicated. Separation of the reaction products by preparative thin-layer chromatography afforded 70% of 1 and 30% of 7. Compound 1 consisted of a mixture of ca. 90% *Z* and 10% *E* isomers and was identical to the product obtained in the alkyl nitrate nitration of *N*-propylidene-*tert*-butylamine.[1] The NMR spectrum of recovered 7 indicated that it was 100% of the *E* configuration.

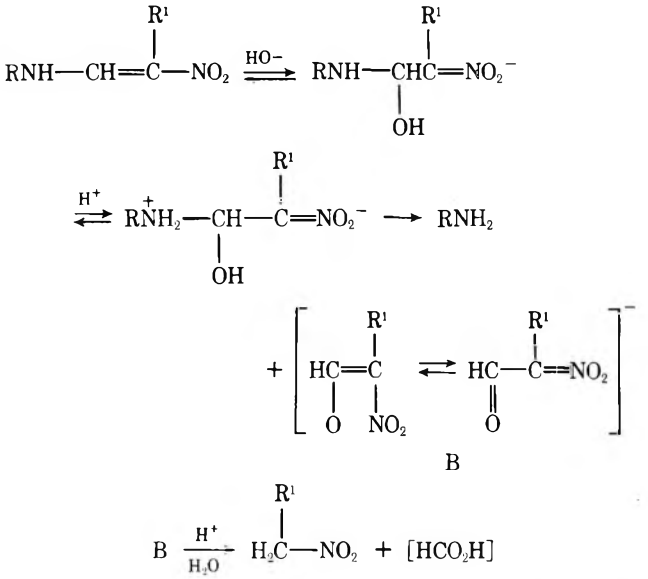
The reaction of 7 with primary amines appeared to be quite general. As shown in Table I, *tert*-butylamine, *n*-propylamine, and isopropylamine afforded the respective transamination products 1, 1-(*n*-propylamino)-2-nitro-1-propene (10), and 1-(isopropylamino)-2-nitro-1-propene (11). Compounds 1, 10, and 11 were identical with those obtained in the alkyl nitrate nitration of the respective aldimines.[1] The NMR spectra indicated that they were of the *Z* configuration. Thus, the reaction proceeded with inversion of configuration.

Aminonitroolefin 9, which did not react with pyrrolidine, underwent transamination with *tert*-butylamine readily. As determined by NMR, a mixture consisting of 1 (39%) and 9 (55%) was obtained. Separation of the mixture by column chromatography on neutral alumina could not be achieved, but NMR analysis of the mixture indicated that both 1 and 9 were of the retained *Z* configuration. The olefinic proton of 1 and 9 resonated at δ 7.09 and 7.03.[1]

The experimental evidence of the transamination reactions with aminonitroolefins suggests that the stereochemistry of the product is subject to thermodynamic control in the product-development step. In reactions involving the formation of secondary aminonitroolefins, the stereochemistry of the product was invariably of the *Z* configuration. This preference is believed to be due to intramolecular hydrogen bonding. In reactions involving the generation of tertiary aminonitroolefins, in which intramolecular hydrogen bonding is not possible, the less hindered *E* isomer appeared to be the exclusive product.

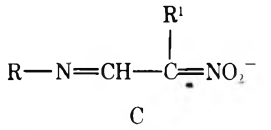
Hydrolysis. The secondary and tertiary aminonitroalkenes underwent rapid hydrolysis on treatment with aqueous potassium hydroxide to give the corresponding amines and nitroalkanes. The latter were obtained after acidification of the reaction mixture. For example, 1 and 7 were cleaved, respectively, to *tert*-butylamine, pyrrolidine, and nitroethane. The hydrolysis might occur by an addition–elimination-type reaction as shown in Scheme I. It is very likely that α-nitro al-

Scheme I



dehyes are intermediates in this reaction. Indirect evidence for this was reported by Hurd and Sherwood. Alkaline hydrolysis of 2-piperidino-1-nitroethene gave piperidine and the potassium salt of nitroethanal. The latter was directly oxidized to dipotassium nitroacetate.[6] It is suggested that on acidification the carbonyl group is eliminated as formic acid.

The possibility that the hydrolysis of a secondary aminonitroalkene, which contains an amino hydrogen, proceeded by the prior formation of a nitroimine salt C was unlikely,



based on the results of a control test. When the potassium salt of **1**, prepared by treating **1** with potassium amide in liquid ammonia, was dissolved in water, no *tert*-butylamine was observed in the strongly alkaline solution. Acidification with acetic acid led to a 67% recovery of **1**.

Experimental Section

***N*-(2-Bromo-2-nitropropylidene)-*tert*-butylamine (2).** To a solution of 1-(*tert*-butylamino)-2-nitro-1-propene (**1**,[1] 3.16 g, 0.02 mol) and pyridine (1.97 g, 0.025 mol) in 25 mL of chloroform at 0 °C was added dropwise during 15 min a solution of bromine (3.20 g, 0.020 mol) in 15 mL of chloroform. The reaction mixture was stirred at 0 °C for 30 min and then washed with three 25-mL portions of cold water and dried ($MgSO_4$). The chloroform was removed in vacuo, and the residue, a yellow oil, was distilled in vacuo to afford **2** (3.65 g, 77%): bp 64–65 °C (4.3 mm); $n^{20}D$ 1.4700; IR (neat) 1665 (C=N), 1570 and 1339 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 1.22 (s, 9, $(CH_3)_3C$), 2.35 (s, 3, CH_3), 7.93 (s, 1, CH=N).

Anal. Calcd for $C_7H_{13}BrN_2O_2$: C, 35.46; H, 5.53; Br, 33.70; N, 11.82. Found: C, 35.23; H, 5.44; Br, 33.94; N, 11.60.

Molecular weight ($(CH_3)_2CO$) Calcd: 237. Found: 244.1.

From the distillation residue there was recovered 0.02 g (1%) of **1**, mp 107–110 °C.

Hydrolysis of *N*-(2-Bromo-2-nitropropylidene)-*tert*-butylamine (2). To a solution of **2** (1.08 g, 4.6 mmol) in 25 mL of water at 0 °C was added 0.5 mL of 0.02 N hydrochloric acid. The reaction mixture was stirred at 0 °C for 5 min and then extracted with ether. The extracts were dried ($MgSO_4$) and the ether was removed in vacuo to afford 0.79 g of a mixture of 1-bromo-1-nitroethane and a compound believed to be 2-bromo-2-nitropropanal: IR ($CHCl_3$) 1718 (C=O), 1565 and 1346 cm^{-1} (NO_2).

Distillation of the mixture afforded 1-bromo-1-nitroethane (0.25 g, 36%) as a colorless lachrymatory liquid, bp 27–28 °C (5 mm); IR ($CHCl_3$) 1567 and 1348 cm^{-1} (NO_2) [lit.[7] bp 72–73 °C (48 mm); IR (neat) 1567 and 1354 cm^{-1} (NO_2)]; NMR ($CDCl_3$) δ 2.24 (d, 3, CH_3), 6.25 (q, 1, $CHBrNO_2$).

Bromination of 1-(*tert*-Butylamino)-2-nitro-1-butene (3). To a stirred solution of **3** (1.72 g, 0.01 mol) and pyridine (1.20 g, 0.015 mol) in 15 mL of chloroform at 0 °C was added dropwise during 15 min a solution of bromine (1.60 g, 0.01 mol) in 20 mL of chloroform. The reaction mixture was stirred for 1 h at 0 °C and then quickly washed with three 25-mL portions of ice water and dried ($MgSO_4$). Removing the chloroform in vacuo gave 2.24 g of a light yellow liquid which was shown by NMR to consist of a mixture of *N*-(2-bromo-2-nitrobutylidene)-*tert*-butylamine (**4**, 70%), 1-bromo-1-nitropropane (**5**, 10%), and a compound believed to be 2-bromo-2-nitrobutanal (**6**, 20%): IR (neat) 1748 (C=O), 1667 (C=N), 1567 and 1331 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 1.03 (t, 3, CH_3), 1.20 (s, 9, $(CH_3)_3C$), 2.60 (m, 2, CH_2), 5.90 (t, 1, $CHBrNO_2$), 7.78 (s, 1, CH=N), 9.40 (s, 1, CH=O).

Distillation of the mixture at reduced pressure afforded fractions which contained all three components. The higher boiling fractions contained increasing quantities of **5**.

1-Pyrrolidino-2-nitro-1-propene (7). To a stirred solution of 1-(*tert*-butylamino)-2-nitro-1-propene (**1**,[1] 1.58 g, 0.01 mol) in 50 mL of absolute methanol was added a solution of pyrrolidine (0.78 g, 0.011 mol) in 10 mL of absolute methanol. The reaction mixture was heated to 45 °C for 90 min and then cooled to room temperature and poured into 500 mL of absolute ether. The ethereal solution was concentrated in vacuo and the residue triturated with cold hexane to afford a mass of fine, bright yellow crystals. Recrystallation from hexane gave **7** (1.18 g, 76%) as yellow needles: mp 93–94 °C; UV max (95% C_2H_5OH) 382 nm (ϵ 14 800), 256 (1600); IR ($CHCl_3$) 1633 (C=C or C=N), 1375 and 1250 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 2.00 (m, 4, CH_2 ring), 2.32 (s, 3, CH_3), 3.59 (m, 4, CH_2 ring), 8.45 (s, 1, CH=C); mass spectrum (75 eV), *m/e* (relative intensity) 156 (100), 139 (44), 126 (16), 110 (44), 109 (91).

Anal. Calcd for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.74; N, 17.94. Found: C, 54.05; H, 8.01; N, 17.79.

Molecular weight (C_6H_6) Calcd: 156. Found: 160.1.

1-Pyrrolidino-2-nitro-1-butene (8). To a solution of 1-(*tert*-butylamino)-2-nitro-1-butene (**3**,[1] 6.88 g, 0.04 mol) in 50 mL of chloroform was added a solution of pyrrolidine (3.12 g, 0.044 mol) in 10 mL of chloroform. The homogeneous orange solution was allowed to stand at room temperature for 115 h and then was poured into 500 mL of absolute ether and concentrated in vacuo. Triturating the residue with cold hexane gave 5.88 g of crude product as a lemon yellow solid. Recrystallization from hexane afforded 4.70 g of a mixture of **8** and **3**, mp 81.5–82.5 °C.

Chromatographing on a silica gel column (13 × 2.5 cm) and eluting with absolute ether gave an analytical sample of **8** (23%) as yellow needles, mp 82–82.5 °C; IR ($CHCl_3$) 1630 (C=N), 1390, 1271, and 1220 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 1.13 (t, 3, CH_3), 2.01 (m, 4, CH_2 ring), 2.75 (q, 2, CH_2CH_3), 3.62 (m, 4, CH_2 ring), 8.43 (s, 1, CH=C); mass spectrum (75 eV), *m/e* (relative intensity) 170 (33), 154 (16), 152 (10), 124 (14), 123 (26), 108 (52), 41 (100).

Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.34; H, 8.11; N, 16.51.

Molecular weight ($(CH_3)_2CO$) Calcd: 170.2. Found: 173.9.

Unreacted **3** was recovered in 23% yield.

Reaction of 1-Pyrrolidino-2-nitro-1-propene (7) with Primary Amines. A. Employing Excess *tert*-Butylamine. Compound **7** (0.50 g, 3.2 mmol) was dissolved in 20 mL of *tert*-butylamine, and the solution was refluxed for 90 min. The reaction mixture was cooled to room temperature, and excess *tert*-butylamine was removed in vacuo. The yellow solid was triturated with hexane, filtered, and washed with a small quantity of cold ether to afford 1-(*tert*-butylamino)-2-nitro-1-propene (**1**, 0.46 g, 90%) as a yellow amorphous powder, mp 108–113 °C. The IR and NMR spectra were identical with those of authentic **1**.[1]

B. Employing 2.0 Molar Equivalents of *tert*-Butylamine. To a solution of **7** (0.16 g, 0.01 mol) in 1.5 mL of deuteriochloroform was added *tert*-butylamine (0.15 g, 0.02 mol) dissolved in 1 mL of deuteriochloroform. The solution was stirred briefly and transferred to an NMR tube, and the spectrum was recorded from 5 min to 22 h. The progress of the reaction was monitored by observing the olefinic methyl signals of **7** and **1** at δ 2.32 and 2.08, respectively.

After 22 h, when the NMR spectrum indicated that the reaction was 74% complete, an aliquot of the reaction mixture was transferred to a preparative TLC plate (20 cm × 20 cm × 1 mm, silica gel PF 254) and eluted with absolute ether to afford two fractions. Each was washed from the silica with absolute methanol, and the methanol was removed in vacuo to afford unreacted **7** (17 mg, 30%) and **1** (39 mg, 70%). The IR and NMR spectra were identical with those of authentic samples.[1]

C. Employing 2.2 Molar Equivalents of Isopropylamine. To **7** (0.29 g, 1.9 mmol) dissolved in 10 mL of chloroform was added iso-

propylamine (0.24 g, 4.0 mmol) dissolved in 5 mL of chloroform. The reaction mixture was stirred briefly and allowed to stand for 73 h at room temperature. Then the solvent was removed in vacuo, and the residue was triturated with cold petroleum ether (30–60 °C) and filtered to give 0.23 g of a 50:50 mixture of 1-(isopropylamino)-2-nitro-1-propene (**11**, 41%) and unreacted **7** (41%), as determined by NMR analysis of the olefinic methyl singlets of **11** and **7** at δ 2.00 and 2.32, respectively.

***D.* Employing 1.1 Molar Equivalents of *n*-Propylamine.** A solution of **7** (0.32 g, 2.0 mmol) and *n*-propylamine (0.13 g, 2.2 mmol) in 17 mL of absolute methanol was stirred at room temperature for 48 h. Then the reaction mixture was subjected to TLC plates on silica gel PF 254 and eluted with absolute ether to afford two fractions. Each fraction was washed from the silica gel with absolute methanol, and the methanol was evaporated in vacuo. In this manner a solid and a liquid product were obtained. Recrystallization of the solid material from hexane gave recovered **7** (47 mg, 14%), mp 88–90 °C.

The liquid was 1-(*n*-propylamino)-2-nitro-1-propene (**10**, 110 mg, 38%). The IR and NMR spectra were identical with those of authentic **10**.[1] The high-resolution mass spectrum of **10** exhibited a molecular ion at *m/e* 244.0906 (calcd *m/e* 244.0899).

Reaction of 1-Cyclohexylamino-2-nitro-1-propene (9) with Excess *tert*-Butylamine. Compound **9** (0.50 g, 2.7 mmol) was dissolved in 20 mL of *tert*-butylamine. The solution was refluxed for 1 h and cooled to room temperature, and excess *tert*-butylamine was removed in vacuo to afford 0.47 g of a mixture of unreacted **9** (55%) and 1-(*tert*-butylamino)-2-nitro-1-propene (**1**, 39%), as determined by NMR analysis of the olefinic methyl signals of **9** and **1** at δ 2.04 and 2.08, respectively.

Alkaline Hydrolysis of 1-(*tert*-Butylamino)-2-nitro-1-propene (1). Compound **1** (3.16 g, 0.02 mol) was dissolved in 25 mL of 2 N potassium hydroxide, and one-half of the hydrolysate was distilled into a receiver containing 5 mL of concentrated hydrochloric acid. Evaporating the distillate to dryness in vacuo and recrystallizing the residue from absolute ethanol gave *tert*-butylamine hydrochloride (1.89 g, 87%). The IR spectrum was identical with that of an authentic sample.

Benzamide: mp 138–139 °C (lit.[8] mp 134 °C).

The remainder of the hydrolysate was acidified to pH 1 with hydrochloric acid and extracted with ether. The ether extracts were washed first with a saturated potassium bicarbonate solution, then with water, and dried ($MgSO_4$). Evaporation of the ether in vacuo gave nitroethane (0.74 g, 45%): IR (neat) 1563 and 1370 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 1.57 (t, 3, CH_3), 4.45 (q, 2, CH_2NO_2).

Potassium *N*-Propylidene-*tert*-butylamine-2-nitronate. To a suspension of potassium amide (0.018 mol) in 150 mL of liquid ammonia at −40 °C was added **1** (3.16 g, 0.02 mol) in one portion. The reaction mixture was stirred for 30 min, and the ammonia was replaced with absolute ether (3 h). The suspension was filtered to give a solid which immediately began to darken on exposure to the atmosphere. The solid was dissolved in absolute ethanol and reprecipitated with absolute ether to afford the salt (3.17 g, 91%) as a cream-colored amorphous powder, mp 190–195 °C dec; IR (KBr) 1610 (C=N), 1524 and 1297 cm^{-1} (NO_2^-); NMR (Me_2SO-d_6) δ 1.07 (s, 9, $(CH_3)_3C$), 1.85 (s, 3 CH_3), 8.60 (s, 1, CH=N). Due to its instability, the salt could not be purified sufficiently for elemental analysis. NMR analysis indicated that it was approximately 90% pure.

Acidification of Potassium *N*-Propylidene-*tert*-butylamine-2-nitronate. The salt (0.98 g, 5.0 mmol) was dissolved in 50 mL of distilled water at 0 °C, and the solution was acidified with 10% aqueous acetic acid to pH 5–6. The yellow suspension was extracted with three 15-mL portions of chloroform and dried ($MgSO_4$), and the chloroform was removed in vacuo to afford 1-(*tert*-butylamino)-2-nitro-1-propene (**1**, 0.53 g, 67%), mp 111–113 °C. The IR and NMR spectra were identical with those of authentic **1**.

Acknowledgment. The support of this work by a grant from the Eli Lilly and Company is greatly appreciated.

Registry No.—(*Z*)-**1**, 64331-63-1; (*E*)-**1**, 64331-62-0; **2**, 64957-53-5; (*Z*)-**3**, 64331-65-3; (*E*)-**3**, 64331-64-2; **4**, 64957-54-6; **5**, 5447-96-1; **6**, 64957-55-7; (*E*)-**7**, 64957-56-8; (*E*)-**8**, 64957-57-9; (*Z*)-**9**, 64331-56-2; 2-bromo-2-nitropropanal, 64957-58-0; 1-bromo-1-nitroethane, 563-97-3; pyrrolidine, 123-75-1; nitroethane, 79-24-3; potassium *N*-propylidene-*tert*-butylamine-2-nitronate, 65000-07-9; potassium amide, 17242-52-3.

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Notes

Fluoronitroanilines. Reaction Control via Hydrogen Bonding

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Recent work[1,2] has shown that although pentafluoronitrobenzene reacts with most nucleophiles to give predominantly displacement of a *p*-fluorine atom, it reacts with ammonia and methylamine to give mainly *o*-fluorine displacement. The higher percentage of ortho replacement for amine nucleophiles was attributed to hydrogen bonding between the attacking amine and the nitro group. However, evidence for the hydrogen-bonding hypothesis was not unequivocal since the ortho/para ratio for the reaction of ammonia and methylamine with pentafluoronitrobenzene (69:31 and 65:35, respectively) was not far from statistical and the preferential ortho (relative to para) directing effect of the fluorine atoms in nucleophilic substitution was a complicating factor.[3]

We have found that treatment of 2,4,6-trifluoronitrobenzene (**1**) with ammonia in tetrahydrofuran gives essentially all ortho-displacement product. Thin-layer chromatographic analysis[4] shows only trace amounts of two unidentified products in addition to the ortho-displacement product, 3,5-difluoro-2-nitroaniline (**2**), which was isolated in 88% yield (a small amount of unreacted **1** is also present). Similarly, treatment of 1,3-dinitro-2,4,6-trifluorobenzene (**3**) with ammonium hydroxide in tetrahydrofuran at −10 °C gives only one monoamine, 3,5-difluoro-2,6-dinitroaniline (**4**). A small amount of diamine, 2,6-dinitro-5-fluoro-1,3-phenylenediamine (**5**), is formed from further reaction of **4** with ammonia but no other products were detected by thin-layer chromatographic analysis.[5]

It is significant that substitution occurs exclusively at the more hindered ortho positions in compounds **1** and **3**. These results strongly support the hypothesis of Allen et al.[2] that the reaction of ammonia with fluoronitrobenzenes is controlled by the degree of hydrogen bonding in the reaction intermediates.[6] For compound **1**, stabilization of the reaction intermediate by hydrogen bonding can occur at the position ortho to nitro but not at the position para. For compound **3**, the in-

termediate formed by attack at the 2-fluorine can be stabilized by hydrogen bonding to two nitro groups[7] whereas attack at the 4-fluorine gives an intermediate stabilized by hydrogen bonding to only one nitro group.

Fluoronitroanilines have found recent use as reagents for analysis of amino acids and peptides.[8] Previously, most fluoronitroanilines had been prepared by nitration of fluoroacetanilides followed by removal of the acetyl group. The fact that hydrogen bonding gives sufficient reaction control to produce essentially only one product from ammonia and trifluoronitrobenzenes suggests that this is a convenient route for the preparation of other fluoronitroanilines.

Attempts to prepare 3,5-difluoro-2,4,6-trinitroaniline (**7**) by nitration of **2** or **4** were unsuccessful.[9] Under mild conditions the nitration product from **4** was the nitramine derivative, *N*-2,6-trinitro-3,5-difluoroaniline (**8**). Compound **8** was also isolated from the nitration of **2**. Presumably **2** first forms the nitramine derivative, *N*-2-dinitro-3,5-difluoroaniline, which rearranges to **4**, but the analogous rearrangement of **8** to **7** does not take place. Evidently $NNO_2 \rightarrow o\text{-}NO_2$ rearrangement in this series is strongly preferred to $NNO_2 \rightarrow p\text{-}NO_2$.[10]

Experimental Section[11]

Fluoronitrobenzenes and Their Derivatives Should be Handled with Care as 2,4-Dinitro-1-fluorobenzene Has Mutagenic and Carcinogenic Properties (M. Levitt and C. Bon, Chemical and Engineering News, Vol. 55, No. 29, July 18, 1977, p 30).

3,5-Difluoro-2-nitroaniline (2). A solution of 5.3 g of 2,4,6-trifluoronitrobenzene[12] in 50 mL of tetrahydrofuran was stirred at ambient temperature as ammonia gas was bubbled in over a period of 7 h. The mixture was filtered to remove precipitated ammonium fluoride and the solvent was removed under reduced pressure to give a red-orange solid which was crystallized from benzene–hexane to yield 4.6 g (88%) of yellow-orange crystals, mp 104–108 °C. Recrystallization from benzene gave mp 107–108 °C (lit.[13] mp 107–108 °C): NMR (acetone) δ 6.87 (broad s, NH_2) 6.64–6.24 (two multiplets with slight overlap, 13 peaks); mass spectrum *m/e* 174 (M^+).

***N*-Acetyl-3,5-difluoro-2-nitroaniline.** A solution of 1.40 g of 3,5-difluoro-2-nitroaniline in 14 mL of acetyl chloride (dissolve by warming) was allowed to stand overnight at ambient temperature before the acetyl chloride was removed to give 1.73 g (100%) of a yellow-orange crystalline residue, mp 98–100 °C. Crystallization from hexane gave mp 100–101 °C (lit.[14] mp 137–138 °C): NMR (acetone) δ 9.46 (broad s, 1 H, NH), 7.92–7.76 (m, 6 peaks, 1 H), 7.19–6.97 (m, 7 peaks, 1 H), 2.15 (s, 3 H, CH_3); IR (KBr) 3285 (NH), 1680 (C=O) cm^{-1}.

Anal. Calcd for $C_8H_6N_2F_2O_3$: C, 44.45, H, 2.80; N, 12.96; F, 17.58. Found: C, 44.64; H, 2.88; N, 12.80; F, 17.83.

3,5-Difluoro-2,6-dinitroaniline (4) and 2,6-Dinitro-5-fluoro-1,3-phenylenediamine (5). A solution of 1.1 g (0.005 mol) of 1,3-dinitro-2,4,6-trifluorobenzene[15] in 10 mL of tetrahydrofuran was well stirred at −10 °C during the dropwise addition of 0.65 mL (0.01 mol) of ammonium hydroxide (29% NH_3) over a 1-min period. Stirring at −10 °C was continued for an additional 3 min before the reaction mixture was poured into ice water to precipitate a yellow solid (0.92g) which was immediately removed, washed with cold water, and dried in vacuo. TLC of the yellow solid showed mainly **4** with a small amount of **5**. The yellow solid was stirred with 15 mL of methylene chloride at ambient temperature for 10 min before the insoluble material (diamino compound, 66 mg) was removed. Concentration of the methylene chloride solution and addition of hexane gave 0.61 g (55%) of yellow crystals of 3,5-difluoro-2,6-dinitroaniline, mp 113–117 °C. The analytical sample (mp 117.5–118.5 °C) was obtained by column chromatography on silica gel: NMR (acetone) δ 7.61 (broad s, 2 H, NH_2), 6.81 (t, 1 H, aromatic H); IR (KBr) 3535, 3410 (NH_2) cm^{-1}; mass spectrum *m/e* 219 (M^+). Anal. Calcd for $C_6H_3N_3O_4F_2$: C, 32.89; H, 1.38; N, 19.18; F, 17.34. Found: C, 33.05; H, 1.48; N, 19.33; F, 17.57.

The diamino compound (2,6-dinitro-5-fluoro-1,3-phenylenediamine) after crystallization from acetone has mp 284–85 °C dec: NMR (Me_2SO) δ 9.21 (s, 2 H, NH_2), 8.64 (s, 2 H, NH_2), 6.07 (d, 1 H, aromatic H); mass spectrum *m/e* 216 (M^+). Anal. Calcd for $C_6H_5N_4O_4F$: C, 33.33; H, 2.33; N, 25.92; F, 8.79. Found: C, 33.20; H, 2.36; N, 25.76; F, 9.01.

***N*-Acetyl-3,5-difluoro-2,6-dinitroaniline.** A solution of 625 mg of 3,5-difluoro-2,6-dinitroaniline in 3.5 mL of acetyl chloride was allowed to stand at ambient temperature overnight (crystals precipitate). Ether (10 mL) was added and the crystals (647 mg, 87%, mp 198–199 °C) were removed and washed with ether. Recrystallization from 1,2-dichloroethane gave pale yellow needles, mp 198–199 °C: NMR (acetone) δ 9.72 (broad s, 1 H, NH), 7.71 (t, 1 H, aromatic H), 2.12 (s, 3 H, CH_3); IR (KBr) 3285 (NH), 1685 (C=O) cm^{-1}. Anal. Calcd for $C_8H_5N_3F_2O_5$: C, 36.79; H, 1.93; N, 16.09; F, 14.55. Found: C, 36.86; H, 1.98; N, 15.94; F, 14.73.

***N*-2,6-Trinitro-3,5-difluoroaniline (8) (Caution! 8 is an Explosive and Can be Detonated with a Hammer Blow).** Nitric acid (90%) (3.6 mL) was added to 20 mL of 30% fuming sulfuric acid with cooling. To the nitric–sulfuric acid mixture stirred in an ice bath was added 1.2 g of 3,5-difluoro-2,6-dinitroaniline in small portions. The solution was stirred for 1 h at room temperature and then was poured onto ice and extracted with 3 × 50 mL of ether. The extracts were combined and dried over magnesium sulfate. The ether was removed under reduced pressure to give 1.3 g of a yellow solid which was crystallized from methylene chloride to yield 1.1 g (76%) of yellow crystals, mp between 80 and 85 °C dec depending on the rate of heating: NMR (acetone) δ 10.56 (broad s, 1 H, NH), 8.14 (t, 1 H, aromatic H); IR (KBr) 3385 (NH) 3120 (aromatic H) cm^{-1}.

Anal. Calcd for $C_6H_2N_4F_2O_6$: C, 27.28; H, 0.76; N, 21.21; F, 14.39. Found: C, 27.28; H, 0.76; N, 21.09; F, 14.53.

Registry No.—**1**, 315-14-0; **2**, 361-72-8; **3**, 392-51-8; **4**, 64884-81-7; **5**, 64884-82-8; **8**, 64884-83-9; *N*-acetyl-3,5-difluoro-2-nitroaniline, 361-71-7; acetyl chloride, 75-36-5; *N*-acetyl-3,5-difluoro-2,6-dinitroaniline, 64884-84-0; nitric acid, 7697-37-2; 1,3,5-trifluorobenzene, 372-38-3.

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(1) G. M. Brooke, J. Burdon, and J. C. Tatlow, *J. Chem. Soc.*, 802 (1961).
(2) J. G. Allen, J. Burdon, and J. C. Tatlow, *J. Chem. Soc.*, 1045 (1965).
(3) Pentafluorobenzene, with its electronically neutral hydrogen substituent, is substituted by nucleophiles almost entirely in the position para to hydrogen. Pentafluoroanisole, even though it contains the strongly deactivating methoxyl group, still gives the isomer para to methoxy as the major substitution product. From these results the authors[1] concluded that the activating influence of the five fluorine atoms to nucleophilic substitution must be considerable.
(4) The analyses were performed on silica gel F-254 TLC plates (Brinkmann). Benzene was the developer and the spots were visualized with UV light.
(5) The structures for **2**, **4**, and **5** were assigned on the basis of their NMR spectra. The spectra of **2** and its acetyl derivative each show two types of ring protons. The isomer of **2**, 3,5-difluoro-4-nitroaniline, would contain equivalent fluorine atoms and ring protons. The spectra of **4** and its acetyl derivative show the expected triplet for a ring proton ortho to two equivalent fluorine atoms. Such a spectrum is not possible for 3,5-difluoro-2,4-dinitroaniline, the isomer of **4**. Compound **5** contains nonequivalent amino groups which is consistent with the structure assigned.
(6) C. F. Bernasconi and R. H. deRossi, *J. Org. Chem.*, **41**, 44 (1976). These authors have also suggested that such intermediates are formed in the reaction of fluoronitro-aromatic compounds with amines. Similar intermediates can be envisioned for the reaction of **1** and **3** with ammonia.
(7) The interatomic potential curves [J. R. Holden and C. Dickinson, *J. Phys. Chem.*, **81**, 1505 (1977)] indicate there would be attraction between ammonia hydrogen atoms and the oxygens from both nitro groups as the ammonia approached to form the reaction intermediate. An amino group between two nitro groups can simultaneously hydrogen bond to both. J. R. Holden, *Acta Crystallogr.*, **22**, 545 (1967); H. H. Cady and A. C. Larson, *ibid.*, **18**, 485 (1965).
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(9) Procedures for the preparation of pentanitroaniline, 2,3,4,6-tetranitroaniline, and 2,4,6-trinitroaniline from 3,5-dinitroaniline, 3-nitroaniline, and 2-nitroaniline, respectively, have been reported. B. Flürscheim and E. Holmes, *J. Chem. Soc.*, 3041 (1928); B. Flürscheim, *J. Soc. Chem. Ind., London*, **40**, 97 (1921); O. Witt and E. Witte, *Ber.*, **41**, 3090 (1908). These procedures with **2** or **4** did not give **7**.
(10) This result is not unambiguous. Some **7** could be formed during the nitration and then lost due to conversion to its nitramine derivative. However, **8** in 30% fuming sulfuric acid did not rearrange to **7** even after prolonged reaction time. Conversion of **7** to its nitramine derivative under these conditions could only occur if **4** were also formed. No **4** was observed.
(11) NMR spectra were determined on a Varian HA-100 spectrometer and the chemical shifts are relative to tetramethylsilane. The melting points are corrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.
(12) PCR, Inc., Gainesville, Fla.
(13) G. C. Finger, F. H. Reed, and J. L. Finnerty, *J. Am. Chem. Soc.*, **73**, 154 (1951).
(14) Reference 13. The reason for the discrepency in the melting points is not known. In ref 13 the crystallization solvent was *m*-fluorobenzo trifluoride and an elemental analysis was not given.

(15) The dinitrotrifluorobenzene was prepared as follows: 120 mL of 90% nitric acid was added to 180 mL of 30% fuming sulfuric acid with cooling; 52.8 g of 1,3,5-trifluorobenzene[12] was added dropwise with stirring at 10–15 °C and the mixture was warmed to 45–50 °C for 45 min; the cooled reaction mixture was poured onto ice and the precipitated product was immediately removed, washed with cold water, and dried in vacuo to give 79.5 g (90%), mp 47–52 °C; crystallization from dry carbon tetrachloride gave mp 51–53 °C (lit. mp 52–53 °C: G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc.*, **78**, 6036 (1956)).

Azetidinone Antibiotics. 19. A Simple Method for the Removal of *p*-Nitrobenzyl Acid Protective Group[1]

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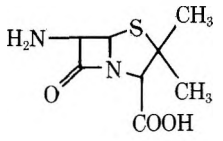
Received September 19, 1977

The chemistry of azetidinone antibiotics has undergone considerable progress during the last two decades.[3] This outstanding development has been largely possible due to the appropriate blocking of the amino and carboxyl groups in the nucleii **1** and **2**. In particular, the protection of the carboxyl



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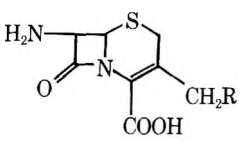

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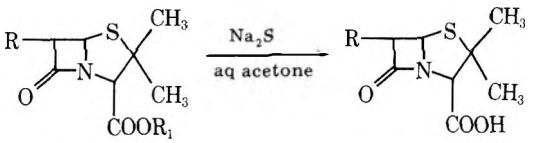
group from undesirable side reactions has been very beneficial. A wide variety of carboxyl protective groups, together with different methods for their selective removal, has been utilized. These include the *tert*-butyl, trichloroethyl, *p*-methoxybenzyl, phenacyl, 2-haloethyl, alkoxymethyl, benzyl, benzhydryl, *p*-nitrobenzyl, and others. Among these the *p*-nitrobenzyl (pNB) group has been frequently used in the chemical modifications of bicyclic azetidinones.[4] The pNB esters of penicillins and cephalosporins are easily prepared by treating the corresponding acid with *p*-nitrobenzyl bromide in the presence of base at temperatures between 0 and 20 °C. The significant advantage of the pNB protective group is relative stability to most acidic and basic reaction conditions. The additional advantage is that it can be selectively removed by catalytic or chemical reduction. Chemical reductions have been widely used in a number of circumstances. Catalytic hydrogenolysis has also been used although these sulfur-containing molecules occasionally caused a "poisoning" effect on hydrogenation catalysts.

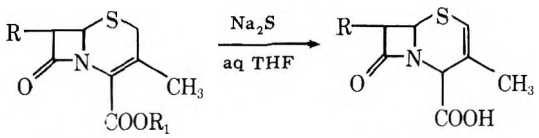
In connection with our work on the removal of the phthaloyl group,[5] a simple, rapid, and high-yield method for the removal of the *p*-nitrobenzyl group from highly sensitive azetidinone antibiotics has been found and our results are reported here.

We have observed that the pNB group can be removed easily by alkaline hydrolysis with sodium sulfide ($Na_2S·9H_2O$). The hydrolysis is performed in an aqueous THF, DMF, or acetone solution at ice-bath temperature within 25–35 min. The progress of hydrolysis can be followed by thin-layer chromatography. The expected acid is usually isolated by acidification of an aqueous portion and if desired recrystallized from the appropriate solvent.

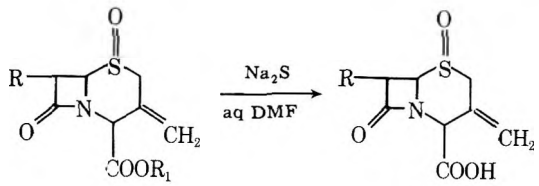
When this method was applied to *p*-nitrobenzyl esters of penicillin G and V (**3g** and **3v**), the corresponding penicillanic acids **4g** and **4v** were obtained in about 80% yield. A similar hydrolysis of deacetoxycephalosporin esters **5h, 5g,** and **5v** afforded 2-cephem acids **6h, 6g,** and **6v** in 75–83% yield. Apparently, in the case of pNB esters of 3-cephem derivatives, the ester group was hydrolyzed, and at the same time, the double bond was isomerized from the Δ^3 to the Δ^2 position. Accordingly, this is a very practical method for preparation of 2-cephem acids **6**.



3g or 3v **4g or 4v**



5h, 5g, or 5v **6h, 6g, or 6v**



7v **8v**

g, R = $PhCH_2CONH-$; v, R = $PhOCH_2CONH-$; h, R = NH_2, R_1 = *p*-nitrobenzyl (pNB)

However, an analogous hydrolysis of the pNB ester of 3-methylene cepham **7v** with $Na_2S·9H_2O$ in aqueous DMF resulted only in the removal of the ester group without isomerization of the exocyclic double bond. The acid **8v** was isolated in 45% yield.

The results described in this paper demonstrate that the hydrolysis of pNB esters of various azetidinone derivatives with $Na_2S·9H_2O$ is feasible, even with highly sensitive azetidinone antibiotics. Removal of the pNB group may be used as an alternative to chemical reduction and hydrogenolysis, although the simplicity, expediency, and high yields could be considered as being advantageous. Therefore, we believe that the hydrolysis with $Na_2S·9H_2O$ will find widespread application in the removal of the pNB group.

Experimental Section

Representative Hydrolyses of pNB Esters of Azetidinone Antibiotics. A. 6-Phenylacetamidopenicillanic Acid. A solution of 469 mg (1 mmol) of *p*-nitrobenzyl 6-phenylacetamidopenicillanate in 12 mL of THF and 6 mL of water was cooled in an ice bath, and a solution of 240 mg (1 mmol) of $Na_2S·9H_2O$ in 5 mL of water was added. The mixture was stirred at 0–5 °C for 25 min, 1 mL of 1 N HCl added, and THF was evaporated in vacuo. In order to remove the nonacidic material, 15 mL of ethyl acetate was added to the aqueous solution, pH adjusted to 8.5, and the organic layer was discarded. The pH of the aqueous solution was adjusted to 2.5 with 1 N HCl, and the desired acid was extracted with 20 mL of ethyl acetate. The extract was washed with brine and dried ($MgSO_4$). After evaporation of the solvent 270 mg (81%) of the corresponding acid was obtained. NMR, IR, and TLC of this material were in agreement with those of an authentic sample.

B. 7-Phenoxyacetamido-3-methyl-2-cephem-4-carboxylic Acid. A mixture of 4.83 g (10 mmol) of *p*-nitrobenzyl 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate, 100 mL of THF, 10 mL of water, and 2.4 g (10 mmol) of $Na_2S·9H_2O$ was stirred in an ice bath for 30 min.

HCl (10 mL, 1 N) was added and THF was evaporated on a rotavapor and the solution was extracted with 30 mL of ethyl acetate. The extract was discarded. The pH of the aqueous layer was adjusted to 3.2 with hydrochloric acid, and soon the oily product commenced to

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crystallize. The crystalline acid was filtered and dried in a vacuum oven overnight. Yield, 3.0 g (83%); NMR ($CDCl_3$ + DMSO-d_6) τ 8.02 (s, 3 H, CH_3), 5.4 (s, 2 H, $PhOCH_2$), 5.33 (bs, 1 H, C_4–H), 4.65 (d, J = 5.0, 1 H, C_6–H), 4.36 (q, J = 5 and 9, 1 H, C_7–H), 3.14–2.52 (m, 5 aromatic H), and 2.1 (d, J = 9.0 Hz, NH). Anal. Calcd for $C_{16}H_{16}N_2O_5S$: C, 55.16; H, 4.63; N, 8.04; O, 22.96; S, 9.20. Found: C, 54.82; H, 4.74; N, 7.72; O, 22.79; S, 8.98.

C. 7-Phenoxyacetamido-3-methylenecepham-4-carboxylic Acid 1-Oxide. *p*-Nitrobenzyl 7-phenoxyacetamido-3-methylenecepham-4-carboxylate 1-oxide,[6] 1.5 g (3 mM) was dissolved in 36 mL of dimethylformamide and 20 mL of water and cooled in an ice–water bath for addition of sodium sulfide, 1.1 g (4.5 mM), in 10 mL of water. The reaction mixture was stirred in the cold for 30 min. The mixture was poured into a mixture of 5% HCl and ethyl acetate. The organic layer was separated and washed with 5% HCl and then water. The ethyl acetate solution was slurried with water; the pH was adjusted to 7. The aqueous layer was separated and slurried with ethyl acetate and the pH was readjusted to 2.5. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to dryness in vacuo. The amorphous residue weighed 600 mg and was made to crystallize by trituration with ether. Yield of pure product; 500 mg (46%); NMR ($CDCl_3$ + DMSO-d_6) τ 6.19 (s, 2 H, C2-H_2), 5.45 (s, 2 H, α-CH_2), 4.97–4.87 (d and s, 3 H, C4-H and C6-H), 4.60 and 4.30 (2s, 2 H, C3-CH_2), 4.09 (q, 1 H, C7-H), 3.14–2.52 (m, 5 H, aromatic H), and 0.21 (d, 1 H, amide-NH); IR (Nujol mull) 1668, 1735 and 1758 cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_2O_6S$: C, 52.74; H, 4.43; N, 7.69. Found: C, 52.72; H, 4.54; N, 7.91.

D. 7-Amino-3-methyl-2-cephem-4-carboxylic Acid. A suspension of 798 mg (2 mmol) of *p*-nitrobenzyl 7-amino-3-methyl-3-cephem-4-carboxylate in 10 mL of THF and 8 mL of water was cooled in an ice bath and a solution of 480 mg (2 mmol) of Na_2S-$9H_2O$ in 4.0 mL of water was added. The mixture was stirred at 0–5 °C for 35 min, then 2.0 mL of 1 N HCl was added, and THF was evaporated in vacuo. The resulting aqueous solution (pH 8.5) was extracted with 20 mL of ethyl acetate, and the extract was discarded. The pH of the aqueous solution was adjusted to 3.9 with 1 N HCl while being cooled in an ice bath. After approximately 3 min, the precipitate began to form. After 30 min the solid was filtered and dried in a vacuum oven overnight. Yield of 6 h, 320 mg (75%); *m/e* 214. Anal. Calcd for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.70; N, 13.08; O, 22.40; S, 14.97. Found: C, 44.90; H, 4.70; N, 13.94; O, 22.14; S, 15.17.

Registry No.—**3g**, 27487-21-4; **4g**, 61-33-6; **5h**, 29124-83-2; **5v**, 28974-31-4; **6h**, 56487-68-4; **6v**, 10209-07-1; **7v**, 63427-57-6; **8v**, 64811-71-8.

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(2) Deceased May 5, 1977.
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(4) R. R. Chauvette and P. A. Pennington, *J. Am. Chem. Soc.*, **96**, 4986 (1974); *J. Med. Chem.*, **18**, 403 (1975); *J. Org. Chem.*, **38**, 2994 (1973); D. H. R. Barton, F. Comer, D. G. T. Greig, P. G. Sammes, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *J. Chem. Soc. C*, 3540 (1971).
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Regiospecificity of Enol Ether Formation in the Catalyzed Decomposition of Ethyl Diazoacetate in the Presence of Unsymmetrical Ketones

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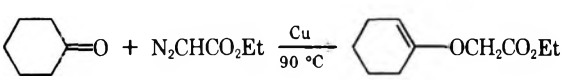
In 1953, Kharasch and co-workers[1] reported (among other products) the formation of ethyl (cyclohexen-1-oxy)ethanoate (**1**) in 43% yield from the reaction of excess cyclohexanone with ethyl diazoacetate in the presence of copper at 90 °C. We have found that the use of copper(I) chloride in place of copper gives similar results.



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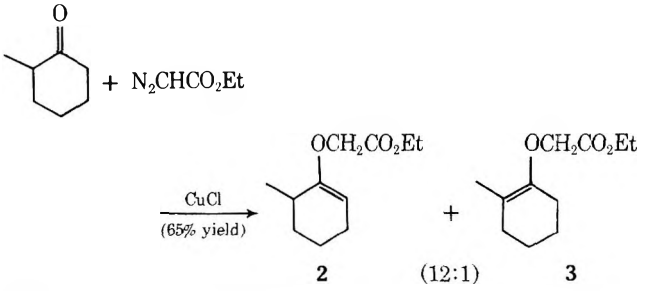
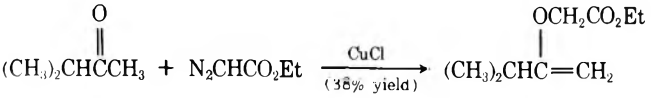
As part of an investigation of the reactions of carbenes and carbenoids with enolizable ketones, we report two examples of the decomposition of ethyl diazoacetate in the presence of copper(I) chloride and an excess of an unsymmetrical ketone which resulted in modest yields of the simple enol ether in which the least-substituted isomer dominated. For example, the use of 2-methylcyclohexanone results in a 65% yield of an isomer mixture in which approximately 92% is enol ether **2**.[2]



2 (12:1) **3**

When the same reaction was carried out with 3-methyl-2-butanone, the only low-boiling product observed was enol ether **4**. The observed dominance of the least-substituted enol



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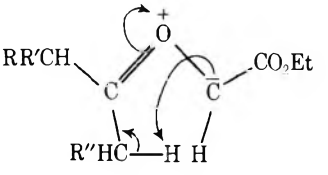
ether is consistent with simple steric and electronic considerations for the intramolecular proton abstraction required to get from the presumed intermediate carbonyl ylide **5** to the product.



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Products which had a boiling point substantially higher than that of the simple enol ethers already described were not investigated for the reaction of 3-methyl-2-butanone and have been described previously by Kharasch[1] for the reaction with cyclohexanone.

Experimental Section

Elemental analyses were done by the Department of Medicinal Chemistry at the University of Kansas. Mass spectra were obtained on a Varian CH-5 mass spectrometer. Infrared spectra were obtained on a Beckman IR-8 (sodium chloride optics). Varian A-60 and T-60 spectrometers were used for determining NMR spectra of samples as solutions in chloroform-*d* containing an internal tetramethylsilane standard. An F&M Model 700 chromatograph (thermal-conductivity detector) was used for VPC analyses with the following columns: 10% QF-1 (a fluorosilicone; Dow Corning) on 80–100 mesh Gas Chrom Q (10 ft × 0.25 in. copper column) and 10% Hi-EEF 8 AP (a polycyclohexane–dicarbinol adipate; Applied Science Laboratory) on 60–80 mesh Gas Chrom Q (8 ft × 0.25 in. copper column).

Copper(I) chloride was prepared from copper(II) sulfate[4] and purified by washing several times each with glacial acetic acid, absolute ethanol, and anhydrous diethyl ether. Ethyl diazoacetate was prepared by the method of Searle.[5] All ketones were distilled prior to each reaction.

Cyclohexanone Reaction. A solution of ethyl diazoacetate (8.0 g, 0.0701 mol) and cyclohexanone (16 g, 0.163 mol) was added slowly (1.5–2.0 h) with stirring to a mixture of copper(I) chloride (0.10 g) and cyclohexanone (32.0 g, 0.326 mol) maintained at 90–95 °C (N_2 atmosphere). When the addition was complete and nitrogen evolution

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had ceased, the excess cyclohexanone was distilled, bp 25–35 °C (3–4 Torr).

Distillation of the residue produced fraction A, bp 45–105 °C (0.05–0.1 Torr), and fraction B, bp 105–125 °C (0.05–0.01 Torr). Redistillation of fraction A with a short-path still resulted in 7.36 g (0.04 mol, 57% yield) of ethyl (cyclohexen-1-oxy)ethanoate (1): bp 60–65 °C (0.05–0.1 Torr) [lit.[1] bp 103.5–104.5 (6 Torr)]; single peak by VPC analysis on QF-1 at 210 °C. NMR, τ 8.73 (3 H, t, J = 7 Hz). 5.80 (2 H, q, J = 7 Hz), 5.76 (2 H, s), 8.15–8.60 (4 H, m), 7.50–8.60 (4 H, m), 5.32–5.58 (1 H, m); IR 2990 (m), 2939 (s), 2860 (m), 2850 (m), 1752 (s), 1725 (s), 1660 (m) cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75; mol wt 184. Found: C, 65.14; H, 8.68; mol wt 184 (MS, 70 eV, 140 °C).

A sample of the compound was hydrolyzed with an excess of a 2% (w/v) solution of HCl in 90% ethanol for 1.5 h at reflux. Removal of excess ethanol followed by distillation of the residue and treatment of successive portions of the distillate with 2,4-dinitrophenylhydrazine and *p*-nitrobenzoyl chloride produced the corresponding derivatives of cyclohexanone and ethyl glycolate, respectively. The NMR spectrum of the distillate confirmed the presence of a mixture of cyclohexanone and ethyl glycolate.

2-Methylcyclohexanone Reaction. The reaction was carried out in the same manner as with cyclohexanone to give as the lower boiling product(s) (short-path distillation unit) a clear liquid, bp 55–60 °C (0.05–0.10 Torr), identified as a mixture of ethyl (6-methyl-1-cyclohexen-1-oxy)ethanoate (2) (60% yield) and ethyl (2-methyl-1-cyclohexen-1-oxy)ethanoate (3) (5% yield). The NMR spectrum showed peaks (areas only approximate) at τ 8.82 (3 H, t, J = 7 Hz), 8.64 (3 H, d, J = 7 Hz), 7.2–9.1 (7 H, broad envelope), 5.76 (2 H, q, J = 7 Hz), 5.70 (2 H, s), 5.36–5.59 (1 H, m); with addition of $Pr(fod)_3$, the lower field portion of the spectrum showed peaks at τ 6.34 (1 H, t, J = 4 Hz, C=CH), 6.90 (0.17 H, s, OCH_2CO of minor isomer), 723 (2 H, q, J = 7 Hz, CH_2OCO), 7.55 (2 H, s, OCH_2CO of major isomer); IR (neat) 2980 (m), 2920 (s), 2850 (m), 1745 (s), 1720 (s), 1650 (m) cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; mol wt 198. Found: C, 66.68; H, 9.14; mol wt 198 (MS, 70 eV, 48 °C).

3-Methyl-2-butanone Reaction. The reaction was carried out in the same manner as with cyclohexanone to give as the lower boiling product a clear liquid, bp 35–40 °C (15–20 Torr), identified as ethyl (3-methyl-1-buten-2-oxy)ethanoate (4). The NMR spectrum showed absorptions at τ 8.90 (6 H, d, J = 7 Hz), 8.73 (3 H, t, J = 7 Hz), 7.62 (1 H, sept, J = 7 Hz), 6.19 (2 H, doublet of doublets, J = 13, and 3 Hz), 5.77 (2 H, q, J = 7 Hz), 5.68 (2 H, s); IR (neat), 2970 (s), 2930 (m), 2870 (m), 1750 (s), 1725 (s), 1644 (m), 1600 (m) cm^{-1}.

Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36; mol wt 172. Found: C, 62.76; H, 9.58; mol wt 172 (MS, 70 eV, 60 °C). As much as 1% of the isomeric enol ether might have been present but could not be definitely identified.

Acknowledgments. The authors are grateful for support from the University of Kansas General Research Fund.

Registry No.—**1**, 64825-54-3; **2**, 64825-55-4; **3**, 64825-56-5; **4**, 64825-57-6; cyclohexanone, 108-94-1; ethyl diazoacetate, 623-73-4; 2-methylcyclohexanone, 583-60-8; 3-methyl-2-butenone, 563-80-4.

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Formyl-*d* Aromatic Aldehydes

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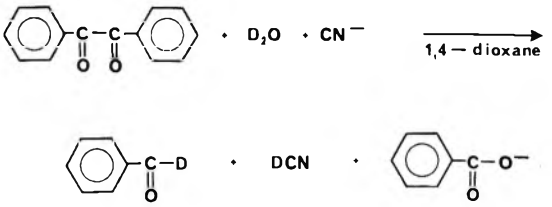
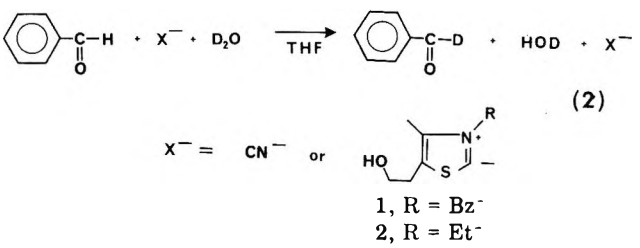
Aldehydes labeled with deuterium at the formyl carbon are useful precursors for a variety of labeled compounds containing deuterium at a specified position.[2] Although several procedures are available which provide such compounds by deuteration of an acyl anion equivalent[3] or by degradation of labeled precursors,[4,5] simple exchange reactions cannot be used to prepare these compounds.[9] Currently the simplest procedure for preparation of benzaldehyde and other aromatic aldehydes deuterated at the formyl position is that described by Schowen and co-workers in which benzil is cleaved by stoichiometric amounts of cyanide ion in deuterium oxide (eq 1).[5] We wish to report that a simple exchange reaction can be



(1)

successfully accomplished with several aromatic aldehyes, a catalytic or stoichiometric amount of either potassium cyanide or a thiazolium salt, a weak Lewis base, and deuterium oxide as the deuterium source. This reaction (eq 2) can be evaluated



(2)

easily with small amounts of substrate by NMR and is a straightforward, simple method for incorporation of deuterium into some aldehydes without the isolation of any intermediates.

Since the proton transfer reactions in the benzoin condensation are known to occur faster than carbon–carbon bond formation,[6] we reasoned that a reaction like eq 2 would be synthetically useful as an exchange procedure leading to labeled aldehydes. In fact, when benzaldehyde was allowed to react with a catalytic amount of potassium cyanide in ethanol/deuterium oxide (benzoin reaction conditions), about 50% deuterium incorporation occurred as measured by NMR before significant amounts of benzoin product began to form. By using excess potassium cyanide and a phase isolation procedure (vide infra), the deuterium incorporation could be raised to 96% without appreciable amounts of benzoin product forming. Similar experiments shown in Table I establish that this procedure is applicable to other aromatic aldehydes in addition to benzaldehyde.

A phase isolation technique was used to slow the rates of condensation reactions relative to those for proton exchange, thus minimizing competing side reactions. In this procedure, an organic solvent containing the aldehyde is stirred vigorously with a solution of potassium cyanide in deuterium oxide. We presume that under these conditions aldehyde in the deuterium oxide phase exchanges its formyl proton via the cyanohydrin anion and that the condensation reaction is suppressed because the concentration of free aldehyde in the deuterium oxide phase is low. This phase isolation technique has other applications.[7]

Like the benzoin condensation, the exchange reaction we have described apparently involves transient formation of an acyl anion equivalent. We have found that both cyanide anion and alkyl or aryl thiazolium salts in the presence of mild bases like triethylamine or sodium acetate can be used for these reactions.[8] With different catalysts the rates of deuterium

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Table I. Formyl-*d* Aldehydes by Exchange with Deuterium Oxide

Aldehyde	Registry no.	Catalyst (equiv)	Organic phase	Time, h	Formyl-*d*,[a] %	Registry no.	Isolated yield, %
Benzaldehyde	100-52-7	KCN (1)	Et_2O	72	96	3592-47-0	62
		KCN (2)	Ph-H	72	>90		*b*
		1, NaOAc (1)[c]	THF	170	>90		*b*
		2, Et_3N (1)[c]	THF	18	>90		*b*
1-Naphthaldehyde	66-77-3	KCN (2)	Et_2O	98	~50	42007-09-0	*b*
		1, Et_3N (1)[c]	THF	2	>90		50
2-Chlorobenzaldehyde	89-98-5	KCN (2)	Et_2O	27	>98	64852-98-8	75
4-Chlorobenzaldehyde	104-88-1	KCN (2)	Et_2O	67	96	1517-47-1	76
3,4-Dimethoxybenzaldehyde	120-14-9	KCN (2)	Et_2O	119	81	27167-79-9	75
9-Anthraldehyde	642-31-9	**1**, Et_3N (1)[c]	THF	18	82	64852-99-9	70
Heptanal	111-71-7	**1**, Et_3N (1)[c]	THF	120	~60	64853-00-5	*d*
		2, Et_3N (1)[c]	THF	48	30		~50[e]

[a] Determined by NMR on isolated product where applicable. [b] The product was not isolated in this case. [c] Equimolar mixtures of the thiazolium salt and base were used. [d] The aldehyde product was purified by preparative gas chromatography. Gas chromatographic yields in similar reactions were less than 30%. [e] Yield determined by gas chromatography.

incorporation and condensation appear to be altered, but no systematic study has been carried out to measure these effects. In general, the thiazolium salts worked well with unsubstituted aromatic aldehydes and potassium cyanide worked best with substituted aromatic aldehydes. Extension of these reactions to aliphatic aldehydes was unsuccessful. For example, heptanal slowly exchanged its formyl proton for deuterium under our reaction conditions, but we were only able to isolate low yields of incompletely deuterated product (see Table I). Although NMR spectra of reaction mixtures containing stoichiometric amounts of heptanal, **2** (eq 2), and triethylamine showed that the aldehydic formyl proton had disappeared after two days, workup and isolation of the heptanal showed only ca. 30% deuterium incorporation (ca. 50% recovery of starting aldehyde by GLPC). Although we have not continued these studies, we believe that 1,2 addition or reversible condensation occurs under these conditions, making this reaction impractical for the synthesis of formyl-*d* aliphatic aldehydes. Some aromatic aldehydes also failed in these reactions. For example, *p*-nitrobenzaldehyde failed to incorporate deuterium using either potassium cyanide or thiazolium salts as catalysts. In this case, side reactions appeared to consume the starting aldehyde rapidly.

The thiazolium salt or potassium cyanide catalyzed exchange of aromatic aldehyde formyl protons for deuterium described above appears to be an efficacious procedure for the synthesis of some deuterated aldehydes. Advantages include its experimental simplicity, its ease of evaluation by NMR, and the absence of isolated synthetic intermediates. Disadvantages include its lack of complete generality, especially for aliphatic aldehydes, and the excessive reaction times needed in some cases.

Experimental Section

Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were determined on a Varian T-60 spectrometer. Aldehydes used in these experiments were purchased from commercial sources in reagent quality and tested for purity by NMR prior to use. Other organic reagents were used as supplied. Deuterium oxide was purchased from either Aldrich Chemical Co. or Merck Sharp & Dohme Canada Ltd. and was 99.8% *d*. Gas chromatographic analyses of aldehydes were carried out using a Varian Model 2440 gas chromatograph and a 3% SE-30 on 80–100 Chromosorb G column at 100–150 °C.

3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (1) was prepared according to a literature procedure[7] in 72% yield and had mp 138.5–140.5 °C (lit.[7] mp 140–140.5 °C).

3-Ethyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium bromide (2) was prepared according to a literature procedure[7] in 67% yield from 5-(2-hydroxyethyl)-4-methyl-1,3-thiazole and ethyl bromide and had mp 81–80 °C (lit.[7] mp 85–86.5 °C); NMR (Me_2SO-d_6) δ 1.5 (t, 3 H), 2.5 (s, 3 H), 3.1 (t, 2 H), 3.6 (m, 2 H), 4.5 (m, 2 H), 10 (s, 1 H).

General Experimental Procedure. A solution of aldehyde in an organic solvent (1–2 M) and a solution of catalyst (1 or 2 equiv of either thiazolium salt 1 or 2 with an equal amount of base or potassium cyanide) in an equal volume of deuterium oxide were mixed and stirred vigorously at room temperature with a magnetic stirrer. Throughout all reactions two distinct phases were present. The reaction could be monitored periodically by stopping the stirring and examining the organic layer by NMR to determine the amount of deuterium incorporation at the formyl position of the aldehyde. After the exchange had gone to completion, the deuterated aldehyde was isolated by an extractive procedure followed by distillation or column chromatography, or, in the case of heptanal, preparative gas chromatography. Deuterium incorporation in the purified product was measured by NMR, and the product's purity was established by comparison with literature spectra, thin-layer or gas chromatography, melting point, and by conversion of liquid products to an established solid derivative using standard procedures. All of the reactions reported with isolated yields in Table I were run on 10–50 mmol of aldehyde.

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Registry No.—Deuterium-oxide, 7789-20-0; **1**, 16311-68-5; **2**, 54016-70-5.

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Rearrangements and Ring Expansions of 4*H*-Cyclopenta[*def*]phenanthrene Derivatives

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4*H*-Cyclopenta[*def*]phenanthrene (**1**)[1] is of interest because it is a strained molecule combining special features of both the fluorene and the phenanthrene structures, but the reactivities of **1** have been scarcely reported.[2]

The present paper deals with rearrangements and ring expansions on the active methylene bridge of **1**.

Pyrene (**2**) and its homologues were synthesized in good yields by Wagner–Meerwein rearrangements of the corresponding alcohols, which were obtained through the series of reactions indicated below. Alcohols **3** and **4** were converted into **5**[3] and **6**[4] without the formation of cyclopropane and vinyl by-products.

$$1 \longrightarrow 7 \longrightarrow 8 \longrightarrow 9 \longrightarrow 2;\ 7 \longrightarrow 13 \longrightarrow 14 \longrightarrow 3 \longrightarrow 5$$
$$10 \qquad\qquad 11 \qquad\qquad 1 \longrightarrow 15 \longrightarrow 16 \longrightarrow 4 \longrightarrow 6$$
$$12$$

Heterocyclic compounds **17**,[5] **18**,[6] and **19**[5] were obtained by methods similar to those employed in fluorene derivatives as follows.

$$1 \rightarrow 20 \rightarrow 21 \rightarrow 17;\ 20 \rightarrow 18;\ 20 \rightarrow 22 \rightarrow 19$$

The IR and NMR spectra of lactam **17** showed that there was no detectable amount of the enol form.

3,4-Benzocoumarin[7] was cleaved to 2′-hydroxydiphenyl-2-carboxylic acid under the basic conditions; however, the same scission in lactone **18** did not occur. This suggests that two groups, 4-COONa and 5-ONa, at the phenanthrene skeleton are large enough to prevent their existence in the same plane.

Pinacol **23** was changed into pinacolone **24** by pinacolic rearrangement, which was in turn converted into fluorescent hydrocarbon **25** through retro-pinacol rearrangement of its reduction product **26**. The scission of spiro carbon and carbonyl carbon atoms in **24** was resisted under the same basic conditions which resulted in the formation of 2′-(9-fluorenyl)diphenyl-2-carboxylic acid from 10-(2,2′-biphenylylene)-9-phenanthrone.[8] This finding can be ascribed to cause a similar reaction to that cited for **18** vs. 3,4-benzocoumarin.

The Wolff–Kishner reduction of **24** was attempted under the ordinary conditions and gave alcohol **26** but not the expected hydrocarbon. Actually, **24** could not form hydrazone derivatives. It is therefore evident that hydrazine hydrate behaves simply as a reductant in regard to **24**.

Experimental Section

All the melting points are uncorrected. All the new compounds gave correct elemental analyses. The instruments used in these analyses have been described elsewhere.[9]

4,5-Phenanthryleneacetic Acid (7).[1] A solution of 1.9 g (10 mmol) of **1** in 25 mL of xylene was added dropwise to an *n*-BuLi solution prepared from 2.0 g (15 mmol) of *n*-BuBr; crushed dry ice (ca. 5.0 g) was added gradually to the mixture at −10 °C. The resulting mixture was refluxed for 1 h to afford 1.30 g (56%) of **7**, mp 250–251 °C (dec). Methyl ester (**13**),[10] mp 63.5–64.5 °C. Ethyl ester (**8**): mp 51.5–53.0 °C; IR 1730 cm^{-1}; NMR (CCl_4) δ 1.25 (3 H, t, J = 6.0 Hz), 4.17 (2 H, q), 5.19 (1 H, s), and 7.30–8.03 (8 H, m).

When the reaction was carried out using 6.0 g (44 mmol) of *n*-BuBr, 5-(4,5-phenanthrylene)nonane (**10**) was obtained in 1.45-g (48%) yield: mp 88.5–89.5 °C; mass spectrum *m/e* 302 (M^+), 245, and 203.

4-Acetylcyclopenta[*def*]phenanthrene (15). This compound was prepared by the reaction[11] of **1** with EtOAc in 48% yield: mp 89–91 °C; NMR (CCl_4) δ 1.66 (3 H, s), 5.14 (1 H, s), and 7.45–8.00 (8 H, m).

Methyl 2-(4,5-Phenanthrylene)propionate (14) and 4-Methyl-4-acetylcyclopenta[*def*]phenanthrene (16). Ester **13** (1.00 g, 4 mmol) was dissolved in MeOH containing NaOMe (0.38 g or 0.0165 g-atom of Na in 25 mL of MeOH); then the mixture was stirred with 4.56 g (32 mmol) of MeI for 24 h at room temperature to yield 0.93 g (89%) of **14**: mp 108.0–109.5 °C; IR 1722 cm^{-1}; mass spectrum *m/e* 262 (M^+); NMR (CCl_4) δ 1.88 (3 H, s), 3.52 (3 H, s), and 7.52–8.10 (8 H, m).

Compound **16** was obtained in 94% yield: mp 99–100 °C; IR 1698 cm^{-1}; mass spectrum *m/e* 246 (M^+), 203, 202, and 189; NMR (CCl_4) δ 1.37 (3 H, s), 1.73 (3 H, s), and 7.45–7.94 (8 H, m).

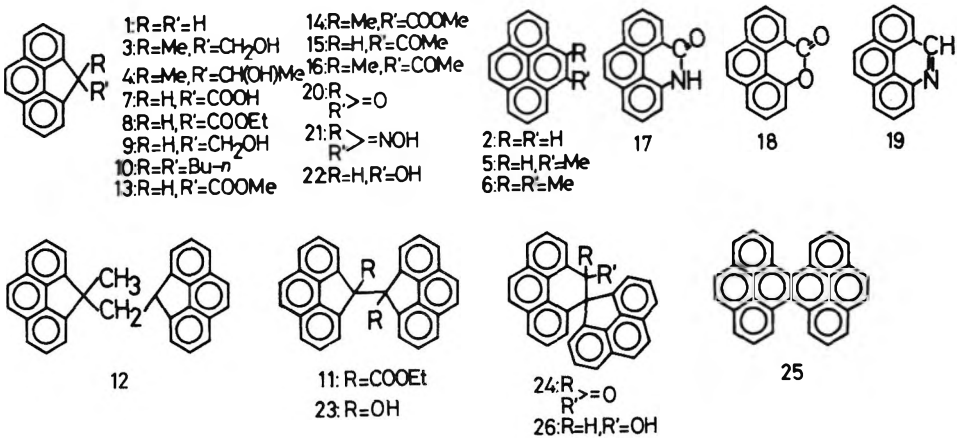
2-(4,5-Phenanthrylene)ethanol (9) and its Homologues. To a suspension of $LiAlH_4$ (0.10 g, 2.6 mmol) in 20 mL of ether was added dropwise 1.00 g (3.8 mmol) of **8** in 20 mL of ether with stirring over 30 min. The mixture was stirred for 1 h at room temperature and refluxed over an additional 30 min to yield, after workup, 0.40 g (48%) of **9**: mp 159–160 °C; IR 3210 and 3120 cm^{-1}; mass spectrum *m/e* 220 (M^+); NMR (C_6D_6) δ 3.68 (2 H, d, J = 7.2 Hz), 4.34 (1 H, t), 7.19 (1 H, s), and 7.43–8.07 (8 H, m). In addition, 0.06 g (6%) of ethyl 1,2-di(4,5-phenanthrylene)succinate (**11**) was isolated, mp 226–227 °C; IR 1721 cm^{-1}; NMR (C_6D_6) δ 0.79 (6 H, t, J = 7.2 Hz), 4.03 (4 H, q), and 7.03–7.80 (16 H, m).

The reduction was done using 1.44 g (38 mmol) of $LiAlH_4$ to afford 0.18 g (23%) of 1,3-di(4,5-phenanthrylene)butane (**12**): mp 175.5–177.0 °C; mass spectrum *m/e* 406 (M^+), 217, 203, and 189; NMR (C_6D_6) δ 1.55 (3 H, s), 2.74 (2 H, d, J = 4.5 Hz), 3.55 (1 H, t), and 6.55–7.74 (16 H, m).

2-(4,5-Phenanthrylene)propanol (**3**) was prepared from **14** in 84% yield: mp 108–109 °C; IR 3275 cm^{-1}; mass spectrum *m/e* 234 (M^+); NMR (C_6D_6) δ 1.39 (1 H, s), 1.55 (3 H, s), 3.57 (2 H, s), and 7.23–7.97 (8 H, m).

3-(4,5-Phenanthrylene)-2-butanol (**4**) was obtained from **16** in 50% yield: bp 203–207 °C (2 Torr, uncorrected); IR 3570 and 3420 cm^{-1}; mass spectrum *m/e* 248 (M^+), 204, 202, and 189; NMR (CCl_4) δ 0.61 (3 H, d, J = 6.3 Hz), 1.57 (3 H, s), 1.70 (1 H, s), 4.12 (1 H, q), and 7.32–7.93 (8 H, m).

Wagner–Meerwein Rearrangements of Alcohols 3, 4, and 9.



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A mixture of **9** (0.25 g, 1.1 mmol) and P_2O_5 (0.50 g) in xylene (20 mL) was refluxed for 2 h to give 0.22 g (95%) of **2**, which was identical in all respects with an authentic specimen.

By the same method, **3** was converted into 4-methylpyrene (**5**) in 82% yield, mp 147.5–148.5 °C.

4,5-Dimethylpyrene (**6**) was produced from **4** in 85% yield, mp 215–216 °C.

Beckmann Rearrangement of 4-Hydroxyiminocyclopenta[*def*]phenanthrene (21). A mixture of **21**[5] (1.095 g, 5 mmol, prepared from **20**[1] in 96% yield) and PPA (80%, 30 g) was stirred at 175–180 °C for 5 min to yield 0.62 g (57%) of 4,5-dihydro-4-azapyren-5-one (**17**): mp 348–350 °C (dec); IR 3160 and 1661 cm^{-1}.

Reaction of 4-Oxocyclopenta[*def*]phenanthrene (20) with Hydrogen Peroxide. To a solution of **20** (0.51 g, 2.5 mmol) in HOAc (30 mL) were added dropwise concentrated H_2SO_4 (7 mL) and then H_2O_2 (28%, 2.5 mL). The mixture was stirred at room temperature for 2 h to afford 0.45 g (82%) of 4-oxapyren-5-one (**18**): mp 200.5–201.5 °C; IR 1727 cm^{-1}.

4-Azapyrene (19). Concentrated H_2SO_4 (2 mL) was added to a suspension of NaN_3 (0.57 g, 8.8 mmol) in $CHCl_3$ (5 mL) at −10 °C with stirring for 30 min; then a suspension of 4-hydroxycyclopenta[*def*]-phenanthrene (**22**)[12] (1.03 g, 5 mmol, prepared from **20** in 86% yield) in $CHCl_3$ (50 mL) was added to the first mixture at 25 °C during a period of 20 min. After stirring at room temperature for an additional 1 h, ice (20 g) was added and the resulting mixture was allowed to stand overnight; **19** (0.43 g, 43%), mp 157.5–159.0 °C, was isolated.

Di(4,5-phenanthrylene)-1,2-ethanediol (23). Ketone **20** (2.04 g, 10 mmol) was treated with $TiCl_4$ (3.0 g, 15.8 mmol) and Zn dust (1.96 g, 0.03 g-atom) in THF (140 mL) according to the method described elsewhere[9] to give 1.73 g (84%) of **23**: mp 230.5–232.0 °C (dec); IR 3525 cm^{-1}; NMR (Me_2SO-d_6) δ 3.40 (2 H, s) and 6.25–8.05 (16 H, m).

Pinacol–Pinacolone Rearrangement of 23. A solution of 0.30 g (0.73 mmol) of **23** in 15 mL of HOAc was refluxed for 1 h with a few drops of concentrated H_2SO_4 to yield 0.25 g (87%) of **24**: mp 230–230.5 °C; IR 1667 cm^{-1}; mass spectrum *m/e* 392 (M^+) and 364.

Retro-pinacol Rearrangement of 4,5-Dihydro-4-oxo-5-(4,5-phenanthrylene)pyrene (24). A solution of 0.45 g (1.1 mmol) of **24** in 45 mL of HOAc was refluxed for 18 h with HI (57%, 1 mL) and red P_4 (1.0 g) to give 0.39 g (91%) of tetrabenzo[*de,hi,mn,qr*]naphthacene (**25**): mp 296–297 °C; mass spectrum *m/e* 376 (M^+) and 202; NMR (C_5D_5N) δ 8.00–8.52 (16 H, m).

4,5-Dihydro-4-hydroxy-5-(4,5-phenanthrylene)pyrene (26). A solution of **24** (0.5 g, 1.3 mmol) in THF (60 mL) was refluxed with $LiAlH_4$ (0.12 g, 3.2 mmol) for 3 h to afford 0.42 g (84%) of **26**: mp 151–152 °C (dec); IR 3570 and 3460 cm^{-1}; NMR (C_6D_6) δ 1.50 (1 H, d, J = 6.3 Hz), 5.08 (1 H, d), and 6.75–7.85 (16 H, m).

Alcohol **26** (0.37 g, 74%) was also isolated by the reaction of **24** (0.5 g, 1.3 mmol) with hydrazine hydrate (90%, 0.2 g, 4 mmol) and KOH (0.1 g, 1.8 mmol) in diethylene glycol (60 mL) at 100–110 °C for 1 h and then at 200–210 °C for additional 3 h.

Wagner–Meerwein Rearrangement of 26. A mixture of **26** (0.25 g, 0.63 mmol), HI (57%, 0.4 mL), and red P_4 (0.07 g) in HOAc (20 mL) was refluxed for 30 min; 0.21 g (88%) of **25** was obtained.

Registry No.—**1**, 203-64-5; **2**, 129-00-0; **3**, 64884-30-6; **4**, 64884-31-7; **5**, 3353-12-6; **6**, 15679-25-1; **7**, 5660-87-7; **8**, 64884-32-8; **9**, 64884-33-9; **10**, 64900-53-4; **11**, 64884-34-0; **12**, 64884-35-1; **13**, 64884-36-2; **14**, 64884-37-3; **15**, **64884-38-4**; **16**, 64884-39-5; **17**, 64884-40-8; **18**, 23702-49-0; **19**, 194-03-6; **20**, 5737-13-3; **21**, 64884-41-9; **22**, 64884-42-0; **23**, 64884-43-1; **24**, 64913-41-3; **25**, 385-13-7; **26**, 64884-44-2; BuBr, 109-65-9; EtOAc, 141-78-6.

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A New Preparative Method for α,β-Unsaturated δ-Lactones from the Reaction of 3-Hydroxy Acids with 1,3,5-Trioxane

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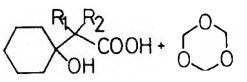
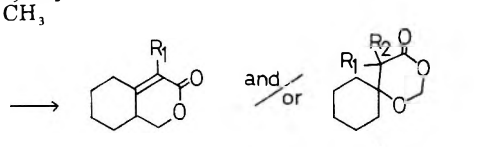
Various methods for the preparation of lactones are well known; for example, saturated lactones are prepared by oxidation of cyclobutanones,[1] reduction of cyclic carboxylic acid anhydrides,[2] cyclization of 4-hydroxy acids,[3] and so on. Synthetic methods for unsaturated lactones[4] and α-methylene lactones[5] are also well known. However, a synthesis of α,β-unsaturated δ-lactones from 3-hydroxy acids has not been known. We now wish to report a synthesis of α,β-unsaturated δ-lactones **2** from the reaction of 3-hydroxy acids **1** with



1

a, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = C_2H_5$; $R_2 = H$
d, $R_1 = n\text{-}C_3H_7$; $R_2 = H$
e, $R_1 = i\text{-}C_3H_7$; $R_2 = H$
f, $R_1 = n\text{-}C_4H_9$; $R_2 = H$
g, $R_1 = R_2 = CH_3$



2

a, $R_1 = H$
b, $R_1 = CH_3$
c, $R_1 = C_2H_5$
d, $R_1 = n\text{-}C_3H_7$
e, $R_1 = i\text{-}C_3H_7$
f, $R_1 = n\text{-}C_4H_9$

3

a, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = C_2H_5$; $R_2 = H$
d, $R_1 = n\text{-}C_3H_7$; $R_2 = H$
e, $R_1 = i\text{-}C_3H_7$; $R_2 = H$
f, $R_1 = n\text{-}C_4H_9$; $R_2 = H$
g, $R_1 = R_2 = CH_3$

1,3,5-trioxane or paraformaldehyde. When a mixture of 2-(1′-hydroxycyclohexan-1′-yl)propionic acid (**1b**), 1,3,5-trioxane, and sulfuric acid was refluxed in acetic acid for 0.5

Table I. Reaction of 2-(1′-Hydroxycyclohexan-1′-yl)propionic Acid (1b) with 1,3,5-Trioxane or Paraformaldehyde in the Presence of Acidic Materials[a]

Acidic materials	Yield (%)[b] of **3b**[f]	Yield (%)[b] of **2b**[g]	Yield (%)[b] of **3b**[g]
H_2SO_4	71	88[d]	
	(55)[c]	(80)	*c,e*
H_3PO_4	33	61	
	(33)[c]	(1)	(55)[c]
$ZnCl_2$	19	61	23
	(19)[c]	(5)	(48)[c]
$AlCl_3$	96	97	
	(78)[c]	(52)	(25)[c]
BF_3–ether complex	99	66	
	(59)[c]	(56)	*e*
Polyphosphoric acid	99	50	
	(48)[c]	(51)	*c*

[a] 3-Hydroxy acid **1b** (8.6 g, 50 mmol), 1,3,5-trioxane (2.7 g, 30 mmol), acidic materials (25 mmol), and acetic acid (50 mL) were used. [b] The yield are based on 3-hydroxy acid used. [c] In these cases, paraformaldehyde was used. [d] Reaction time was 0.5 h. [e] Reaction time was 2 h. [f] At 25 °C for 8 h. [g] At 118 °C for 8 h.

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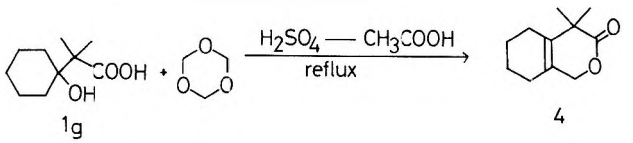
Table II. Reaction of 3-Hydroxy Acids 1 with 1,3,5-Trioxane or Paraformaldehyde in the Presence of 97% Sulfuric Acid[a]

Compd	Registry no.	Temp, °C	Product	Registry no.	Yield,[b,f] (%)	Bp, °C (mm)	IR (film), cm^{-1}, $\nu_{C=O}$	UV (CH_3OH) λ_{max}, nm (ϵ)	^1H NMR spectra (CCl_4 soln), δ (ppm)
1a	14399-63-4	118	**2a**	6051-18-9	59 (20)[c]	115–118 (5)	1695, 1720	223 (10 000)	1.2–2.1 [m, 6 H, $-(CH_2)_3-$], 2.2–2.7 (m, 2 H, $-CH_2C{=}C$), 2.6 (m, 1 H, $-CHC{=}C$), 3.4–4.5 (m, 2 H, $-COOCH_2$), 5.6 (s, 1 H, $-CH{=}C$)
1b	34239-39-9	118	**2b**	64884-47-5	88[d] (80)[c,e]				
1c	512-16-3	118	**2c**	64884-48-6	64 (44)[c]	130–132 (4)	1710	234 (9500)	1.0 (t, J = 7 Hz, 3 H, CH_3CH_2), 1.5–1.9 [m, 6 H, $-(CH_2)_3-$], 2.0 (t, J = 7 Hz, 2 H, $-CH_2{=}C$), 2.3 (q, J = 7 Hz, 2 H, CH_3CH_2), 2.6 (m, 1 H, $-CH{=}C$), 3.6–4.4 (m, 2 H, $-COOCH_2-$)
1d	58888-86-1	118	**2d**	64884-49-7	88 (31)[c]	135–138 (4)	1710	234 (7500)	0.9 (t, J = 6 Hz, 3 H, CH_3CH_2), 1.2–1.8 [m, 8 H, $-(CH_2)_3-$, CH_3CH_2], 2.0 (t, J = 7 Hz, 2 H, $-CH_2C{=}C$), 2.3 (t, J = 6 Hz, 2 H, $CH_3CH_2CH_2$), 2.7 (m, 1 H, $-CHC{=}C$), 3.6–4.4 (m, 2 H, $-COOCH_2-$)
1e	64884-45-3	118	**2e**	64884-50-0	59 (16)[c]	130–134 (4)	1710	232 (7000)	1.0 [d, J = 7 Hz, 6 H, $(CH_3)_2CH$], 1.4–2.1 [m, 8 H, $-(CH_2)_4-$], 2.9 [m, 2 H, $(CH_3)_2CH$, $CHC{=}C$], 3.6–4.3 (m, 2 H, $-COOCH_2-$)
1f	27925-40-2	118	**2f**	64884-51-1	64 (37)[c]	132–136 (3)	1710	235 (6900)	0.95 (t, J = 6 Hz, 3 H, CH_3CH_2), 1.1–1.5 [m, 10 H, $-(CH_2)_3-$, $CH_3CH_2CH_2$)], 2.0 (t, J = 7 Hz, 2 H, $-CH_2C{=}C$), 2.25 (t, J = 7 Hz, 2 H, $-CH_2C{=}C$), 2.8 (m, 1 H, $-CHC{=}C$), 3.6–4.4 (m, 2 H, $-COOCH_2-$)
1a		25	**3a**	64884-52-2	25 (23)[c]	86–88 (6)	1760		1.4–1.8 [m, 10 H, $-(CH_2)_5-$], 2.5 (s, 2 H, $-CH_2COO-$), 5.25 (s, 2 H, $-OCH_2O-$)
1b		25	**3b**	64884-53-3	71 (55)[c]				
1c		25	**3c**	64884-54-4	43 (22)[c]	110–113 (4)	1755		1.0 (t, J = 6 Hz, 3 H, CH_3CH_2), 1.3–1.8 [m, 12 H, $-(CH_2)_5-$, CH_3CH_2], 2.4 (d, J = 9 Hz, 1 H, $-CHCOO-$), 5.35 (q, J_{AB} = 6 Hz, 2 H, $-OCH_2O-$)
1d		25	**3d**	64884-55-5	67 (20)[c]	112–115 (3)	1755		1.0 (t, J = 6 Hz, 3 H, CH_3CH_2), 1.3–1.8 [m, 14 H, $-(CH_2)_5-$, $-(CH_2)_2-$], 2.45 (d, J = 9 Hz, 1 H, $-CHCOO-$), 5.35 (q, J_{AB} = 6 Hz, 2 H, $-OCH_2O-$)
1e		25	**3e**	64884-56-6	60 (36)[c]	110–113 (3)	1745		1.05 and 1.1 (d, J = 6 Hz, 6 H, CH_3CH 2×), 1.4–1.85 [m, 10 H, $-(CH_2)_5-$], 2.0 (m, 1 H, $(CH_3)_2CH-$), 2.2 (d, J = 9 Hz, 1 H, $-CHCOO-$), 5.3 (q, J_{AB} = 6 Hz, 2 H, $-OCH_2O-$)
1f		25	**3f**	64884-57-7	51 (30)[c]	126–129 (4)	1755		0.95 (t, J = 6 Hz, 3 H, CH_3CH_2), 1.2–1.9 [m, 16 H, $-(CH_2)_5-$, $-(CH_2)_3-$], 2.45 (d, J = 9 Hz, 1 H, $-CHCOO-$), 5.3 (q, J_{AB} = 6 Hz, 2 H, $-OCH_2O-$)
1g	27925-40-2	25	**3g**	64884-58-8	80 (34)[c]	126–128 (3)	1740		1.15 [s, 6 H, $(CH_3)_2$], 1.3–1.8 [m, 10 H, $-(CH_2)_5-$], 5.3 (s, 2 H, $-OCH_2O-$)

[a] 3-Hydroxy acid 1 (50 mmol), 1,3,5-trioxane (30 mmol), 97% sulfuric acid (2.5 g), and acetic acid (50 mmol) were used; reaction time, 8 h. [b] The yields are based on 3-hydroxy acid. [c] Paraformaldehyde was used instead of 1,3,5-trioxane. [d] Reaction time, 0.5 h. [e] Reaction time, 2 h. [f] Satisfactory analytical data (±0.3% for C, H) were reported for all compounds.

h, α,β-unsaturated δ-lactone **2b** was obtained in 88% yield; interestingly, at 25 °C for 8 h only spirolactone **3b** was obtained in 71% yield. The structures of compounds **2b** and **3b** were confirmed by spectral and elemental analyses. The same technique was used for the synthesis of **2b** and **3b** using several acidic materials. The results are listed in Table I. The reaction has also been extended to other 3-hydroxy acids. As shown in Table II, α,β-unsaturated δ-lactones **2** and spirolactones **3** are obtained in good yield. In the case of 2-(1′-hydroxycyclohexan-1′-yl)isobutyric acid (**1g**), β,γ-unsaturated δ-lactone **4** was obtained. These observations indicate that the reaction at lower temperature gives spirolactones **3**, but at higher temperature gives unsaturated δ-lactones **2**, respectively.



1g 4

Experimental Section

The reaction products were analyzed by GLC on a Shimadzu Model GC-3BF chromatograph using a 3 m × 3 mm column of 15% silicone DC 200 on 60–80 mesh Celite 545. NMR spectra were obtained using carbon tetrachloride as a solvent on a Hitachi Model R-24 spectrometer. The chemical-shift values are expressed in δ values (parts per million) relative to a tetramethylsilane internal standard. IR spectra were obtained on a Jasco Model IR-G infrared spectrophotometer. UV spectra were obtained on a Hitachi Model EPS-3T spectrophotometer. Mass spectra were obtained on a Hitachi Model RMU-7M mass spectrometer.

Synthesis of Starting Materials. 3-Hydroxy acids **1** were prepared from carboxylic acids and cyclohexanone as reported previously.[6]

α,β-Unsaturated δ-Lactone 2b. A mixture of 2-(1′-hydroxycyclohexan-1′-yl)propionic acid (**1b**) (8.6 g, 50 mmol), 1,3,5-trioxane (2.7 g, 30 mmol), and 97% sulfuric acid (2.5 g) in 50 mL of acetic acid was refluxed for 0.5 h. To the reaction mixture, 200 mL of water was slowly added. It was then extracted with diisopropyl ether. The organic extract was washed with water and dried over sodium sulfate, the solvent was removed, and the residue was distilled in vacuo to give 7.3 g of **2b** (yield 88%): bp 124–125 °C (4 mm); IR (film) ν_{max} 1710 cm^{-1}; UV (CH_3OH) λ_{max} 232 nm (ε 10 000); NMR δ 1.1–1.7 [m, 6 H, $-(CH_2)_3-$], 1.8 (s, 3 H, $CH_3C{=}C$), 2.0 (m, 2 H, $-CH_2C{=}C$), 2.7 (m, 1 H, $CHC{=}C$), 3.2–4.4 (m, 2 H, $-COOCH_2-$); MS (*m/e*) M$^+$ 166.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.08; H, 8.50.

Spirolactone 3b. A mixture of 3-hydroxy acid **1b** (8.6 g, 50 mmol), 1,3,5-trioxane (2.7 g, 30 mmol), and 97% sulfuric acid (2.5 g) in 50 mL of acetic acid was stirred for 8 h at 25 °C. Workup in the usual fashion gave 6.5 g of **3b** (yield 71%): bp 117–119 °C (4 mm); IR (film) ν_{max} 1745 cm^{-1}; NMR δ 1.0 (d, J = 6 Hz, CH_3CH), 1.3–2.1 [m, 10 H, $-(CH_2)_5-$], 2.65 (q, J = 6 Hz, 1 H, CH_3CH), 5.3 (q, J = 6 Hz, $-OCH_2O-$); MS (m/e): M$^+$ = 184.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.21; H, 8.80.

β,γ-Unsaturated δ-Lactone 4. A mixture of 3-hydroxy acid **1g** (9.3 g, 50 mmol), 1,3,5-trioxane (2.7 g, 30 mmol), 97% sulfuric acid (2.5 g), and 50 mL of acetic acid was refluxed for 0.5 h. The mixture was treated in the usual way to give 7.5 g of β,γ-unsaturated δ-lactone **4** (yield 83%): bp 118–120 °C (5 mm); IR (film) ν_{max} 1735 cm^{-1}; NMR δ 1.2 [s, 6 H, $(CH_3)_2$], 1.65 (m, 4 H, $-CH_2CH_2-$), 1.9 (m, 4 H, $-CH_2C{=}CCH_2-$), 4.5 (s, 2 H, $-C{=}CCH_2O-$); MS (*m/e*) M$^+$ 180.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.19; H, 8.99.

When paraformaldehyde was used instead of 1,3,5-trioxane, 3.0 g of **4** was obtained (yield 33%).

Registry No.—**4**, 64884-59-9; 1,3,5-trioxane, 110-88-3; paraformaldehyde, 30525-89-4.

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Phosphorus Nuclear Magnetic Resonance Spectra of Complexes of Aluminum Chloride with Phosphorus(III) Chlorides: Structure of the Reaction Product from the Phenylphosphonous Dichloride Complex with Tetramethylethylene[1]

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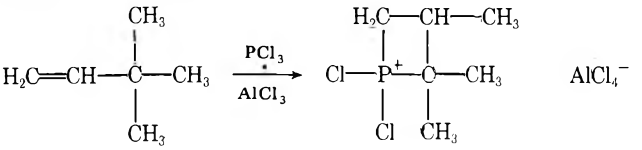
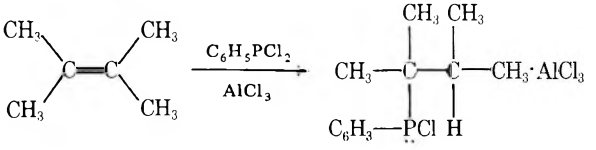
The use of aluminum chloride to activate phosphorus trichloride toward reaction with aromatic compounds dates back nearly one hundred years and has provided a standard method for the preparation of arylphosphonous dichlorides.[2] More recently, carbon–phosphorus bonds have been established by the reaction of olefins and mixtures of $AlCl_3$ and phosphorus(III) halides; the products are diverse and controlled by the structure of the olefin. The best known reaction of this type involves an olefin having a branched carbon attached to the double bond, which leads to the phosphetane system[3,4] via a skeletal rearrangement. A number of olefins have been used



in this process,[3,4] and other phosphorus halides that participate include $C_6H_5PCl_2$,[4] CH_3PCl_2,[4] and PBr_3.[5] Another course is followed with tetramethylethylene[6] and $C_6H_5PCl_2$; the product is noncyclic and alleged to have trivalent phosphorus in a complex with $AlCl_3$ (**1**). A reaction also occurs between



1

ethylene and PCl_3[7] or PBr_3[8] in the presence of the corresponding aluminum halide; the products are more complex but depend in part on addition of a PX_2 fragment and halogen to the double bond. Phenylphosphonous dichloride gives the product $C_6H_5P(Cl)CH_2CH_2Cl$ in this reaction.[9] Extension of the reaction to dienes[10,11] has provided novel heterocyclic systems from participation of the second double bond.

In some of the reports on these reactions,[3-6,10,11] it has been assumed that the $AlCl_3$–PCl_3 interaction forms an ionic complex ($Cl_2\overset{+}{P}$ $AlCl_4^-$) and that the cation is the species attacking the olefin. Similar structures are also sometimes assumed to be formed from phosphonous dichlorides. While formation of such ionic complexes seems reasonable, there is actually no experimental evidence in the literature that points to their existence. Indeed, there is evidence to the contrary in the case of PCl_3; it is explicitly stated[12,13] that no complex, ionic or molecular, is formed in detectable amount from $AlCl_3$ and PCl_3, and recent reviews[2,14] of the reaction of such mixtures with aromatics are careful to point out that the attacking

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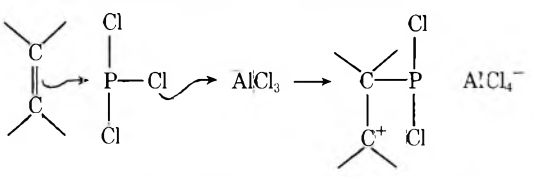
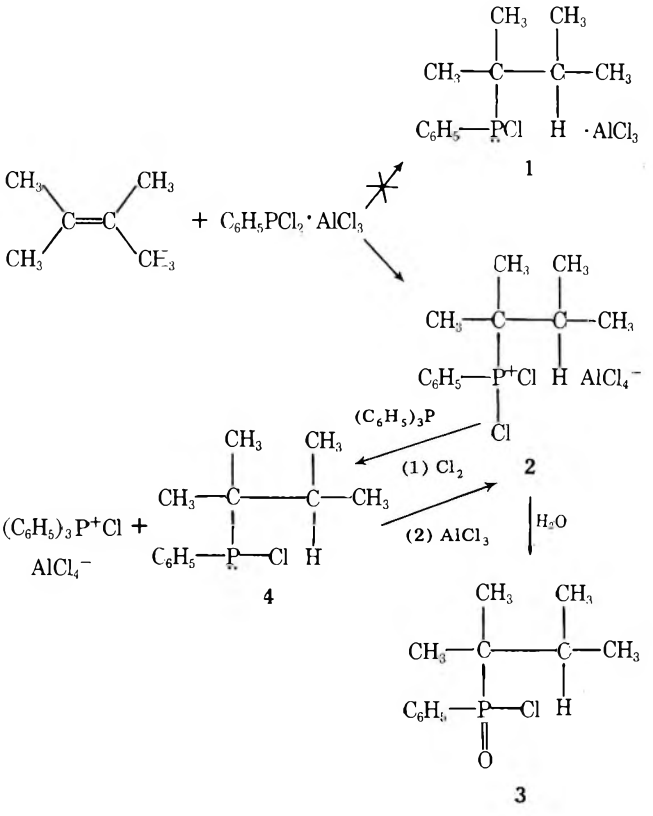
electrophilic species is of unknown structure. A new textbook[15] also refrains from showing the positive ion as the attacking species in reactions with aromatics or olefins. On the other hand, several papers have presented convincing evidence that amino-substituted phosphorus halides can be converted to cationic species with Lewis acids such as PCl_5,[16] $AlCl_3$,[17,18] and PF_5.[19] The nitrogen electrons are presumed to stabilize the positive charge in these products. The ^{31}P NMR chemical shifts are particularly indicative of the positive charge developing on phosphorus; very large downfield shifts occur relative to the neutral trivalent species (e.g.,[13] $(Me_2N)_2PCl$ δ +160, $(Me_2N)_2P^+$ δ +264; chemical shifts are referenced to 85% H_3PO_4, with positive values downfield). However, when nonionic complexes are formed from Lewis acids, chemical shift effects are small[18] and sometimes in the upfield direction, as with tertiary phosphines interacting with $AlCl_3$.[20]

We have now used ^{31}P NMR to examine the species formed between $AlCl_3$ and those phosphorus(III) halides so useful in the establishment of bonds to carbon. When $C_6H_5PCl_2$ or CH_3PCl_2 was mixed with 1 equiv of $AlCl_3$ in CH_2Cl_2 at 0 °C, clear solutions resulted. In both cases, the original ^{31}P NMR signal of the phosphonous dichloride vanished and was replaced by two strong signals at substantially higher field: CH_3PCl_2 δ +192.1, CH_3PCl_2·$AlCl_3$ δ +131.9 and +97.5; $C_6H_5PCl_2$ δ +161.2, $C_6H_5PCl_2$·$AlCl_3$ δ +112.1 and +84.3). A careful search for a phosphorus cation was made in the remote downfield region, but no measurable amount of such an ion was observed. It is clear that these *phosphonous dichlorides form molecular and not ionic complexes with $AlCl_3$*. The existence of two signals simply implies that complexes with varying ratios of reactants are formed, a phenomenon already observed for tertiary phosphine complexes.[20] This was confirmed by observing the effect of reactant ratio on the ^{31}P spectrum of $C_6H_5PCl_2$ complexes. With a 2:1 ratio of phosphonous dichloride to $AlCl_3$ only one ^{31}P signal was present (δ +110.9); the reverse ratio also gave only one signal but at much higher field (δ +69.1). Diphenylphosphinous chloride (δ +79.2 in CH_2Cl_2) was also included in our study and likewise formed two molecular complexes (δ +68.3 and +41.3) when mixed with 1 equiv of $AlCl_3$. On the other hand, PCl_3 failed to dissolve a noticeable amount of $AlCl_3$ in CH_2Cl_2, and the solution showed only the ^{31}P signal for PCl_3 (δ +219.2). This, of course, is consistent with the conclusions of others derived from different experimental approaches.[12,13]

These observations cast much doubt on the validity of the reaction mechanisms that employ divalent phosphorus cations as an electrophilic species. While the possibility cannot be excluded that a tiny, spectroscopically undetectable amount of such a species could serve as a relay to effect a reaction between the molecular complex or free phosphorus halide, it seems far more plausible to use as the electrophile that species which does exist in the medium. With this view, we assume that $AlCl_3$ serves to increase the electrophilic character of phosphonous dichlorides through complexation; for PCl_3, where no complex is formed, $AlCl_3$ may serve to assist in the removal of chloride as the C–P bond is forming.

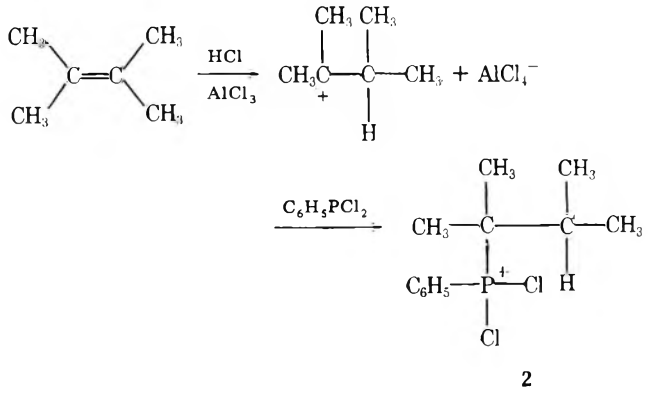


In examining the literature on $AlCl_3$-promoted reactions with olefins, we noticed one case that seemed explainable by a quite different mechanism; furthermore, the report showed a structure for a product that did not entirely satisfy the observed properties. The case is that of reaction of the $C_6H_5PCl_2$–$AlCl_3$ complex in CH_2Cl_2 with tetramethylethylene.[6] The product of this reaction has been assigned structure **1**. While the carbon fragment of the product seemed correctly assigned as depicted in **1**, with the hydrogen on the β-carbon introduced with the $AlCl_3$, it appeared more likely that the phosphorus functionality had the form $RC_6H_5P^+Cl_2$ $AlCl_4^-$ as in **2** rather than the form $RC_6H_5\dot{P}Cl$·$AlCl_3$ of **1**. Thus, it was reported that a phosphinic chloride (**3**) was formed on water treatment of **1**; this would require that air oxidation accompany the process. However, the phosphinic chloride would be the expected product from partial hydrolysis of **2**. Also, the two methyls on the α-carbon were equivalent in their NMR spectra, a fact accommodated by **2** but not by **1**, where phosphorus is a chiral center. If **2** is indeed the correct structure, then the product obtained with $(C_6H_5)_3P$ would be **4**, as assigned,[6] but formed by the well-known halogen exchange reaction and not by decomplexation of **1** as proposed.



We therefore repeated this reaction and observed the same ^1H and ^{13}C NMR spectral properties as reported for the initial product.[6] We also obtained the ^{31}P NMR spectrum, which was not done in the original work, and observed a signal at δ +126.2. No other signals were present, implying complete conversion of the $C_6H_5PCl_2$–$AlCl_3$ complex to the product. This shift is consistent with ionic representation **2**, but does not prove its existence. This proof was then obtained by repeating the synthesis of phosphinous chloride **4** (^{31}P NMR δ +109.2) and treating it with 1 equiv each of chlorine and $AlCl_3$. The product, of necessity having structure **2**, was identical in NMR properties to the initial reaction product from the olefin.

With this revised structure the tentative mechanism[6] needs reconsideration since it cannot account for the formation of **2**. We see special mechanistic significance in the formation of the new carbon–hydrogen bond in **2**. The original work[6] showed conclusively that HCl or H_2O in the $AlCl_3$[21] was the source of this hydrogen, and we propose, as one possible mechanism, that protonation of tetramethylethylene is the initial step in the process leading to **2**. This would form a carbonium ion that could then alkylate the phosphonous dichloride. That a potent alkylating species is formed by in-



2

teraction of the olefin and the $AlCl_3$ reagent is indicated by our observation that the olefin itself is alkylated, rapidly forming a polymer, when the phosphorus compound is omitted from the reaction medium. It is a known property of trivalent phosphorous compounds that they undergo alkylation by carbonium ions; the well-known reaction of Kinnear and Perren[22] employs this principle for C–P bond formation, using alkyl halides as the source of carbonium ions. Other mechanisms are not excluded, however, and one that is attractive involves a phosphirane intermediate, as proposed earlier.[6] If a phosphirane or any other type of intermediate is involved, it must have an extremely short lifetime; on conducting the reaction at −80 °C and examining the product by ^{31}P NMR after only 15 min, we found **2** to be the only species present.

The uniqueness of the behavior of tetramethylethylene to the $C_6H_5PCl_2$–$AlCl_3$ complex needs to be emphasized. No other example is known of a structure where there is net addition of hydrogen and a phosphorus function to the double bond. Tetramethylethylene represents the only tetrasubstituted olefin among the several compounds that have been exposed to the $AlCl_3$–phosphorus halide complexes, and the well-known higher order of nucleophilicity of such olefins may be responsible for its different behavior and postulated sensitivity to protonation. Its failure to form a phosphetane has also been attributed[6] to the high energy requirement for the 1,2-hydride shift (in essence forming a primary carbonium ion) that would have to occur as a prelude to cyclization. The specificity of the differing reaction paths is remarkable; we prepared the reaction mixture from the phosphetane-forming[4] olefin 3,3-dimethyl-1-butene and $C_6H_5PCl_2$ and found only the two ^{31}P NMR signals expected for the *cis*- and *trans*-1-chlorophosphetanium ions (δ +98.6 and +86.5). No trace of a product from hydrogen incorporation was present. If a common intermediate, such as a phosphirane, were involved in the olefin reactions, it would seem quite unlikely that two different pathways, each to the total exclusion of the other, should be followed. We believe this attests further to the unique behavior of tetramethylene and supports the concept of the first step being its protonation.

Experimental Section

General. All manipulations of trivalent phosphorus compounds were conducted under nitrogen in a glove bag. ^{31}P NMR spectra were obtained by the Fourier transform technique on a Bruker HFX-10 system at 36.43 MHz with proton decoupling; chemical shifts are referenced to 85% H_3PO_4, with downfield shifts positive.

Phenylphosphonous Dichloride–Aluminum Chloride Complex. To a slurry of 1.33 g (0.01 mol) of commercial anhydrous aluminum chloride in 7 mL of dried methylene chloride was added 1.79 g (0.01 mol) of $C_6H_5PCl_2$. The mixture was protected with nitrogen and stirred at room temperature for 3 h. A slightly green solution containing a trace of solid was obtained. The ^{31}P NMR spectrum of the solution had strong signals at δ +112.1 and +84.3.

When the complex was prepared from 2.66 g (0.02 mol) of $AlCl_3$ and 1.79 g (0.01 mol) of $C_6H_5PCl_2$, the ^{31}P spectrum had one signal at δ +69.1. A mixture of 1.33 g (0.01 mol) of $AlCl_3$ and 3.58 g (0.02 mol) of $C_6H_5PCl_2$ had one signal at δ +110.9.

Methylphosphonous Dichloride–Aluminum Chloride Complex. The complex was prepared as above from 1.17 g (0.01 mol) of CH_3PCl_2 and 1.33 g (0.01 mol) of $AlCl_3$ in 7 mL of CH_2Cl_2. The ^{31}P NMR spectrum consisted of two strong signals at δ +131.9 and +97.5.

Diphenylphosphinous Chloride–Aluminum Chloride Complex. The complex was prepared from 0.01 mol of each reagent in 20 mL of CH_2Cl_2. The ^{31}P NMR spectrum of the resulting solution had two strong signals, δ +68.3 and +41.3.

Reaction of the Phenylphosphonous Dichloride–$AlCl_3$ Complex with Tetramethylethylene. To the preformed 1:1 complex described previously was added 1.18 mL (0.01 mol) of tetramethylethylene. The heat of the reaction induced reflux. After being stirred for 1 h with no temperature control, the mixture was stripped of solvent and the residue taken up in $CDCl_3$ for NMR studies. The ^{31}P NMR spectrum consisted of one signal at δ +126 for **2**; the ^{13}C and ^1H NMR spectra matched those previously reported.[6] The same NMR results were obtained when complexes formed with the varying reactant ratios were used. The use of freshly sublimed $AlCl_3$ caused no change in the product.

Synthesis and Chlorination of Phenyl(1,1,2-trimethylpropyl)phosphinous Chloride (4). To the reaction mixture of 4.0 g (0.03 mol) of $AlCl_3$, 5.37 g (0.03 mol) of $C_6H_5PCl_2$ and 2.5 g (0.03 mol) of tetramethylethylene in 70 mL of CH_2Cl_2 was added 7.9 g (0.031 mol) of triphenylphosphine. The mixture was stirred at room temperature for 30 min and then diluted with 130 mL of pentane. On cooling, a yellow oil separated; the supernatant liquid was removed and stripped of solvent. Distillation gave 3.0 g (44%) of **4**, bp 89–93 °C (0.05 mm). Its ^1H NMR spectrum agreed with that already reported;[6] ^{31}P NMR (CH_2Cl_2) δ +109.2.

To a solution of 1.7 g (0.0075 mol) of **4** in 25 mL of CH_2Cl_2 at −78 °C was added 5.4 mL of a 0.028 M solution of chlorine (0.0075 mol) in CH_2Cl_2 over a 5-min period. The solution was allowed to warm to room temperature. The ^{31}P NMR spectrum consisted of a single signal at δ +124.7; addition of 0.0075 mol of $AlCl_3$ caused only a small downfield shift to a value (δ +126) agreeing with **2**. The ^1H NMR spectrum also matched that of **2**.

Reaction of 3,3-Dimethyl-1-butene with $C_6H_5PCl_2$·$AlCl_3$. To 15 mL of CH_2Cl_2 and 2.0 g (0.015 mol) of $AlCl_3$ at 0 °C was added 2.7 g (0.015 mol) of phenylphosphonous dichloride. The homogeneous mixture was treated slowly at 0 °C with a solution of 1.26 g (0.015 mol) of 3,3-dimethyl-1-butene in 5 mL of CH_2Cl_2. After about 1 h from the start of the addition, an aliquot was removed and found to have ^{31}P NMR signals at δ +98.6 and +86.5. To confirm that both signals were associated with a 1-chlorophosphetanium ion the mixture was reduced with 3.03 g (0.015 mol) of tri-*n*-butylphosphine at 0 °C. The product was poured into pentane; the pentane layer was collected and distilled (60–65 °C at 0.01 mm) to give 1.6 g (56%) of a mixture of *cis*- and *trans*-2,2,3-trimethyl-1-phenylphosphetane,[5] having δ +3.3 and +27.9.

Registry No.—**2**, 64872-75-9; **4**, 54193-51-0; $PhPCl_2$·$AlCl_3$ complex, 22646-95-3; $AlCl_3$, 7446-70-0; $PhPCl_2$, 644-97-3; $MePCl_2$·$AlCl_3$ complex, 52375-16-3; $MePCl_2$, 676-83-5; Ph_2PCl·$AlCl_3$ complex, 22646-94-2; Ph_2PCl, 1079-66-9; tetramethylethylene, 563-79-1; triphenylphosphine, 603-35-0; 3,3-dimethyl-1-butene, 558-37-2; *cis*-2,2,3-trimethyl-1-phenylphosphetane, 64884-28-2; *trans*-2,2,3-trimethyl-1-phenylphosphetane, 64884-29-3.

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Neurotoxins of *Karwinskia humboldtiana*. Atropisomerism and Diastereomeric Oxidation Products

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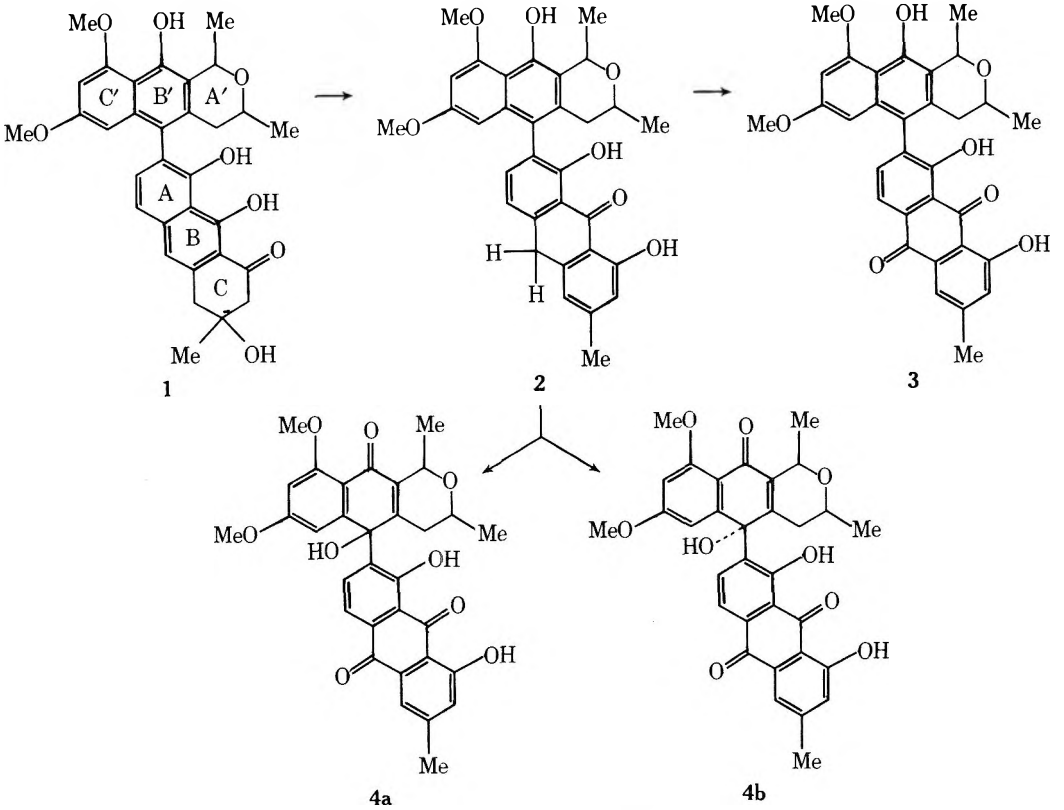
A previous report from this laboratory[2] described the isolation and structure elucidation of several polyphenolic components of the neurotoxic fruit of *Karwinskia humboldtiana*, Zucc. (Rhamnaceae). These polyphenolic neurotoxins include four C_{15} "dimers" which have since been isolated from the roots of the plant by Dominguez and students.[3] We now report evidence from proton nuclear magnetic resonance (^{1}H NMR) studies that, as isolated from seeds of *K. humboldtiana* following extensive fractionation,[2] one of the "dimeric" polyphenolic neurotoxins (1) exists as a mixture of two conformational isomers (i.e., atropicisomers) of the biphenyl type.[4-6] In addition, we report the formation of two oxidation products of **1** which are isomeric at a newly formed chiral center (C-5′, see structures **1**, **4a**, **4b**) and exhibit ^{1}H NMR spectra which are individually quite similar to the spectra of the respective conformational isomers of **1** (and its transformation products **2** and **3**).

The ^{1}H NMR spectrum of **1**, a major component of the neurotoxic extract of *K. humboldtiana*, exhibits a number of features which made initial interpretation difficult.[2] Thus, chromatographically homogeneous samples of **1** exhibited ^{1}H NMR spectra in which the number of hydrogen resonances exceeded the number of hydrogens (32) established by high resolution mass spectrometry. In these spectra, and in spectra of transformation products **2**, derived by dehydration of **1**,[2] and **3**, formed by oxidation of **2**[2] (see Figure 1A for the spectrum of **3**), several specific resonances failed to integrate for an integral number of hydrogens. It became clear that the nonintegral resonances occur in pairs, i.e., they arise from hydrogens which, owing to the existence of two conformational isomers, experience two different magnetic environments. For quinone **3**, this "doubling" of resonance signals was observed for the 1′-methyl, H-5, H-6, H-6′ and the 1- and 8-hydroxyl hydrogen resonances (see Figure 1A). The spectra of **1** and **2** are similar.[2]

When samples of **2** or **3** in $CDBr_3$ were heated, the equilibrium between the conformational isomers was altered. In each case, heating resulted in an increase in the intensity of signals owing to the minor conformational isomer. After heating solutions of **2** and **3** in $CDBr_3$ at 100 °C for ~1 h, the isomer concentrations were approximately equal in each case; heating beyond 1.5 h caused sample decomposition.

When a wet methanol solution of **2** was allowed to stand at room temperature in air for several months, two new products were formed. The products were shown by mass spectrometry to be isomers of empirical formula $C_{32}H_{28}O_9$. The spectral properties of the newly formed isomers were very similar to each other and showed many similarities to those of **3**. Thus, the ultraviolet–visable spectra of the isomers were essentially identical and assignable as an anthraquinone chromophore with a long wavelength band at 435 nm. The ^{1}H NMR spectrum of each (Figures 1B and 1C) showed typical anthraquinone 1,8-dihydroxy resonances at about δ 12, but the characteristic phenolic hydroxy signal associated with the 10′-



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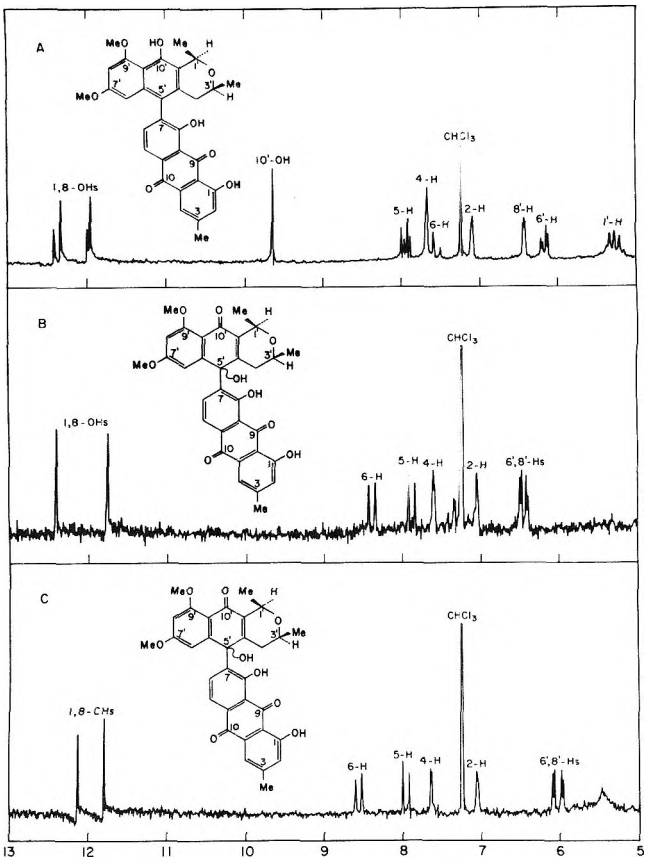

Figure 1. (A) Partial ^1H NMR spectrum of **3** exhibiting resonances of two atropisomers; (B) partial ^1H NMR spectrum of the nonpolar isomer of the diasteriomeric alcohol pair (**4**) obtained by air oxidation of **2**; (C) the partial ^1H NMR of the corresponding polar isomer (**4**).

hydroxy in the starting material[2] (see Figure 1A) was absent. The resonances due to two methoxy groups and the A′-ring aromatic AB system as well as signals due to the corresponding protons in the A′,C′, and C rings of **3** were present in each and could be related to the corresponding signals in **3**.

These results lead us to assign general structure **4** to the new products, designated nonpolar and polar in accord with their relative chromatographic mobilities (see Experimental Section). The existence of two very similar isomers is then due to (a) air oxidation of the ABC system with creation of an anthraquinone moiety and (b) the creation of a new chiral center with hydroxylation at the 5′ position. Since it has been established[2] that the two C-methyl substituents of ring A′ are cis diequatorially related to one another, a chiral center at the 5′ position would place the 5′-hydroxy either cis or trans to the C-methyls (**4a** and **4b**, respectively).

The differences in the ^1H NMR spectra of the nonpolar and polar 5′-hydroxy isomers (**4**) are appreciable (compare Figures 1B and 1C) and must result from differences in hydrogen bonding (5′-OH to O-8)[7] and/or conformational differences. We have been unable to account for the observed differences by inspection of molecular models and, therefore, have not assigned stereochemistries at C-5′ to the isolated isomer pair.

Experimental Section

Isolation of Isomeric 7-[3′,4′-Dihydro-7′,9′-dimethoxy-1′,3′-dimethyl-5′-hydroxy-10′-oxo-1′*H*-naphtho[2′,3′-*c*′]pyran-5′-yl]-1,8-dihydroxy-3-methylanthracene-4,10-diones (4). A methanol filtrate retained following recrystallization of **2**[2] was allowed to stand at room temperature in contact with air for ~4 months. At the end of this time thin layer chromatography showed the presence of several new products. By chromatography on silica gel using chloroform for elution, two components, assigned general structure **4**, were isolated in approximately equal amounts (~5 mg).

The first compound to elute, designated the nonpolar isomer, exhibited spectral data: MS *m/e* 556.1719 ($C_{32}H_{28}O_9$, M^+ ·), *m/e* 541, 526, 511, 496, 482; UV λ_{max} (MeOH) 228, 258, 290, 330, 435 nm; IR ν_{max} (KBr) 3440, 1630, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.44, 11.79 (1, 8-OH's), 8.38 (d, J = 8 Hz, 6-H), 7.87 (d, J = 8 Hz, 5-H), 7.59 (d, J = 1 Hz, 4-H), 7.05 (d, J = 1 Hz, 2-H), 6.49, 6.40 (both d, J = 2 Hz, 6′, 8′-H's), 4.90 (m, 1′-H), 3.90, 3.71 (OMes), 2.42 (3-Me), 1.47 (d, J = 6 Hz, 1′-Me), 1.17 (d, J = 6 Hz, 3′-Me).

The polar isomer exhibited: MS *m/e* 556.1711 ($C_{32}H_{28}O_9$, M^+ ·), 541, 526, 511, 496, 482; UV λ_{max} (MeOH) 228, 258, 290, 330, 435 nm; IR ν_{max} (KBr) 3390, 1625, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.18, 11.84 (1,8-OHs), 8.57 (d, J = 8 Hz, 6-H), 7.96 (d, J = 8 Hz, 5-H), 7.64 (d, J = 1 Hz, H-4), 7.07 (d, J = 1 Hz, H-2), 6.09, 5.98 (both d, J = 2 Hz, 6′-,8′-H's), 5.48 (m, 1′-H), 3.69, 3.65 (OMes), 2.45 (3-Me), 1.43 (d, J = 6 Hz, 1′-Me), 1.21 (d, J = 6 Hz, 3′-Me).

Acknowledgment. We thank the National Institute for Neurological Disease and Stroke (NS 10484) for financial support.

Registry No.—**2**, 56709-27-4; **3**, 56678-20-7; **4** isomer 1, 64957-52-4; **4** isomer 2, 65024-71-7.

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Voleneol Diacetate: a New Sesquiterpenoid from *Lepidotrichilia volensii* Leroy (Meliaceae)

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As the result of a phytochemical investigation of the chloroform extract of the stem bark of *Lepidotrichilia volensii* Leroy (Meliaceae),[1] the diacetate of a new sesquiterpenediol was obtained and characterized as I.

Discussion

One of the constituents of the chloroform extract of *Lepidotrichilia volensii* Leroy was an oil which on acetylation yielded a beautifully crystalline new substance with the molecular formula $C_{19}H_{30}O_4$. The mass spectrum of this diacetate indicated a parent peak at *m/e* 322. The fragmentation pattern was consistent wih successive losses of acetic acid [*m/e* 262 and 202 (base)] and the loss of a methyl (187) and isopropyl radical (159) from the base fragment.

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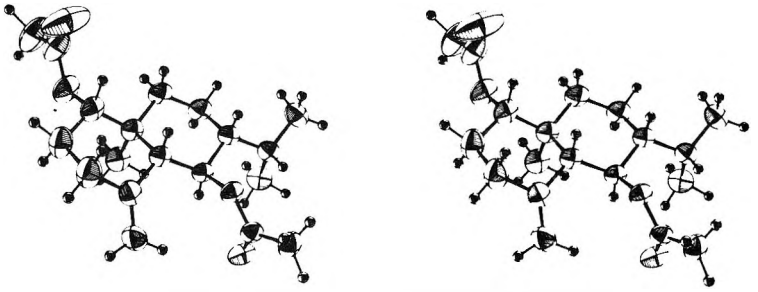
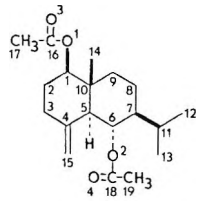
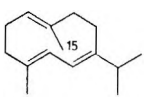


Figure 1. Stereoscopic view of a voleneol diacetate (I) molecule. Hydrogen atoms are shown as spheres and other atoms as 50% probability ellipsoids.



I (dl)



II

The ^{1}H NMR spectrum indicated the presence of a terminal methylene group (δ 4.6 and 4.8), a quaternary methyl group (δ 0.73), two isopropyl methyls (d, δ 0.86 and 0.91, J = 6 Hz), and two acetyl methyls (δ 2.0 and 2.1). The methinyl protons on C-6 and C-1 appeared as a triplet broadened by virtual coupling (δ 5.1, J = 10 Hz) and a doublet of doublets (δ 4.7, J = 5, 10 Hz), respectively. Due to the large coupling constants, the C-6 proton must be axial and split by two adjacent axial protons at C-5 and C-7. After deacetylation with potassium bicarbonate in methanol, a monoacetate was formed in which the doublet of doublets absorbed upfield at δ 3.43 and is thus the C-6 monoacetate. Since the observed rotation of voleneol diacetate was 0°, the compound appeared to be a racemic mixture.

The structure of voleneol diacetate was conclusively determined to be I (*dl*) by x-ray crystallography. Table I lists fractional coordinates, and Figure 1 depicts the molecule. The compound is a *trans*-decalin with both rings in the chair conformation and the acetoxyl and isopropyl substituents equatorial. The isopropyl group adopts the staggered conformation about the C(7)–C(11) bond which puts the hydrogen on C-11 near the bulky acetoxyl group on C-6.

The most surprising feature is that this natural product derivative, with five asymmetric centers, occurs in racemic form, suggesting that it comes from an achiral or easily racemized precursor by nonenzymatic reactions which could occur in the plant, during silica gel chromatography or on acetylation. A reasonable achiral precursor is germacrene C(II), an optically inactive sesquiterpene found as the main constituent of the seeds of *Kadsura japonica* and a key intermediate in the biosynthesis of germacrene D and thus the cadinane family of sesquiterpenoids.[2] Between II and voleneol diacetate (I) an oxidation step is required and probably occurs as a last enzyme-catalyzed step; this could involve allylic oxidation to an optically inactive alcohol such as 15-hydroxygermacrene C or to something optically active with could later easily racemize, such as the allylic rearrangement product of 15-hydroxygermacrene C. Hydrations and cyclizations catalyzed by weak acid could convert this oxidized germacrene derivative to the eudesmoid structure observed.

Experimental Section[3]

Extraction Procedure. The dried and ground stem bark (8 kg) of *Lepidotrichilia volensii* was defatted with petroleum ether and then extracted exhaustively in a Lloyd-type extractor with ethanol. The air-dried ethanol extract was partitioned between chloroform and water (1:1) to yield 460 g of air-dried chloroform extract. The chloroform extract was triturated in ether and the ether-soluble fraction was subjected to a series of silica gel column chromatographies and preparative thick-layer chromatographies to yield 60 mg of an oil.

Table I. Fractional Coordinates of Nonhydrogen Atoms, with Standard Deviations in Parentheses

Atom	x/a	y/b	z/c
O-1	0.0624 (1)	1.2660 (2)	−0.0845 (1)
O-2	0.4144 (1)	0.9031 (2)	0.1096 (1)
O-3	0.1048 (2)	1.5036 (4)	−0.1410 (2)
O-4	0.3961 (1)	0.6389 (2)	0.1619 (1)
C-1	0.1484 (1)	1.2564 (3)	−0.0196 (2)
C-2	0.1274 (2)	1.3017 (4)	0.0623 (2)
C-3	0.2124 (2)	1.2724 (4)	0.1353 (2)
C-4	0.2493 (1)	1.0903 (4)	0.1307 (1)
C-5	0.2755 (1)	1.0594 (3)	0.0504 (1)
C-6	0.3281 (1)	0.8922 (3)	0.0451 (1)
C-7	0.3537 (1)	0.8716 (3)	−0.0380 (1)
C-8	0.2691 (2)	0.8927 (3)	−0.1115 (1)
C-9	0.2185 (2)	1.0606 (4)	−0.1052 (1)
C-10	0.1885 (1)	1.0749 (3)	−0.0242 (1)
C-11	0.4077 (1)	0.7045 (3)	−0.0422 (1)
C-12	0.4510 (2)	0.7074 (4)	−0.1156 (2)
C-13	0.3527 (2)	0.5357 (4)	−0.0443 (2)
C-14	0.1192 (2)	0.9304 (4)	−0.0206 (2)
C-15	0.2514 (2)	0.9724 (4)	0.1890 (2)
C-16	0.0510 (2)	1.3911 (4)	−0.1414 (2)
C-17	−0.0377 (2)	1.3723 (5)	−0.2048 (2)
C-18	0.4428 (2)	0.7646 (3)	0.1590 (1)
C-19	0.5391 (2)	0.7879 (4)	0.2084 (1)

Voleneol Diacetate. Acetylation with acetic anhydride and pyridine yielded a monoacetate after 1 hr and a diacetate after 24 h. Crystallization from ether gave a quantitative yield of voleneol diacetate, mp 99.5–100.5 °C; mass spectrum m/e 322 (M^+), 262, 202 (base), 187, and 159; ^{1}H NMR δ 5.1 (br t, J = 10 Hz, 1 H), 4.8 (s, 1 H), 4.7 (dd, J = 5, 10 Hz, 1 H), 4.6 (s, 1 H), 2.1 (s, 3 H), 2.0 (s, 3 H), 0.91 (d, J = 6 Hz, 3 H), 0.86 (d, J = 6 Hz, 3 H), 0.73 (s, 3 H), 2.3–1.2 (11 H).

Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.81; H, 9.32. Found: C, 70.87; H, 9.26.

Crystallographic Study of Voleneol Diacetate (I). Colorless cyrstals were grown from ether. A needle 0.2 × 0.3 × 0.4 mm was mounted with the b axis parallel to the goniostat ϕ axis. The space group was determined to be $P2_1/c$. A Syntex four circle computer controlled diffractometer ($P2_1$) with a graphite monochrometer (MoK_α, λ 0.71069 Å) and pulse-height analyzer was used for collection of intensities. The cell constants, determined by least-squares treatment of 15 reflections, were a = 15.139 (9), b = 7.596 (4), c = 16.581 (9), β = 105.0°, ρ_{obsd} = 1.15 g/cm^3 (aq KI; ρ_{calcd} 1.13 g/cm^3), and Z = 4. The θ–2θ scan technique was employed at variable scan rate 0.5–29.3°/min (in 2θ). The scan range was 2.0°. The background to scan time ratio was 1.0. A total of 3587 reflections with $2\theta < 50°$ was collected and 2390 > 3σ (I) were considered observed. There were no significant variations in the intensities of three check reflections that were monitored after every 100 reflections. Standard deviations were assigned as described by Corfield et al.,[4] the value of p being 0.02. The intensities were corrected for Lorentz and polarization effects.

Phases for reflections with normalized structure factor E >1.5 were

generated using the direct method program MULTAN.[5] All nonhydrogen atoms were located on the first E map. Full matrix least-squares refinement of positional and isotropic thermal parameters of nonhydrogen atoms reduced R to 0.184. Anisotropic refinement brought R down to 0.065. A difference map at this stage revealed all the hydrogens and two more cycles of refinement (anisotropic for nonhydrogens and isotropic for hydrogens) brought R down to the final value of 0.053. The refinement was based on F_0, the quantity minimized being $\Sigma w(F_o - F_c)^2$. The scattering factors used were those of Hanson et al.[6] No correction was applied for extinction.

Voleneol Monoacetate. Hydrolysis of voleneol diacetate (I) with $KHCO_3$ in methanol yielded a monoacetate after crystallization from ether: mp 89–90 °C; ^{1}H NMR δ 3.43 (dd, J = 5, 10 Hz, 1 H) and 2.0 (s, 3 H). The rest of the spectrum was similar to the diacetate with peaks at δ 4.7 and 2.1 absent.

Acknowledgments. This work was supported in part by Contract NO 1-CM-3-3750 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, the Elsa U. Pardee Foundation, Midland, Michigan, Grant CA10944 from the National Cancer Institute, and the University of Arizona Computer Center.

Registry No.—1, 64784-78-7; 1 monoacetate, 64784-79-8.

Supplementary Material Available: Tables of atomic coordinates of hydrogen atoms, temperature factors, bond distances, bond angles, and torsion angles, and packing diagram (6 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Identification was confirmed by Dr. Robert E. Perdue, Medicinal Plant Resources Laboratory, Agricultural Research Center, Beltsville, Md. A reference specimen was deposited in that herbarium. The plant was collected in Kenya, in June 1973.
(2) K. Morikawa and Y. Hirose, *Tetrahedron Lett.*, 1799 (1969).
(3) Carbon and hydrogen analysis were performed by Chemalytics, Inc., Tempe, Arizona. ^{1}H NMR and mass spectra were determined using a Varian T-60 spectrometer and Hewlett-Packard Model 5930 spectrometer, respectively. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.
(4) P. W. R. Corfield, R. J. Doedens, and J. A. Ibers, *Inorg. Chem.*, **6**, 197 (1967).
(5) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, **26**, 274 (1970).
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Synthesis and Chemistry of Ethyl 2-Diethylphosphonoacrylate

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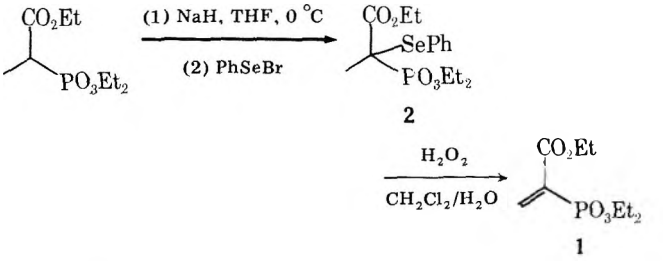
In recent years, vinyl phosphonium salts have found wide applicability in organic synthesis.[1] To date, numerous examples have been provided which demonstrate the utility of these reagents in the synthesis of acyclic,[1a] carbocyclic,[1b,f] and heterocyclic molecules[1c-e] containing carbon–carbon double bonds.

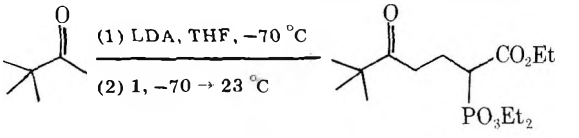
In contrast to the field of vinyl phosphonium salt chemistry, little attention has been given to the study of the synthesis and chemistry of vinyl phosphonates. Although reports of the synthesis of a few vinyl phosphonates have appeared in the literature,[2] the synthetic utility of these reagents has not been explored. Herein we describe a new synthesis of ethyl 2-diethylphosphonoacrylate (1)[2b] and reactions of this compound with a variety of anionic nucleophiles to produce stabilized phosphonate anions capable of undergoing subsequent reaction with aldehydes and ketones to produce unsaturated esters.

We chose to explore the possibility of using a selenoxide elimination as the method for generating the base-sensitive



unsaturation in **1**, due to the mildness of the reaction conditions necessary to achieve this transformation.[3] In fact, reaction of ethyl 2-diethylphosphonopropionate with sodium hydride followed by treatment with phenylselenyl bromide affords the selenylated derivative **2**, which is used without purification in the subsequent oxidation and elimination to give vinyl phosphonate **1** in an overall yield of 82%.

When vinyl phosphonate **1** is added slowly to a solution of the lithium enolate of pinacolone generated at −70 °C with lithium diisopropylamide (LDA) followed by slow warming to room temperature, keto ester phosphonate **3** is obtained in



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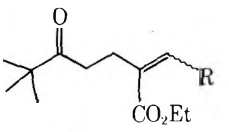
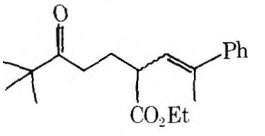
70% yield. If after warming to room temperature the intermediate phosphonate anion is allowed to react with an aldehyde or a ketone at reflux, unsaturated esters are isolated in good yield. Thus, reactions with benzaldehyde, propionaldehyde, 2-phenylpropionaldehyde, and cyclohexanone produce unsaturated esters **4**, **5**, **6** and **7** (~4:1 ratio), and **8** and **9** (~1:1 ratio) in 70, 78, 80, and 54% yields, respectively. We



4, R = Ph
5, R = CH_2CH_3
6, R = $CH(CH_3)Ph$



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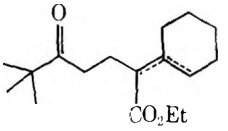

8, α,β isomer
9, β,γ isomer

were unable to obtain any appreciable yield of α,β-unsaturated ester in attempts to react the intermediate phosphonate anion with pivalaldehyde.

Similarly, reaction of the lithium enolates of 3-pentanone and *tert*-butyl acetate with vinyl phosphonate **1** followed by treatment of the resulting phosphonate anion with benzaldehyde at reflux furnishes α,β-unsaturated esters **10** and **11** in 74 and 69% yields, respectively. Treatment of the lithiated derivative of 1,3-dithiane[4] under analogous conditions affords α,β-unsaturated ester **12** in about 40% yield. All attempts to perform the analogous reaction using a 2-substituted 1,3-dithiane (i.e., 2-ethyl-1,3-dithiane) were uniformly unsuccessful.

Unsaturated esters **4**, **5**, **6**, **7**, **10**, **11**, and **12** were isolated as a mixture of stereoisomers. The approximate ratios of these isomers were determined by integration of the appropriate vinyl proton resonances and (where necessary) by a comparison of the intensities of the characteristic resonances corre-

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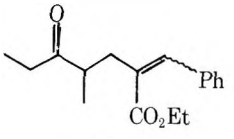
Table I. Stereochemical Results of the Reaction of Anions of Various Compounds with Vinyl Phosphonate 1 and Subsequent Reaction of Resultant Phosphonate Anions with Carbonyl Compounds

Carbanion precursor	Registry no.	Aldehyde or ketone	Registry no.	Products	Registry no.	Ratio	^{1}H-NMR chemical shift of vinyl resonances, δ values (multiplicity)
t-BuCOMe	75-97-8	PhCHO	100-52-7	(*E*)-4	64739-78-2	2	7.61 (s)
				(*Z*)-4	64739-79-3	1	7.20 (s)
t-BuCOMe		CH_3CH_2CHO	123-38-6	(*E*)-5	64739-86-2	1	6.68 (t)
				(*Z*)-5	64754-30-9	1	5.92 (t)
t-BuCOMe		$CH_3CH(Ph)CHO$	93-53-8	(*E*)-6	64739-87-3	1	6.85 (d)
				(*Z*)-6	64739-88-4	7	5.98 (d)
				(*E*)-7	64739-89-5	1	7.2–7.0 (unresolved)
				(*Z*)-7	64739-90-8	1	7.2–7.0 (unresolved)
Et_2CO	96-22-0	PhCHO		(*E*)-10	64739-91-9	1	7.75 (s)
				(*Z*)-10	64739-92-0	2	7.25 (s)
$MeCO_2$-*t*-Bu	540-88-5	PhCHO		(*E*)-11	64754-31-0	1	7.67 (s)
				(*Z*)-11	64739-93-1	1	7.22 (s)
$C_4H_8S_2$	505-23-7	PhCHO		(*E*)-12	64739-94-2	1	7.73 (s)
				(*Z*)-12	64739-95-3	3	7.23 (s)

sponding to the absorption due to the methylene group of the ethyl ester functionality in the ^{1}H-NMR spectrum (i.e., in the case of compounds **6** and **7**; see Table I). It can be expected that the chemical shift of the vinyl resonance in the (*E*)-unsaturated ester will occur at lower field than that observed for the corresponding (*Z*) isomer.[5] Typically, the difference in



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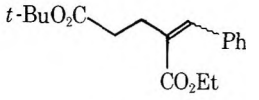

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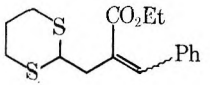

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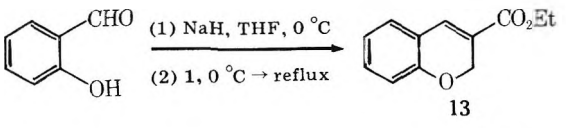
chemical shift is observed to be on the order of 0.4–0.8 ppm. The presence of the β,γ isomer (**9**) is indicated by the presence of a vinyl proton resonance and two resonances corresponding to the ethyl group of the ester functionality in the ^{1}H-NMR spectrum. None of these examples displayed a high degree of stereoselectivity in the olefin-forming reaction. From an examination of the data presented in Table I, no general conclusion can be drawn regarding the origin of the stereochemical outcome of these Wadsworth–Emmons reactions.

In order to make a comparison of the synthetic utility of vinyl phosphonate **1** as compared to that of vinyl phosphonium salts, compound **1** was used in two annelation reactions to form heterocyclic compounds. When the sodium salt of salicylaldehyde is allowed to react with **1** at 0 °C followed by reaction at reflux in THF, the 2*H*-1-benzopyran **13** is isolated in 78% yield. However, we were totally unsuccessful in our attempts to extend this reaction to a similar system by employing the sodium salt of 2′-hydroxyacetophenone. Under analogous conditions, the dihydrofuran **14** is obtained in 39% yield from 2-hydroxycyclohexanone.



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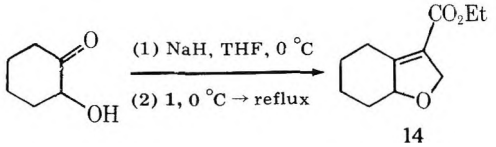

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We have demonstrated that various carbanionic nucleophiles are capable of undergoing Michael addition to vinyl phosphonate **1**, and the intermediate stabilized phosphonate anions react with a number of carbonyl compounds to form unsaturated esters in moderate to good yields. Unfortunately, the stereoselectivity in the reaction to form olefins is disappointingly low. In some systems where the β,γ-unsaturated ester is comparable in thermodynamic stability to the α,β isomer, some isomerization to the former is observed. Finally, vinyl phosphonate **1** has been shown to be of synthetic use for the production of some heterocyclic α,β-unsaturated esters.

Experimental Section

All boiling points are uncorrected. IR spectra were determined with a Perkin-Elmer Model 137 or Model 735 infrared recording spectrophotometer. ^{1}H-NMR spectra were determined at 60 MHz with a Varian Model T-60 NMR spectrometer. The chemical shift values are expressed in δ values (ppm) relative to tetramethylsilane as an internal standard. Significant ^{1}H-NMR data are tabulated in parentheses in the order (number of protons, multiplicity, proton assignments). Mass spectra were obtained with Varian MS-12, Varian M-66, and Consolidated 21-110B mass spectrometers. Mass spectra are given as *m/e* with relative intensities in parentheses. Gas–liquid partition chromatograph (GLC) analyses were performed on a Varian Aerograph 90-P instrument. Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley, Calif.

All reactions involving strong bases or organometallic reagents were performed under a nitrogen atmosphere. Ethereal solvents were dried by distillation from $LiAlH_4$ or sodium/benzophenone just prior to use. Diisopropylamine was dried by distillation from CaH_2 prior to use. Commercial solutions of *n*-butyllithium in hexane (Alfa Inorganics, Inc. or Foote Mineral Co.) were standardized by procedures of Watson and Eastham or Kofron and Baclawski.[6] All aldehydes and ketones used as starting materials were purified by distillation prior to use. 1,3-Dithiane was purified by sublimation.

Ethyl 2-Diethylphosphonoacrylate (1). To a suspension of 7.20 g (0.150 mol) of a 50% oil dispersion of NaH, washed free of oil with dry pentane, in 300 mL of dry THF at 0 °C is added dropwise 23.8 g (0.100 mol) of ethyl 2-diethylphosphonopropionate in 20 mL of dry THF. After the addition, the reaction mixture is stirred at 0 °C for 1.5 h. To the reaction mixture is added a solution of phenylselenyl bromide generated from 18.8 g (60 mmol) of diphenyldiselenide and 9.60 g (60 mmol) of bromine in 50 mL of dry THF. The reaction mixture is stirred for 1 min and poured into a mixture of 250 mL of saturated aqueous $NaHCO_3$, 500 mL of 50% ether/pentane, and ice. The aqueous phase is extracted with 500 mL of 50% ether/pentane, and the combined organic phases are washed with saturated aqueous NaCl solution and dried over Na_2SO_4. Evaporation yields 40.1 g of red-orange liquid which has spectral properties consistent with ethyl 2-diethylphosphono-2-phenylselenylpropionate (**2**): IR (thin film) 1730 cm^{-1}; ^{1}H-NMR (CCl_4) δ 7.8–7.0 (5 H, unresolved multiplets, aryl H's), 4.5–3.8 (6 H, unresolved multiplets, CH_2), 1.7–1.0 (12 H, unresolved multiplets, CH_3).

To a solution of 40.1 g of crude **2** in 300 mL of methylene chloride at 0 °C is added 28.3 g (0.25 mol) of 30% H_2O_2 in 25 mL of water over a 15-min period. The reaction mixture is stirred at 0 °C for 1 h, warmed to room temperature and stirred for an additional 2.5 h, then poured into a mixture of 250 mL of CH_2Cl_2 and 100 mL of 10% aqueous Na_2CO_3 solution. The aqueous layer is extracted with 250 mL of CH_2Cl_2, and the combined organic layers are washed with saturated aqueous NaCl solution and dried over Na_2SO_4. Evaporation and distillation in vacuo through a 15-cm Vigreaux column afford 19.6 g (82%) of **1** as a slightly yellow liquid, bp 88–90 °C (0.3 Torr): IR (thin film) 1720 cm^{-1}; ^1H-NMR (CCl_4) δ 7.03 (1 H, d of d, J = 2 and 25 Hz, vinyl H trans to phosphonate), 6.50 (1 H, d of d, J = 2 and 4 Hz, vinyl H cis to phosphonate), 4.5–3.8 (6 H, unresolved multiplets, CH_2), 1.45 (9 H, t, CH_3); mass spectrum 236 (1.7, M^+), 191 (48), 164 (31), 163 (66), 162 (55), 135 (100). Anal. Calcd for $C_9H_{17}O_5P$: C, 45.77; H, 7.25; P, 13.11. Found: C, 45.68; H, 7.14; P, 13.11.

6-Diethylphosphono-2,2-dimethyl-6-ethoxycarbonyl-3-hexanone (3). To a solution of 304 mg (3.00 mmol) of diisopropylamine in 4 mL of dry THF at 0 °C is added dropwise 1.34 mL (3.00 mmol) of 2.24 M *n*-BuLi in hexane. After 10 min the solution is cooled to −70 °C, and 300 mg (3.00 mmol) of pinacolone is added dropwise over a 3-min period. After 30 min, 709 mg (3.00 mmol) of **1** is added dropwise over a 20-min period by means of a syringe pump. The solution is stirred at −70 °C for 30 min and then warmed to room temperature. A 3-mL sample of saturated aqueous NH_4Cl is added, and the reaction mixture is diluted with water and extracted three times with ether. The combined ether extracts are dried over Na_2SO_4 and evaporated to afford 0.906 g of reddish liquid. Kugelrohr distillation in vacuo gives 704 mg (70%) of **3** as a clear liquid (oven temperature, 105–111 °C (0.3 Torr)): IR (thin film) 1730, 1705 cm^{-1}; ^1H-NMR (CCl_4) δ 4.12 (4 H, m, $POCH_2$), 3.98 (2 H, q, $COOCH_2$), 2.85 (1 H, d of t, J = 7 and 22 Hz, CH), 2.57 (2 H, t, aliphatic CH_2), 2.3–1.7 (2 H, unresolved multiplet, aliphatic CH_2), 1.32 (6 H, t, $POCH_2CH_3$), 1.25 (3 H, t, $COOCH_2CH_3$), 1.12 (9 H, s, Me_3C); HRMS 336.1746 (1.2, M^+ calcd for $C_{15}H_{29}O_6P$: 336.1708), 279 (100), 224 (18), 205 (17), 57 (35). Anal. Calcd for $C_{15}H_{29}O_6P$: C, 53.56; H, 8.69. Found: C, 53.56; H, 8.66.

6,6-Dimethyl-2-ethoxycarbonyl-1-phenyl-1-hepten-5-one (4). Reaction of the stabilized phosphonate anion derived from **3** generated as described above with 318 mg (3.00 mmol) of benzaldehyde at reflux for 30 min, quenching by addition of 3 mL of saturated aqueous NH_4Cl, dilution with water, extraction with ether, drying the ether extracts over Na_2SO_4, evaporation and Kugelrohr distillation in vacuo afford 604 mg (70%) of a 2:1 mixture of (*E*)-**4**/(*Z*)-**4** as a nearly colorless liquid (oven temperature, 85–90 °C (1 Torr)): IR (thin film) 1700, 1640 cm^{-1}; ^1H-NMR (CCl_4) δ 7.61 (0.67 H, s, vinyl H of (*E*) isomer), 7.35 (5 H, s, aryl H's), 7.20 (0.33 H, s, vinyl H of (*Z*) isomer), 4.23 (2 H, q, $COOCH_2$), 2.70 (4 H, broad, aliphatic CH_2), 1.33 (3 H, t, $COOCH_2CH_3$), 1.15 (9 H, s, Me_3C); HRMS 288.1742 (43, M^+ calcd for $C_{18}H_{24}O_3$: 288.1730), 231 (25), 186 (73), 185 (38), 129 (59), 115 (73), 57 (100). Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.64 H, 8.10.

2,2-Dimethyl-6-ethoxycarbonyl-6-nonen-3-one (5). Reaction of the stabilized phosphonate anion derived from **3**, generated as described above, with 174 mg (3.00 mmol) of propionaldehyde at reflux for 1.25 h, work-up, and Kugelrohr distillation afford 561 mg (78%) of a 1:1 mixture of (*E*)-**5**/(*Z*)-**5** as a clear liquid (oven temperature, 85–90 °C (0.5 Torr)): IR (thin film) 1710 cm^{-1}; ^1H-NMR (CCl_4) δ 6.68 (0.5 H, t, vinyl H of (*E*) isomer), 5.92 (0.5 H, t, vinyl H of (*Z*) isomer), 4.18 and 4.15 (2 H, q, $COOCH_2$), 3.7–2.0 (6 H, unresolved multiplets, aliphatic CH_2), 1.28 (3 H, t, $COOCH_2CH_3$), 1.17 (3 H, t, aliphatic CH_3), 1.12 (9 H, s, Me_3C); HRMS 240.1730 (5.2, M^+ calcd for $C_{14}H_{24}O_3$: 240.1725), 183 (65), 155 (47), 81 (46), 57 (100). Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.59; H, 10.06.

2,2-Dimethyl-6-ethoxycarbonyl-8-phenyl-6-nonen-3-one (6). Reaction of the phosphonate anion derived from **3**, generated as described above, with 402 mg (3.00 mmol) of 2-phenylpropionaldehyde at reflux for 3.5 h, work-up, and Kugelrohr distillation in vacuo afford 765 mg (80%) of a 7:1:1:1 mixture of (*Z*)-**6**/(*E*)-**6**/(*Z*)-**7**/(*E*)-**7** as a pale yellow liquid (oven temperature, 120–125 °C (0.4 Torr)): IR (thin film) 1710 cm^{-1}; ^1H-NMR (CCl_4) δ 7.18 (5 H, s, aryl H's), 7.2–7.0 (0.2 H, unresolved multiplets, vinyl H of (*Z*)-**7** and (*E*)-**7**), 6.85 (0.1 H, d, vinyl H of (*E*)-**6**), 5.98 (0.7 H, d, vinyl H of (*E*)-**6**), 5.98 (0.7 H, d, vinyl H of (*Z*)-**6**), 4.53, 4.21, and 4.10 (0.6 H, q, $COOCH_2$ of (*E*)-**6**, (*E*)-**7**, and (*Z*)-**7**), 4.16 (1.4 H, q, $COOCH_2$ of (*Z*)-**6**), 2.53 (5 H, unresolved multiplets, aliphatic CH_2 and benzylic H), 1.6–1.0 (6 H, unresolved multiplets, $COOCH_2CH_3$ and benzylic CH_3), 1.05 (9 H, s, Me_3C); HRMS 316.2016 (4.2, M^+ calcd for $C_{20}H_{28}O_3$: 316.2044), 270 (62), 171 (100), 159 (43), 143 (72), 129 (41), 105.0695 (46), 105.0341 (57), 77 (46), 57 (91). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.42; H, 8.76.

6-Cyclohexylidene-2,2-dimethyl-6-ethoxycarbonyl-3-hexanone (8). Reaction of the phosphonate anion derived from **3**, generated as described above, with 294 mg (3.00 mmol) of cyclohexanone at reflux for 25 h, work-up, and Kugelrohr distillation in vacuo afford 451 mg (54%) of a 1:1 mixture of **8** and its β,γ-unsaturated isomer (**9**) as a pale yellow liquid (oven temperature, 95–100 °C (0.4 Torr)): IR (thin film) 1710 cm^{-1}; ^1H-NMR (CCl_4) δ 5.55 (0.5 H, multiplet, vinyl H of **9**), 4.13 and 4.04 (2 H, q, $COOCH_2$), 2.9–1.0 (13.5 H, unresolved multiplets, aliphatic and cyclohexyl CH_2's), 1.30 and 1.27 (3 H, t, $COOCH_2CH_3$), 1.12 (9 H, s, Me_3C); HRMS 280.2002 (4.2, M^+ calcd for $C_{17}H_{28}O_3$: 280.2038), 168 (81), 153 (41), 57 (100). Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.07. Found: C, 72.50; H, 9.79.

6-Ethoxycarbonyl-4-methyl-7-phenyl-6-hepten-3-one (10). A THF solution of the enolate derived from 258 mg (3.00 mmol) of 3-pentanone by reaction with 3.00 mmol of LDA at −78 °C is treated with 3.00 mmol of compound **1** (as described above) to generate the phosphonate anion. Reaction with 318 mg (3.00 mmol) of benzaldehyde at reflux for 45 min, work-up, and Kugelrohr distillation in vacuo afforded 612 mg (74%) of a 2:1 mixture of (*Z*)-**10**/(*E*)-**10** as a slightly yellow liquid (oven temperature, 105–110 °C (0.3 Torr)): IR (thin film) 1710 cm^{-1}; ^1H-NMR (CCl_4) δ 7.75 (0.33 H, s, vinyl H of (*E*) isomer), 7.40 (5 H, s, aryl H's), 7.25 (0.67 H, s, vinyl H of (*Z*) isomer), 4.25 (1.34 H, q, $COOCH_2$ of (*Z*) isomer), 4.08 (0.66 H, q, $COOCH_2$ of (*E*) isomer), 3.1–2.0 (3 H, unresolved multiplets, aliphatic CH and CH_2), 2.33 (2 H, q, aliphatic CH_2), 1.35 (3 H, t, $COOCH_2CH_3$), 0.98 (3 H, t, aliphatic CH_3); HRMS 274.1535 (38, M^+ calcd for $C_{17}H_{22}O_3$: 274.1569), 229 (44), 172 (41), 117 (48), 115 (66), 57 (100). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.04; H, 8.10.

***tert*-Butyl 4-Ethoxycarbonyl-5-phenyl-4-pentenoate (11).** A THF solution of the enolate derived from reaction of 348 mg (3.00 mmol) of *tert*-butyl acetate by reaction with 3.00 mmol of LDA at −78 °C is treated with 3.00 mmol of compound **1** (as described above) to generate the phosphonate anion. Reaction with 318 mg (3.00 mmol) of benzaldehyde at reflux for 45 min, work-up, and Kugelrohr distillation in vacuo gives 629 mg (69%) of a 1:1 mixture of (*E*)-**11**/(*Z*)-**11** as a nearly colorless liquid (oven temperature, 105–110 °C (0.5 Torr)): IR (thin film) 1725, 1710 cm^{-1}; ^1H-NMR (CCl_4) δ 7.67 (0.5 H, s, vinyl H of (*Z*) isomer), 4.25 (2 H, broad q, $COOCH_2$), 3.0–1.9 (4 H, unresolved multiplets, aliphatic CH_2), 1.43 (9 H, s, Me_3C), 1.30 (3 H, t, $COOCH_2CH_3$); HRMS 248.1044 (53, M^+ calcd for $C_{18}H_{24}O_4$–C_4H_8: 248.1051), 202 (43), 174 (54), 129 (85), 115 (50), 57 (100). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.61; H, 7.89.

2-(2-Ethoxycarbonyl-3-phenyl-2-propenyl)-1,3-dithiane (12). To a solution of 361 mg (3.00 mmol) of 1,3-dithiane in 6 mL of dry THF at −40 °C is added dropwise 1.40 mL (3.15 mmol) of 2.24 M *n*-BuLi in hexane. The solution is stirred for 1.5 h at −40 to −20 °C and cooled to −70 °C, and 709 mg (3.00 mmol) of compound **1** is added dropwise over a 20-min period by means of a syringe pump. The solution is warmed to room temperature, and 318 mg (3.00 mmol) of benzaldehyde is added. The reaction solution is then refluxed for 45 min, cooled to room temperature, and quenched by addition of 3 mL of saturated aqueous NH_4Cl. The resulting mixture is diluted with water and extracted three times with ether. The combined ether extracts are dried over Na_2SO_4 and evaporated. The residue is Kugelrohr distilled in vacuo to afford 645 mg of viscous yellow liquid (oven temperature, 103–108 °C (10^{-3} Torr)), which by NMR was 2:1 mixture of **12** and an unknown compound (~40% yield of **12**). An analytically pure sample of a 3:1 mixture of (*Z*)-**12**/(*E*)-**12** was obtained by preparative GLC (8% SE-30, 5 ft × 0.25 in. 255 °C, retention time 3.2 min): IR (thin film) 1695, 1620 cm^{-1}; ^1H-NMR (CCl_4) δ 7.73 (0.25 H, s, vinyl H of (*E*)-**12**), 7.40 (5 H, s, aryl H's), 7.23 (0.75 H, s, vinyl H of (*Z*)-**12**), 4.5–3.9 (3 H, unresolved multiplets. $COOCH_2$ and SCHS), 3.1–2.5 (6 H, unresolved multiplets, SCH_2 and allylic CH_2), 2.2–1.6 (2 H, unresolved multiplets, CH_2), 1.37 (2.25 H, t, $COOCH_2CH_3$ of (*Z*)-**12**), 1.03 (0.75 H, t, $COOCH_2CH_3$ of (*E*)-**12**); mass spectrum 308 (2.4, M^+), 119 (100), 94 (15), 71 (16), 57 (27), 55 (20). Anal. Calcd for $C_{16}H_{20}O_2S_2$: C, 62.30; H, 6.54. Found: C, 62.34; H, 6.54.

3-Ethoxycarbonyl-2*H*-1-benzopyran (13). To a suspension of 172 mg (3.60 mmol) of a 50% oil dispersion of NaH, washed free of oil with dry pentane, in 10 mL of dry THF at 0 °C is added 366 mg (3.00 mmol) of salicylaldehyde dropwise over a 3-min period. After 2 h, 709 mg (3.00 mmol) of compound **1** is added dropwise over a 5-min period and the reaction mixture is warmed to room temperature and stirred for 2 h. The reaction mixture is then heated at 60–70 °C for 1.5 h, cooled to room temperature, diluted with water, and extracted three times with ether. The combined ether extracts are dried over Na_2SO_4 and evaporated to yield a green liquid. Kugelrohr distillation in vacuo gives 470 mg (78%) of **13** as a clear liquid (oven temperature, 108–114 °C (2 Torr)): IR (thin film) 1710 cm^{-1}; ^1H-NMR (CCl_4) δ 7.4–6.6 (5

H, unresolved multiplets, aryl H's and vinyl H), 4.91 (2 H, d. J = 2 Hz, CH_2O), 4.20 (2 H, q, $COOCH_2$), 1.30 (3 H, t, $COOCH_2CH_3$); HRMS 204.0771 (34, M^+ calcd for $C_{12}H_{12}O_3$: 204.0788), 175 (100), 131 (89), 77 (28). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.26; H, 5.94.

9-Ethoxycarbonyl-7-oxabicyclo[4.3.0]-1(9)-nonene (14). To a suspension of 144 mg (3.00 mmol) of a 50% oil dispersion of NaH, washed free of oil with dry pentane, in 5 mL of dry THF at 0 °C is added 432 mg (3.78 mmol) of freshly distilled 2-hydroxycyclohexanone dropwise over a 3-min period. After 1 h, 709 mg (3.00 mmol) of compound 1 is added dropwise over a 20-min period by means of a syringe pump. The reaction solution is refluxed for 24 NH_4Cl, diluted with water, and extracted and dried over Na_2SO_4, evaporated, and chromatographed on silica gel, eluting with ethyl acetate/hexane (2:6, v/v), to afford 230 mg (39%) of **14** (R_f 0.40 eluting with 40% EtOAc/hexane) as a clear liquid: IR (thin film) 1710 cm^{-1}; ^{1}H-NMR (CCl_4) δ 4.63 (2 H, broad, CH_2O), 4.13 (2 H, q, $COOCH_2$), 3.7–3.3 (1 H, unresolved multiplet, CHO), 2.4–1.0 (8 H, unresolved multiplets, cyclohexyl H's), 1.28 (3 H, t, $COOCH_2CH_3$); HRMS 196.1057 (35, M^+ calcd for $C_{11}H_{16}O_3$: 196.1099), 194 (41), 151 (53), 150 (71), 123 (100), 122 (41). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 66.83; H, 8.17.

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Registry No.—**1**, 20345-61-3; **2**, 64739-80-6; **3**, 64739-81-7; **8**, 64739-82-8; **9**, 64739-83-9; **13**, 57543-58-5; **14**, 64739-84-0; ethyl 2-diethylphosphonopropeionate, 3699-66-9; phenylselenyl bromide, 34837-55-3; cyclohexanone, 108-94-1; salicylaldehyde, 90-02-8; 2-hydroxycyclohexanone, 533-60-8; i, 64739-85-1.

References and Notes

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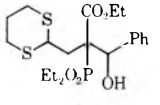
(7) The unknown compound was not distinguishable by TLC from **12** and was not detectable by GLC. From the fact that the ^{1}H-NMR spectrum of the product after Kugelrohr distillation contained an additional aromatic singlet and absorptions characteristic of the methylene protons of a diethylphosphonate functional group, and that the IR spectrum showed a weak OH stretching absorption, the unknown compound was postulated to have structure i.



i

Preparation of 2-(Alkylthiomethyl)acrylates

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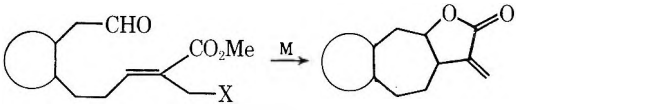
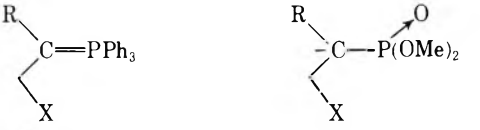
The synthesis of trisubstituted alkenes has been an active area of study in recent years; many general strategies are now available.[1] We are pursuing a plan for synthesis of the sesquiterpene α-methylene-γ-lactones which utilizes intramolecular Reformatsky-type reaction[2] and necessitates the preparation of the 2-substituted acrylate unit as in **1**. Previously developed stereospecific methods were applied to simple systems related to **1** with some success but required



1, X = Br, OH, SR + MeO—M—X

M = metal

several steps, some involving vigorous reaction conditions.[2] Here we report a method for preparation of the desired acrylate unit under mild conditions and with high efficiency. The method is based on Wittig reagents of the sort represented by **2** and **3**. A general technique for preparation of phosphorus reagents such as **2b** is due to Corey[3] and to Schlosser,[4] but we have failed in our attempts to apply that method in preparation of **2a** (X = OH) or **3a** (X = OH). Apparently, reaction of

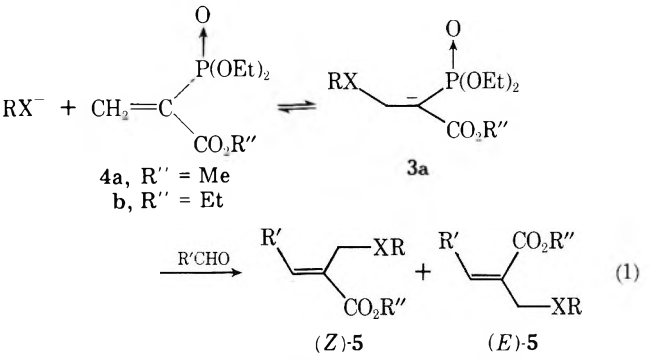


2a, R = CO_2Me; X = OH
b, R = alkyl; X = OH

3a, R = CO_2Me; X = OH
b, R = alkyl; X = OH

2a or **3a** with an aldehyde is slower than elimination of Ph_3PO (from **2a**) and $HOP(O)(OMe)_2$ (from **3a**). With other heteroatom units X in **2a** and **3a** (e.g., X = acetate), elimination of X^- is invariably too rapid.

Nevertheless, we expected that the elimination of X^- could be reversible, still providing useful concentrations of **2a** and **3a**. After a series of unsuccessful experiments with oxygen anions (in eq 1), the thiolate anion (X = S) was found to lead



4a, R'' = Me
b, R'' = Et

3a

(*Z*)-**5** (*E*)-**5** (1)

to the desired conversion. The requisite methyl 2-(diethylphosphono)acrylate **4** was prepared according to the procedure of Pudovik,[5] which is presented in detail in the Experimental Section. The yield of **4** was only moderate, but the procedure is direct, and the reagent can be prepared on large scale, distilled, and stored for later use. Then addition of **4** to a suspension of sodium hydride and the thiol in tetrahydrofuran, followed by an aldehyde (stirring for 2.0 h at 25 °C), affords the 2-(alkylthiomethyl)acrylate (**5**) in high yield.

Table I displays the results of experiments designed to test the effects of solvent polarity, cation type, and structure of the organic unit in the thiolate anion on the efficiency and the stereochemical outcome of the reaction. In this case *n*-heptanal, phosphonoacrylate **4b**, and a thiolate anion were allowed to react under a variety of conditions. The yield of combined *E* and *Z* isomers was high in every case.[6]

The data in Table I demonstrate that the ratio of isomers depends upon counterion, solvent, and the nature of the thiolate anion, although no useful correlation is evident. The

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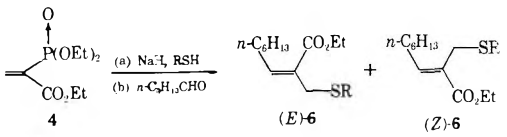
Table I. Effects of Reaction Conditions on Isomer Distribution



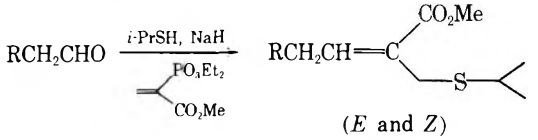
4 (E)-6 (Z)-6

Thiol R	Solvent	Base	E/Z
Isopropyl	THF	*n*-BuLi[a]	46/54
Isopropyl	THF	*n*-BuLi[b]	10/90
Isopropyl	THF	NaH[c]	45/55
Isopropyl	THF	KH[c]	10/90
Isopropyl	THF	Triton B[c]	30/70
Isopropyl	DMF	NaH[c]	10/90
tert-Butyl	THF	NaH[a]	45/55
tert-Butyl	DMF	NaH[a]	10/90
Benzyl	THF	NaH[c]	36/64
Phenyl	THF	NaH[a]	18/82

[a] The reaction time was 1 h. [b] The reaction time was 144 h. [c] The reaction time was 12 h.

ratio of isomers also depends upon whether equilibrium between the isomers is established; addition of 0.1 mol equiv of sodium isopropylthiolate effected rearrangement of pure (*E*)-**6** into an 18:80 mixture of (*E*)-**6**/(*Z*)-**6** in less than 5 min at 25 °C in DMF.[6] A parallel experiment in THF gave the same result, but only after 24 h. Presumably, equilibration of the *E* and *Z* isomers occurs by conjugate addition/elimination of the thiolate. Under conditions designed to minimize the rate of equilibration (nonpolar solvent, deficiency of RS^-), the ratio of isomers is generally about 1:1. After equilibration, the *Z* isomer usually predominates by a factor of 8:1 or 9:1. Chromatographic separation provides samples of the pure isomers with good efficiency.

A number of difunctional aldehydes have been converted to 2-(alkylthiomethyl)acrylates; examples such as 7 and 8 are obtained in high yields. A more demanding example is the preparation of the 4-chlorocrotonate derivatives, **9**, from chloroacetaldehyde under the usual conditions. The yield of (*E*)-**9** and (*Z*)-**9** is 98%, with an isomer ratio of 1:2.8.

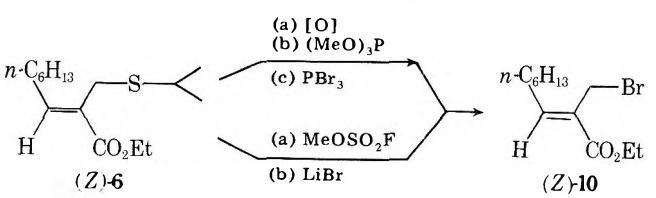


(*E* and *Z*)

7, R = $(CH_2)_4CH(OMe)_2$
8, R = $C(CH_3)_2CH_2CH(OMe)_2$
9, R = Cl

Our planned application of the 2-(alkylthiomethyl)acrylates requires conversion of the allylic thioether to an allylic halide. Preliminary studies provided the desired conversion in low overall yield using the three-step procedure based on the work of Evans:[8] oxidation of the thioether (**6**) to the sulfoxide using *m*-chloroperbenzoic acid, cleavage of the sulfinate ester (from [2.3]sigmatropic rearrangement), and bromination (with allylic rearrangement) of the allylic alcohol. The bromide (**10**) was obtained in 20–25% overall yield as a single isomer (*Z*) starting from either (*Z*)-**6** or (*E*)-**6**.

In an effort to convert (*E*)-**6** or (*Z*)-**6** to the corresponding allylic halides more efficiently and without isomerization of the olefin geometry, direct displacement of sulfur was studied. Methylation of the sulfur in (*Z*)-**6** with methyl fluorosulfonate (to give the sulfonium ion) followed by treatment with excess lithium bromide produced (*Z*)-**10** in high purity (93% yield). Parallel reactions with (*E*)-**6** also gave (*Z*)-**10** exclusively, although by monitoring the reaction by ^1H NMR, the transient formation of (*E*)-**10** was demonstrated.



(*Z*)-**6** (*Z*)-**10**

Finally, it should be mentioned that parallel techniques utilizing addition of carbanions to phosphonoacrylates (**4** and substituted analogues) are under development by C. Heathcock and co-workers at the University of California, Berkeley.[9]

Experimental Section

Preparation of Methyl 2-(Diethylphosphono)acrylate (4a). According to the general procedure of Pudovik,[5] a mixture of paraformaldehyde (19.95 g, 0.665 mol), methyl alcohol (470 mL), and piperidine (5.7 g, 6.63 mL, 0.067 mol) under argon in a 1-L flask equipped with a reflux condenser, magnetic stirrer, and inlet was heated at reflux for 1.5 h. During this time, the paraformaldehyde dissolved to give a colorless solution. To this mixture at 25 °C was added methyl (diethylphosphono)acetate[10] (105 g, 0.50 mol) and the mixture was heated at reflux for an additional 8 h. The solution was cooled and concentrated by rotary evaporation, benzene was added, and the mixture was concentrated again by rotary evaporation. After repeating this procedure, the residual oil was transferred to a 250-mL flask and phosphoric acid (5 mL, 85%) was added all at once. Distillation through an 18-in. vigreux column afforded a middle fraction of bp 95–98 °C (0.15 Torr) (lit.[5] bp 100–101 °C (1.0 Torr)), 31.32 g (28% yield): ^1H NMR (CCl_4) δ 1.33 (6 H, t, *J* = 7 Hz, OCH_2CH_3), 3.81 (3 H, s, OCH_3), 3.73–4.33 (4 H, m, OCH_2CH_3), 6.48 (1 H, dd, *J* = 2 and 2 Hz), 7.01 (1 H, dd, *J* = 2 and 25 Hz). An additional 8.5 g (8% yield) of less pure product was obtained as forerun and tailings.

A parallel preparation using triethyl phosphonoacetate (112 g, 0.50 mol) produced ethyl 2-(diethylphosphono)acrylate (**4b**) with bp 98.5–99.5 °C (0.13 Torr) (lit.[5] bp 101–102 °C (1.0 Torr)), 48.3 g (41% yield): ^1H NMR (CCl_4) δ 1.35 (9 H, t, *J* = 7 Hz, OCH_2CH_3), 3.84–4.45 (6, H, m, OCH_2CH_3), 6.47 (1 H, dd, *J* = 2 and 2 Hz), 7.00 (1 H, dd, *J* = 2 and 25 Hz). An additional 1.36 g (11.5% yield) of less pure material was also obtained.

Preparation of (*E*)-6 and (*Z*)-6 (R = 2-Propyl), 1-(2-Propylthio)-2-ethoxycarbonyl-2-nonene. Typical Procedure. Into a 50-mL three-neck flask equipped with an argon/vacuum inlet, serum cap, and magnetic stirrer was placed sodium hydride (0.084 g as a 57% slurry with mineral oil, 2.0 mmol). The flask was alternately evacuated and filled with argon three times. THF (15 mL, freshly distilled from benzophenone ketyl) was added and the stirred suspension was cooled to 0 °C. Then 2-propanethiol (0.152 g, 0.186 mL, 2.0 mmol) was added dropwise via syringe over 1 min (no apparent gas evolution). Ethyl phosphonoacrylate **4b** (0.47 g, 0.42 mL, 2.0 mmol) was added over several min (gas evolution). After the mixture was stirred for 5 min at 0 °C, heptanal (0.23 g, 0.27 mL, 2.0 mmol) was added over 1 min and the mixture was maintained at 0 °C for 2 h; a gummy precipitate formed. The mixture was partitioned between water and ether, the ether solution was set aside, and the aqueous layer was washed with ether. The combined ether solutions were dried over magnesium sulfate and concentrated by rotary evaporation to afford a colorless oil. Short-path distillation (85°/0.005 torr) gave 0.48 g (89% yield) of a mixture of (*E*)-**6**/(*Z*)-**6** in a ratio of about 1:1 (^1H NMR and GLC analysis).

Separation of the isomers was achieved by preparative GLC (6-ft × 0.375-in. column packed with 3% OV-225 on chromosorb W) and by open column chromatography (60–200 mesh silica gel, increasing proportion of benzene in hexane as eluant). The *E* isomer appeared first.

Compound (*E*)-**6** (R = 2-propyl), (*E*)-1-(2-propylthio)-2-ethoxycarbonyl-2-nonene, showed the following spectral data: IR (neat) 3.40, 3.43, 3.51 (s, CH), 5.83 (s, C=O), 6.10 (w, C=C), 6.85 (m), 7.28 (m), 8.12, 8.34 μm; ^1H NMR (CCl_4) δ 0.77–1.58 (w, 11 H), 0.87 (m, 3 H, OCH_2CH_3), 1.23 (d, 6 H, *J* = 7.5 Hz, $CH(CH_3)_2$), 2.07–3.0 (m, 3 H, CH_2CH=C and $SCH(CH_3)_2$), 3.27 (br s, 2H, CH_2S), 4.17 (q, 2 H, *J* = 7 Hz, OCH_2CH_3), 5.85 (t, 1 H, *J* = 7 Hz, $—CH_2CH$=); mass spectral molecular weight: calcd for $C_{15}H_{28}O_2S$, 272, and found, 272 (electron impact).

Anal. Calcd for $C_{15}H_{28}O_2S$: C, 66.13; H, 10.36; S, 11.77. Found: C, 65.94; H, 10.09; S, 11.93.

Compound (*Z*)-**6** (R = 2-propyl), (*Z*)-1-(2-propylthio)-2-ethoxy-

carbonyl-2-nonene, showed the following spectral data: IR (neat) 3.39, 3.42, 3.50 (s, CH), 5.84 (s, C=O), 6.09 (w, C=C), 6.83 (m), 7.30 (m), 7.80, 8.45 (m, CO), 9.50 μm; ^{1}H NMR (CCl_4) δ 0.68–1.62 (m, 11 H), 0.89 (m, 3 H, OCH_2CH_3), 1.27 (d, 6 H, J = 7Hz, $CH(CH_3)_2$), 1.98–2.45 (m, 2 H, —CH_2CH=), 2.87 (sept, 1 H, J = 7 Hz, $SCHC(CH_3)_2$), 3.41 (br s, 2 H, CH_2S), 4.17 (q, 2 H, J = 7 Hz, OCH_2CH_3), 6.72 (t, 1 H, J = 7.5 Hz, —CH_2CH=); mass spectral molecular weight: calcd for $C_{15}H_{28}O_2S$, 272 and found, 272 (electron impact).

Anal. Calcd for $C_{15}H_{28}O_2S$: C, 66.13; H, 10.36; S, 11.77. Found: C, 66.08; H, 10.13; S, 11.89.

In the same way, the following mixtures were prepared.

(*E*)- and (*Z*)-1-[2-(2-Methylpropyl)thio]-2-ethoxycarbonyl-2-nonene. (6, R = *tert*-Butyl). The yield of the mixture after short-path distillation (120 °C (0.03 Torr)) was 80%. Characteristic ^{1}H NMR signals at: δ 3.30 (br s, 2 H, -CH_2S- in *E* isomer), 3.37 (br s, 2 H, -CH_2S- in *Z* isomer), 5.93 (t, 1 H, J = 7 Hz, CH_2CH= in *E* isomer[6]), 6.62 (t, 1 H, J = 7 Hz, CH_2CH= in *Z* isomer).

Anal. Calcd for $C_{16}H_{30}O_2S$: C, 67.08; H, 10.56; S, 11.19. Found (mixture of *E* and *Z*): C, 67.23; H, 10.61; S, 11.38.

(*E*)- and (*Z*)-1-(Benzylthio)-2-ethoxycarbonyl-2-nonene (6, R = Benzyl). The yield of the mixture after short-path distillation (120 °C (0.03 Torr)) was 85%. Characteristic ^{1}H NMR signals at: δ 3.15 (br s, 2 H, CH_2S in *E* isomer), 3.50 (br s, 2 H, CH_2S in *Z* isomer), 3.59 (s, 2 H, SCH_2Ph in *E* isomer), 3.67 (s, SCH_2Ph in *Z* isomer), 4.19 (q, J = 7 Hz, OCH_2CH_3 in *E* isomer), 4.15 (q, 2 H, OcH_2CH_3 in *Z* isomer), 5.77 (t, 1 H, J = 7 Hz, CH_2CH= in *E* isomer), 6.72 (t, 1 H, J = 7 Hz, CH_2CH= in *Z* isomer).[6] The mixture was separable by GLC on a 6-ft × 0.375-in. column packed with 3% OV-225. Mass spectrometry showed no parent ion (electron impact).

Anal. Calcd for $C_{19}H_{28}O_2S$: C, 71.20; H, 8.81; S, 10.00. Found: C, 71.09; H, 8.82; S, 9.90.

(*E*)- and (*Z*)-1-(Phenylthio)-2-ethoxycarbonyl-2-nonene (6, R = phenyl). The yield of the mixture after short-path distillation (110 °C (0.05 Torr)) was 89%. Characteristic ^{1}H NMR signals at: δ 3.59 (br s, 2 H, -CH_2S- in *E* isomer), 3.71 (br s, 2 H, -CH_2S- in *Z* isomer), 4.13 and 4.15 (q, J = 7 Hz, 2 H each, OCH_2CH_3), 5.67 (t, 1 H, J = 7 Hz, —CH_2CH= in *E* isomer), 6.66 (t, 1 H, J = 7 Hz, —CH_2CH= in *Z* isomer).[6]

Anal. Calcd for $C_{18}H_{26}O_2S$: C, 70.54; H, 8.55; S, 10.46. Found: C, 70.76; H, 8.46; S, 10.45.

(*E*)- and (*Z*)-1-(2-Propylthio)-2-methoxycarbonyl-8,8-dimethoxy-2-octene ((*E*)-7 and (*Z*)-7). On a 10-mmol scale according to the typical procedure, the yield of the mixture before separation of *E*/*Z* isomers was 95%. Column chromatography on 300 g of silica gel (2.5-cm i.d. column, elution with 25% v/v ether in hexane) allowed partial separation of isomers.

Pure (*E*)-7 eluted first: 0.53 g; ^{1}H NMR (CCl_4) δ 1.08–1.66 (m, 6 H), 1.20 [d, 6 H, J = 7 Hz, $CH(CH_3)_2$], 2.12–3.08 [m, 3 H, $CH(CH_3)_2$ and —CH_2CH_2C=], 3.21 [s, 6 H, $CH(OCH_3)_2$], 3.29 (s, 2 H, -CH_2S-), 3.70 (s, 3 H, CO_2CH_3), 4.26 (distorted t, 1 H, CH_2CH), and 5.91 (t, 1 H, J = 7 Hz, —CH_2CH=).

Anal. Calcd for $C_{15}H_{28}O_4S$: C, 59.18; H, 9.27; S, 10.53. Found: C, 59.43; H, 9.39; S, 10.34.

Pure (*Z*)-7 eluted last: 0.50 g; ^{1}H NMR (CCl_4) δ 1.09–1.67 (m, 6 H), 1.23 [d, 6 H, J = 7 Hz, $CH(CH_3)_2$], 2.01–2.43 (m, 2 H, -CH_2CH_2CH=), 2.86 [sept, 1 H, J = 7 Hz, $CH(CH_3)_2$], 3.31 [s, 6 H, $CH(OCH_3)_2$], 3.37 (s, 2 H, CH_2S), 3.70 (s, 3 H, CO_2CH_3), 4.26 (distorted t, 1 H, CH_2CH), and 6.69 (t, 1 H, J = 7 Hz, —CH_2CH=).

An intermediate fraction was a mixture of *E* and *Z* isomers, 1.60 g. The combined yield of both isomers was 2.63 g (86%).

(*E*)- and (*Z*)-1-(2-Propylthio)-2-methoxycarbonyl-5,5-dimethyl-7,7-dimethoxy-2-heptene ((*Z*)-8 and (*E*)-8). According to the typical procedure (above), 3,3-dimethyl-5,5-dimethoxypentanal[11] (0.880 g, 5.05 mmol) was converted to a mixture of (*E*)-8 and (*Z*)-8. The yield of the crude material was 1.55 g (97%); ^{1}H NMR analysis suggested high purity. Column chromatography (silica gel, eluting with 12% ether in hexane) produced 1.23 g (77% yield) of a mixture of *E*/*Z* isomers, 43/57 [integration of ^{1}H NMR signals centered at δ 5.99 (*E* vinyl H) and at 6.80 (*Z* vinyl H)]. The mixture was not further purified. ^{1}H NMR (CCl_4) δ 0.94 [s, 6 H, $C(CH_3)_2$, *E*], 0.98 [s, 6 H, $C(CH_3)$, *Z*], 1.22 [d, 6 H, J = 7 Hz, $SCH(CH_3)_2$, *E*], 1.25 [d, 6 H, J = 7 Hz, $SCH(CH_3)_3$, *Z*], 1.48 (d, 2 H, J = 6 Hz, CH_2CH, *E*), 1.51 (d, 2 H, J = 6, CH_2CH, *Z*), 2.19 (d, 2 H, J = 7 Hz, CH_2C=C, *Z*), 2.40 (d, 2 H, J = 7 Hz, CH_2C=C, *E*), 2.85 (septet, 2 H, J = 7 Hz, $SCH(CH_3)_2$ *E* and *Z*), 3.21 (s, 6 H, $CHOCH_3$, *E* and *Z*), 3.33 (s, 2 H, C=C=CCH_2S, *E*), 3.36 (s, 2 H, C=C=CCH_2S, *Z*), 3.72 (s, 6 H, CO_2CH_3, *E* and *Z*), 4.40 [t, 2 H, J = 6 Hz, $CH(OCH_3)_2$, *E* and *Z*], 5.99 (t, 1 H, J = 7 Hz, vinyl H in *E*), 6.80 (t, 1 H, J = 7 Hz, vinyl H in *Z*); IR (CCl_4) 3.39, 3.53, 5.80 (C=O), 6.09 (C=C), 7.24, 8.9, 9.5, 10.4 (C=CH) μm.

Anal. Calcd for $C_{16}H_{30}O_4S$: C, 60.34; H, 9.50; S, 10.07. Found: C, 60.37; H, 9.48; S, 9.99.

Methyl (*E*)- and (*Z*)-29[(2-propyl)thiomethyl]-4-chloro-2-butenoates ((*E*)-9 and (*Z*)-9). According to the typical procedure, chloroacetaldehyde[12] (0.385 mg, 4.9 mmol, 32% excess), sodium hydride (0.155 g, 3.8 mmol), 2-propanethiol (0.292 g, 3.8 mmol), and phosphonoacrylate **4a** (0.825 g, 3.7 mmol) were converted at −78 °C to a mixture of (*E*)-**9** and (*Z*)-**9**, 0.850 g (98% yield), which showed only two components by TLC analysis and no significant spurious signals in the ^{1}H NMR spectrum of the mixture. Integration of the ^{1}H NMR signals δ 4.5 (d, CH_2Cl in (*E*)-**9**) and 4.2 (d, CH_2Cl in (*Z*)-**9**) were in the ratio of 1:2.8.

Medium pressure preparative LC of the mixture (15:1 hexane/ether at 10 psi, 100 × 2.5-cm column, silica gel) afforded 0.221 g (27%) of (*E*)-**9** (fraction 2), 0.085 g of a mixture of (*E*)-**9** and (*Z*)-**9**, and 0.310 g (38%) of (*Z*)-**9** (fraction 3). Compound (*Z*)-**9** began to decompose slowly upon removal of solvent at 25 °C.

Short-path distillation of fraction 1 (50–65 °C (0.001 Torr)) afforded 0.186 g (23%) of (*E*)-**9** as a colorless liquid. IR (neat) 5.81 (s) and 6.10 (m) μm; ^{1}H NMR ($CDCl_3$) δ 1.21 [d, 6 H, J = 7 Hz, $CH(CH_3)_2$], 2.84 [sept, 1 H, J = 7 Hz, $CH(CH_3)_2$], 3.37 (s, 2 H, CH_2S), 3.78 (s, 3 H, CO_2CH_3), 4.46 (d, 2 H, J = 7 Hz, $ClCH_2$), 6.13 (t, 1 H, J = 7 Hz, C=C**H**). Attempted combustion analysis was not successful, presumably due to significant decomposition during several days at 25 °C (also indicated in the ^{1}H NMR spectrum).

Short-path distillation of fraction 3 (50–65 °C (0.001 Torr)) afforded 0.127 g (16%) of (*Z*)-**9** as a colorless liquid which began to turn yellow within minutes at 25 °C. Working quickly the following spectral data were obtained: IR (neat) 5.82 (s) and 6.10 (m) μm; ^{1}H NMR ($CDCl_3$) δ 1.28 [d, 6 H, J = 7 Hz, $CH(CH_3)_2$], 2.94 [sept, 1 H, J = 7 Hz, $CH(CH_3)_2$], 3.50 (s, 2 H, CH_2S), 3.81 (s, 3 H, CO_2CH_3), 4.25 (d, 2 H, J = 7 Hz, CH_2Cl), 6.88 (t, 1 H, J = 7 Hz, C=C**H**), with detectable and increasing signals at δ 3.9 and 1.8 (impurities and/or decomposition products).

Preparation of (Z)-1-Bromo-2-ethoxycarbonyl-2-nonene (10). In a 50 mL three-neck flask equipped with an argon/vacuum inlet, serum cap, and magnetic stirrer was placed 0.20 g (0.74 mmol) of (*Z*)-1-(2-propylthio)-2-ethoxycarbonyl-2-nonene. The flask was alternately evacuated and filled with argon (3×). Methylene chloride (10 mL) was added and the mixture was cooled in an ice bath. Methyl fluorosulfonate (0.086 g, 0.061 mL, 0.75 mmol) was added all at once via syringe. After 0.5 h at 0 °C, the mixture was stirred at 20 °C for an additional 2.5 h and then cooled again to 0 °C. Lithium bromide (anhydrous, 0.35 g, 4.0 mmol) was added all at once. The suspension was stirred at 2 °C for 40 h, then methylene chloride was added and the mixture was filtered. Concentration by rotary evaporation provided 0.19 g (93%) of the allylic bromide (>90% pure by ^{1}H NMR analysis). Preparative layer chromatography afforded pure (*Z*)-**10**: 0.13 g (55% yield). ^{1}NMR (CCl_4) δ 0.68–1.73 (m, 14 H), 2.04–2.52 (m, 2 H, —CH_2CH_2CH=), 4.14 (s, 2 H, $BrCH_2C$=), 4.20 (q, J = 7 Hz, 2 H, OCH_2CH_3), 6.85 (t, J = 7 Hz, 1 H, —CH_2CH=); mass spectral molecular weight calcd for $C_{12}H_{21}BrO_2$, 276 and 278, and found, 276 and 278 (chemical ionization).

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Registry No.—**4a**, 993-88-4; **4b**, 20345-61-3; (*Z*)-**6** (R = *i*-Pr), 64600-31-3; (*E*)-**6** (R = *i*-Pr), 64600-32-4; (*Z*)-**6** (R = *t*-Bu), 64600-33-5; (*E*)-**6** (R = *t*-Bu), 64600-34-6; (*Z*)-**6** (R = CH_2-Ph), 64600-35-7; (*E*)-**6** (R = CH_2-Ph), 64600-36-8; (*Z*)-**6** (R = Ph), 64600-37-9; (*E*)-**6** (R = Ph), 64600-38-0; (*Z*)-**7**, 64626-93-3; (*E*)-**7**, 64600-39-1; (*Z*)-**8**, 64600-40-4; (*E*)-**8**, 64600-41-5; (*Z*)-**9**, 64600-42-6; (*E*)-**9**, 64600-43-7; (*Z*)-**10**, 64600-44-8; methyl diethyl phosphonoacetate, 1067-74-9; paraformaldehyde, 30525-89-4; triethyl phosphonoacetate, 867-13-0; 2-propanethiol, 75-33-2; *tert*-butylthiol, 75-66-1; benzylthiol, 100-53-8; phenylthiol, 108-98-5; 7,7-dimethoxyheptanal, 55489-11-7; 3,3-dimethyl-5,5-dimethoxypentanal, 64600-45-9; chloroacetaldehyde, 107-20-0.

References and Notes

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boalkoxy unit appears ca. 0.9 ppm downfield (ca. δ 5.8) relative to the vinyl proton (ca. δ 6.7) arranged trans to a carbomethoxy group.[7] Isomerization of α,β-unsaturated esters through reversible Michael addition of thiols has been noted: R. E. Ireland, M. I. Dawson, C. J. Kowalski, C. A. Lipinski, D. R. Marshall, J. W. Tilley, J. Bordner, and B. L. Trus, *J. Org. Chem.*, **40**, 1 (1975).
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(8) D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974).
(9) (a) Personal communication, August, 1975; (b) Abstract ORGN 85, American Chemical Society National Meeting, New Orleans, La., March, 1977; (c) see preceding note in this issue.
(10) This compound is now available commercially, for example, from Aldrich Chemical Co.
(11) Prepared from 3,3-dimethylglutaric anhydride by conventional techniques.
(12) Cf. H. O. House, V. K. Jones, and G. A. Frank, *J. Org. Chem.*, **29**, 3327 (1969).

Allylic Trifluoroacetylation Proceeding via an Additive Pummerer Rearranged Intermediate

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The rearrangement of sulfoxides to give α-substituted derivatives of the corresponding sulfides is well-known as the Pummerer reaction.[1,2] Recently, several instances of an interesting variation on this reaction, the so-called additive Pummerer rearrangement, have been reported.[3,4,5] In these examples the rearrangement of vinylogous sulfoxides yielded α,β-disubstituted derivatives of the corresponding sulfides. Evidence for a vinylogous Pummerer rearrangement involving an allylic methylene position has also been presented[6] and we have recently demonstrated a transannular-type Pummerer rearrangement with a para-substituted phenol sulfoxide.[7] In both the aforementioned cases the preferential abstraction of a distant hydrogen atom was thought responsible for the substitution pattern. We now report the first example of a reaction sequence involving the functionalization of an allylic methyl group proceeding via an additive Pummerer rearranged intermediate. This novel reaction provides ready access to a number of previously unavailable 2-oxymethyl analogues of the highly active and widely used systemic fungicide carboxin[8] (5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide).

Results and Discussion

Carboxin sulfoxide (**1**, Scheme I) on treatment with trifluoroacetic anhydride in benzene at room temperature rapidly underwent an additive Pummerer rearrangement to yield the spectroscopically homogeneous bis(trifluoroacetoxy)-1,4-oxathiane **2**. The proposed mechanism for the additive Pummerer reaction[4] would predict the possible formation of two diastereomers. However, in the present case, steric considerations appear to favor the trans-substitution pattern only. This would result in production of just the one stereoisomer presently observed. A somewhat analogous result has been reported previously.[5] A related reaction sequence demonstrated that the N–H moiety does not participate in the reaction with trifluoroacetic anhydride; i.e., the *N*-methyl analogue of carboxin sulfoxide yielded the similar bis(trifluoroacetate) **10**. The structure of compound **2** was further elucidated by methanolysis to the dimethoxy analogue **3**.

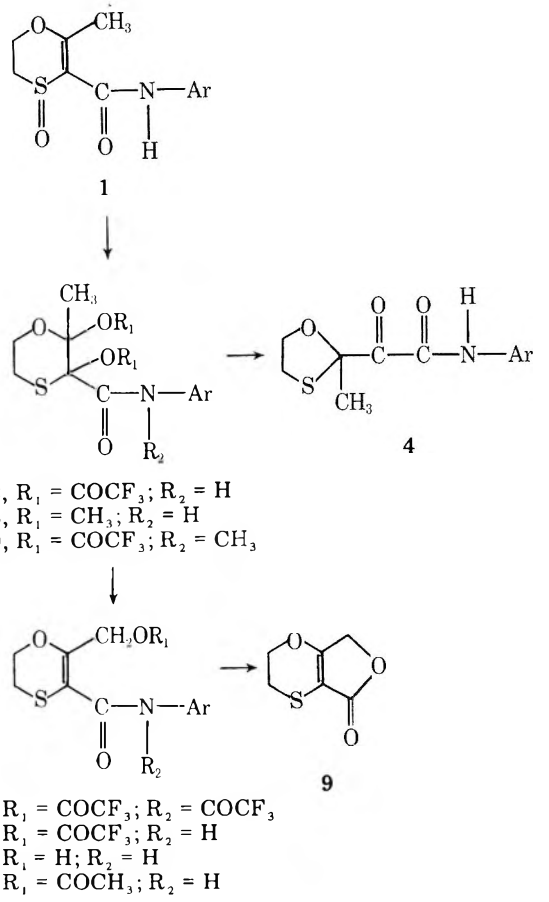
When subjected to mild hydrolytic conditions (i.e., aqueous dimethylformamide), **2** was converted to a 1,3-oxathiolane (**4**). In addition to having the requisite NMR and IR properties, mass spectral data of **4** showed a parent ion of *m/e* 251 and a prominent fragment ion of *m/e* 103, corresponding to the 2-methyl-1,3-oxathiolane moiety. An analogous rearrangement of 2,3-diacetoxy-1,4-dithane has been reported[9] and is similar to the well-known rearrangement of β-halo sulfides.[10]

When a benzene solution of compound **2** (with or without trifluoroacetic anhydride present) was refluxed for 1 h or alternately left to stand at room temperature overnight, it was converted to another compound which was assigned structure **5** on the basis of its spectroscopic properties. Infrared data showed strong absorption at 1795 and 1745 cm^{-1}, indicative of O- and N-trifluoroacetylated groups, respectively, and the NMR spectrum indicated loss of the C-2 methyl signal and the appearance of a two-proton singlet at δ 5.17.

Selective removal of the *N*-trifluoroacetyl group from compound **5** with saturated $NaHCO_3$ solution was shown by loss of the IR absorption band at 1745 cm^{-1} and reappearance of the N–H proton signal at δ 8.02 in the spectral data of the monotrifluoroacetate **6**. Mild treatment of **6** with pyridine hydrolyzed the remaining trifluoroacetyl group. A substantial shift upfield (δ 1.09) in the methylenic proton signal of the resultant alcohol **7** confirmed the postulated site of the trifluoroacetyl group prior to its removal. Acetylation of **7** with acetic anhydride–pyridine afforded the acetate analogue **8**. Prolonged hydrolysis of compounds **5**, **6**, and **7** resulted in quantitative degradation to the α,β-unsaturated-γ-lactone **9**.

Investigations regarding the mode of conversion from compound **2** to **5** suggest a concerted reaction involving participation of the anilide group; i.e., TLC and NMR studies of the reaction mixture failed to detect the presence of any stable intermediates such as the monotrifluoroacetate **6**, and the *N*-methylbis(trifluoroacetyl) analogue **10** once formed did not undergo a similar rearrangement.

Scheme I



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Experimental Section

Melting points are uncorrected and were determined on a Kofler hot stage microscope. NMR spectra were recorded on a Varian T-60 NMR spectrometer with Me_4Si as an internal standard. IR spectra were determined as Nujol mulls using a Beckman IR-20A spectrophotometer. MS were determined by a Finnigan 3100 GC–MS coupled to a D6000 data acquisition system. Thin-layer chromatograms were run on glass plates coated with Silica Gel F-254. Separated components were detected by UV fluorescence and iodine vapor.

2,3-Bis(trifluoroacetoxy)-2-methyl-1,4-oxathian-3-carboxanilide (2). A suspension of carboxin sulfoxide (**1**,[11] 510 mg) in benzene (10 mL) was treated with an excess of trifluoroacetic anhydride (0.5 mL) and stirred for 15 min at room temperature. Removal of the benzene and unreacted trifluoroacetic anhydride with a stream of dry N_2 yielded, after recrystallization from anhydrous diethyl ether, the bis(trifluoroacetate) **2** (793 mg), mp 98–100 °C: IR (Nujol) 3224, 1795, 1700, 1540 cm^{-1}; NMR ($CDCl_3$) δ 7.92 (1 H, s, NH), 7.35 (5 H, m, pH), 2.57–4.17 (4 H, m, ring H), 1.91 (3 H, s, CH_3); MS *m/e* 461 (M^+). Anal. Calcd for $C_{16}H_{13}O_6NSF_6$: F, 24.73. Found: F, 24.41.

2,3-Bis(methoxy)-2-methyl-1,4-oxathian-3-carboxanilide (3). A solution of **2** (300 mg) in 95% methanol (10 mL) was stirred overnight. After dilution with water (40 mL) the mixture was neutralized by the addition of sodium bicarbonate and then extracted with chloroform (2 × 60 mL). After drying (anhydrous sodium sulfate) the chloroform was removed under vacuum, and the residue was purified by preparative thin-layer chromatography (ethyl acetate–hexane, 1:1). Crystallization of the major component (119 mg) from diethyl ether–hexane gave the dimethoxy analogue **3**, mp 120–122 °C: NMR ($CDCl_3$) δ 8.14 (1 H, s, NH), 7.36 (5 H, m, Ph), 2.24–4.02 (4 H, m, ring H), 3.62 (3 H, s, OMe), 3.38 (3 H, s, OMe), 1.42 (3 H, s, Me); MS *m/e* 297 (M^+).

2-Methyl-1,3-oxathiolan-2-ketocarboxanilide (4). A solution of **2** (200 mg) in dimethylformamide (20 mL) and H_2O (5 mL) was stirred overnight. Removal of the solvents under vacuum yielded, after recrystallization from aqueous ethanol, the 1,3-oxathiolane **4** (78 mg), mp 130–131 °C: IR (Nujol) 3335, 1710, 1690, 1545 cm^{-1}; NMR ($CDCl_3$) δ 9.10 (1 H, s, NH), 7.40 (5 H, m, Ph), 3.01–4.44 (4 H, m, ring H), 2.12 (3 H, s, Me); MS *m/e* 251 (M^+) −103 (M^+ − 148).

***N*-Trifluoroacetyl-5,6-dihydro-2-trifluoroacetoxymethyl-1,4-oxathiin-3-carboxanilide (5).** A solution of **2** in benzene or alternately a solution of **1** in benzene plus an excess of trifluoroacetic anhydride refluxed for approximately 1 h or left to stir overnight afforded (after removal of solvents with a stream of N_2) a near quantitative yield of the 2-trifluoroacetoxymethyl derivative **5**, which did not crystallize but showed one spot on TLC (ethyl acetate–hexane, 3:2): IR (Nujol) 1795, 1745, and 1705 cm^{-1}; NMR ($CDCl_3$) δ 7.36 (5 H, m, Ph), 5.17 (2 H, s, CH_2O), 2.86–4.48 (4 H, m, ring H); MS *m/e* 443 (M^+). Anal. Calcd for $C_{16}H_{11}O_5NSF_6$: F, 25.74. Found: F, 25.84.

5,6-Dihydro-2-trifluoroacetoxymethyl-1,4-oxathiin-3-carboxanilide (6). A solution of **5** (250 mg) in chloroform (40 mL) in a separatory funnel was shaken with saturated sodium bicarbonate solution (25 mL) for several minutes. The chloroform layer was separated and dried over anhydrous sodium sulfate, and the chloroform was removed under vacuum. Recrystallization of the residue from hexane gave the monotrifluoroacetate **6** (174 mg), mp 92–93 °C: IR (Nujol) 3255, 1790, 1650, 1545 cm^{-1}; NMR ($CDCl_3$) δ 8.02 (1 H, s, NH), 7.38 (5 H, m, Ph), 5.36 (2 H, s, CH_2O), 2.98–4.45 (4 H, m, ring H); MS *m/e* 347 (M^+).

5,6-Dihydro-2-hydroxymethyl-1,4-oxathiin-3-carboxanilide (7). A solution of **6** (150 mg) in benzene (10 mL) containing pyridine (5 mL) was stirred for 1 h. The solution was then taken up in chloroform (50 mL) and shaken with water (2 × 30 mL) in a separatory funnel. After separation, drying (anhydrous sodium sulfate), and removal of the chloroform and traces of pyridine under vacuum, washing the crystalline residue with hexane afforded the alcohol **7** (82 mg), mp 87–89 °C: IR (Nujol) 3360, 3295, 1650, 1535 cm^{-1}; NMR ($CDCl_3$) δ 8.22 (1 H, s, NH), 7.42 (5 H, m, Ph), 4.28 (2 H, s, CH_2O), 2.98–4.52 (4 H, m, ring H); MS *m/e* 251 (M^+).

2-Acetoxymethyl-5,6-dihydro-1,4-oxathiin-3-carboxanilide (8). A solution of **7** (140 mg) in acetic anhydride (5 mL) and pyridine (3 mL) was stirred for 3 h at room temperature and then neutralized by decantation into a cold saturated solution of sodium bicarbonate. After extraction of the neutral solution with chloroform (2 × 50 mL), the chloroform extracts were dryed and concentrated under vacuum. Any residual pyridine was removed with a stream of N_2, and the residue was crystallized from hexane to yield the acetate **8** (113 mg), mp 90–91 °C: IR (Nujol) 3255, 1730, 1650, 1545 cm^{-1}; NMR ($CDCl_3$) δ 8.98 (1 H, s, NH) 7.40 (5 H, m, Ph), 4.97 (2 H, s, CH_2O), 3.00–4.37 (4 H, m, ring H), 2.92 (3 H, s, OAc); MS *m/e* 337 (M^+).

5,6-Dihydro-2-(hydroxymethyl)-1,4-oxathiin-3-carboxylic Acid γ-Lactone (9). **5**, **6**, or **7** in benzene and pyridine stirred overnight after workup inevitably yielded the α,β-unsaturated-γ-lactone **9**, which after crystallization from hexane had mp 117–118 °C: IR (Nujol) 1750 cm^{-1}; NMR ($CDCl_3$) δ 4.74 (2 H, s, CH_2O), 3.04–4.65 (4 H, m, ring H); MS *m/e* 158 (M^+). Anal. Calcd for $C_6H_6O_3S$: C, 45.56; H, 3.82. Found: C, 45.75; H, 3.73.

***N*-Methyl-2,3-bis(trifluoroacetoxy)-2-methyl-1,4-oxathian-3-carboxanilide (10).** A suspension of *N*-methylcarboxin sulfoxide[11] (200 mg) in benzene (5 mL) was treated with an excess of trifluoroacetic anhydride and stirred for 15 min. Benzene and unreacted trifluoroacetic anhydride were removed with a stream of N_2. Recrystallization of the residue from anhydrous diethyl ether furnished the *N*-methylbis(trifluoroacetoxy) compound **10**, mp 190 °C dec: IR (Nujol) 1795, 1645 cm^{-1}; NMR ($CDCl_3$) δ 7.34 (5 H, m, Ph), 2.18–5.14 (4 H, m, ring H), 4.38 (3 H, s, N–Me), 1.88 (3 H, s, Me).

A solution of **10** in benzene with or without trifluoroacetic anhydride on refluxing for several hours or after stirring at room temperature for up to 3 days did not produce any change in the compound.

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Registry No.—**1** (Ar = Ph), 17757-70-9; **2** (Ar = pH), 64754-69-4; **3** (Ar = Ph), 64754-70-7; **4** (Ar = Ph), 64754-74-1; **5** (Ar = Ph), 64754-72-9; **6** (Ar = Ph), 64754-73-0; **7** (Ar = Ph), 64754-75-2; **8** (Ar = Ph), 42825-80-9; **9**, 64754-76-3; **10** (Ar = Ph), 64754-71-8; trifluoroacetic anhydride, 407-25-0; acetic anhydride, 108-24-7; *N*-methylcarboxins sulfoxide, 17757-81-2.

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Transition Metal Catalyzed Reactions of Lithium Aluminum Hydride with Alkyl and Aryl Halides

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The reduction of organic halides to the corresponding hydrocarbons is an important transformation in organic synthesis. Recently, $2LiAlH(OCH_3)_3$–CuI[1] and LiCuHR[2] compounds (where R = alkyl and alkynyl) were evaluated as reagents for removal of halo and mesoloxy groups. $TiCl_3$–Mg[3] and $(\pi\text{-Cp})_2TiCl_2$–Mg[4] have been used for the same purpose at almost the same time by different research groups. More recently, we have been able to synthesize complex metal hydrides of copper and have demonstrated their ability to remove the halo and tosylate group from alkyl and aryl halides and tosylates.[5] We wish to report here that $LiAlH_4$ in the presence of first row transition-metal halides is a powerful and convenient reagent for the removal of halo and tosylate groups.

$LiAlH_4$ is not as effective a reagent for the removal of halo

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Table I. Reduction of Halides by $LiAlH_4$–Transition-Metal Chlorides at Room Temperature in THF Solvent[a]

Expt	Halide substrate[d]	Registry no.	Transition-metal chloride[b]	Reaction time, h	Product	Yield, %
1.	1-Chlorodecane[e]	1002-69-3	None	24	*n*-Decane	68
2.			VCl_3			75
3.			$CrCl_3$			90
4.			$MnCl_2$			19
5.			$FeCl_3$			100
6.			$FeCl_2$			95
7.			$FeCl_2$[c]			85
8.			$CoCl_2$[c]			100
9.			$NiCl_2$[c]			100
10.			$TiCl_3$[c]			100
11.	1-Bromodecane[e]	112-29-8	None	1	*n*-Decane	92
12.			VCl_3			40
13.			$CrCl_3$			65
14.			$MnCl_2$			43
15.			$FeCl_3$			50
16.			$FeCl_2$			100
17.			$FeCl_2$[c]			90
18.			$CoCl_2$			98
19.			$CoCl_2$[c]			98
20.			$NiCl_2$			100
21.			$NiCl_2$[c]			100
22.			$TiCl_3$			96
23.			$TiCl_3$[c]			98
24.	1-Iododecane	2050-77-3	None		*n*-Decane	98
25.			$FeCl_2$			98
26.			$CoCl_2$[c]			98
27.			$NiCl_2$[c]			98
28.			$TiCl_3$[c]			100
29.	1-Fluorodecane	334-56-5	None	24	*n*-Decane	0
30.			$FeCl_2$			16
31.			$CoCl_2$[c]			10
32.			$NiCl_2$[c]			7
33.			$TiCl_3$[c]			9
34.	*n*-Octyltosylate	3386-35-4	None	24	*n*-Octane	92
35.			$FeCl_2$			25
36.			$CoCl_2$[c]			100
37.			$NiCl_2$[c]			98
38.			$TiCl_3$[c]			54
39.	3-Bromooctane	999-64-4	None	24	*n*-Octane	75
40.			$FeCl_2$			90
41.			$CoCl_2$			98
42.			$NiCl_2$			92
43.			$TiCl_3$			88
44.	Bromocyclohexane	108-85-0	None	24	Cyclohexane	0
45.			$FeCl_2$			97
46.			$CoCl_2$			99
47.			$NiCl_2$			99
48.			$TiCl_3$			100
49.	Chlorocyclohexane	542-18-7	None	24	Cyclohexane	0
50.			$FeCl_2$			98
51.			$CoCl_2$			92
52.			$CoCl_2$[c]			3
53.			$NiCl_2$			95
54.			$NiCl_2$[c]			5
55.			$TiCl_3$			95
56.			$TiCl_3$[c]			95
57.	1-Bromoadamantane	768-90-1	None	24	Adamantane	70
58.			$FeCl_2$			100
59.			$CoCl_2$			100
60.			$NiCl_2$			100
61.			$TiCl_3$[c]			100
62.	Chlorobenzene	108-90-7	None	24	Benzene	0
63.			$FeCl_2$			72
64.			$CoCl_2$			25
65.			$CoCl_2$[c]			0
66.			$NiCl_2$			100
67.			$NiCl_2$[c]			0
68.			$TiCl_3$[c]			45
69.	Bromobenzene	108-86-1	None	24	Benzene	0
70.			$FeCl_2$			80
71.			$CoCl_2$			74

Table I (*Continued*)

Expt	Halide substrate[d]	Registry no.	Transition-metal chloride[b]	Reaction time, h	Product	Yield, %
72.			$CoCl_2$[c]			23
73.			$NiCl_2$			100
74.			$NiCl_2$[c]			87
75.			$TiCl_3$[c]			91
76.	Iodobenzene	591-50-4	None	24	Benzene	38
77.			$FeCl_2$			98
78.			$CoCl_2$			98
79.			$NiCl_2$			100
80.			$TiCl_3$[c]			92

[a] All reactions were carried out in THF at −78 °C for 10 min and then warmed to room temperature by removing the cooling bath. The reaction time was counted beginning with the period at −78 °C. Yields were determined by GLC using a suitable internal standard. [b] Molar ratio of $LiAlH_4$ to transition-metal chloride is 1:1, except when noted. [c] Used 10% molar equivalent. [d] Halide substrate was used in equivalent molar amount to $LiAlH_4$ except when noted. [e] Halide substrate was one-half equivalent with respect to $LiAlH_4$.

or tosylate groups from organic molecules as the reagent $LiAlH_4$–transition-metal halide. For example, $LiAlH_4$ reduces 1-iododecane, 1-bromodecane, and *n*-octyl tosylate to the corresponding hydrocarbon in 92–98% yields, but reduces 1-chlorodecane in only 68% yield and exhibits no effect at all in the reduction of bromocyclohexane and bromobenzene under the same reaction conditions (room temperature, 24 h, stoichiometric 1:1 molar ratio of $LiAlH_4$–halide substrate). The admixture of $LiAlH_4$–transition-metal chloride (VCl_3, $CrCl_3$, $MnCl_2$, $FeCl_2$, $FeCl_3$, $CoCl_2$, $NiCl_2$, and $TiCl_3$) in stoichiometric or catalytic amount was allowed to react with alkyl or aryl halides in order to compare the reactivity of these mixed reagents with $LiAlH_4$ itself. The results are shown in Table I.

In the reactions of 1-chlorodecane and 1-bromodecane, $FeCl_2$, $CoCl_2$, $NiCl_2$, and $TiCl_3$ (stoichiometric or catalytic) show superior reducing ability compared to the other catalysts evaluated (i.e., VCl_3, $CrCl_3$, $MnCl_2$, and $FeCl_3$). The admixture of $LiAlH_4$–VCl_3, –$CrCl_3$, –$MnCl_2$, and –$FeCl_3$ (stoichiometric) reduced 1-chlorodecane and 1-bromodecane to *n*-decane in only low yields compared to the reactions involving $FeCl_2$, $CoCl_2$, $NiCl_2$, and $TiCl_3$ under the same reaction conditions. Furthermore, $LiAlH_4$ with 10 mol % $FeCl_2$, $CoCl_2$, $NiCl_2$, and $TiCl_3$ reduced 1-chlorodecane in 85, 100, 100, and 100% yields, respectively. These results reveal the relative catalytic ability of transition-metal chlorides; i.e., $CoCl_2$, $NiCl_2$, and $TiCl_3$ are more effective catalysts than $FeCl_2$.

Since $FeCl_2$, $CoCl_2$, $NiCl_2$, and $TiCl_3$ admixed with $LiAlH_4$ were found to be the most effective catalysts for reduction of 1-chlorodecane and 1-bromodecane, only these catalysts were used in further studies of other halides. Decyliodide was reduced to *n*-decane in nearly quantitative yield by the above transition-metal halides; however, fluorodecane was reduced in only 7–16% yield. *n*-Octyl tosylate was reduced to *n*-octane in 98–100% yield by $LiAlH_4$ and a catalytic amount (10 mol %) of $NiCl_2$ and $CoCl_2$, but in significantly lower yields by $FeCl_2$ and $TiCl_3$. The secondary halide, 3-bromodecane, was also reduced in high yield (88–98%) when the transition-metal halides were used in stoichiometric amount. Bromocyclohexane and chlorocyclohexane, which are inert to $LiAlH_4$, can be reduced by $LiAlH_4$ with stoichiometric amounts of $FeCl_2$, $CoCl_2$, and $NiCl_2$, or a catalytic amount (10 mol %) of $TiCl_3$, to produce cyclohexane in excellent yields (92–100%). However, a catalytic amount (10 mol %) of $CoCl_2$ or $NiCl_2$ was not effective in the reduction of bromocyclohexane. Also, 1-bromoadamantane was reduced to adamantane in quantitative yield by all four catalysts.

Phenyl halides (X = I, Br, and Cl) were also allowed to react with these new reagents. The substrates were reduced in the order I > Br > Cl, and the superior reagent for the reduction of aromatic halides was found to be $LiAlH_4$–$NiCl_2$ (1:1), which reduced iodo-, bromo-, and chlorobenzene to benzene in 100% yield.

In conclusion, admixtures of $LiAlH_4$ with stoichiometric or catalytic amounts of $FeCl_2$, $CoCl_2$, $NiCl_2$, and $TiCl_3$ have been found to be powerful reagents for removal of the halo or tosylate group in organic substrates. Especially, the reagent $LiAlH_4$–$NiCl_2$ can reduce primary, secondary, cyclic, and even aromatic halides (X = I, Br, and Cl) in essentially quantitative yield in each case.

Experimental Section

Apparatus. Reactions were performed under nitrogen at the bench using Schlenk tube techniques.[6] ^1H NMR spectra were obtained at 60 MHz using a Varian T-60 NMR spectrometer. Mass spectra were obtained on a Varian Model M-66 mass spectrometer. GLC analyses were performed on F & M Models 700 and 720 gas chromatographs.

Materials. Tetrahydrofuran (Fisher Certified Reagent Grade) was distilled under nitrogen over $NaAlH_4$. Transition-metal chlorides and organic substrates were purchased commercially and used without further purification.

General Reactions. A 10-mL Erlenmeyer flask with a Teflon-coated magnetic stirring bar was dried in an oven and allowed to cool under a nitrogen flush. The transition-metal chloride (ca. 0.2 mmol for stoichiometric and ca. 0.02 mmol for catalytic reactions) was transferred to the flask in a drybox, sealed with a rubber septum, removed from the drybox, and connected by means of a needle to a source of nitrogen. The calculated amount of organohalide in THF solution was syringed into the transition-metal halide in the flask at −40 °C (controlled by a dry-ice bath). The designated amount of $LiAlH_4$ in THF solution was added slowly. On addition a black color was immediately produced with gas evolution. After 10 min the reaction vessel was warmed to room temperature. After an indicated reaction time the reaction mixture was quenched with a minimum of distilled water and the resultant solution dried over $MgSO_4$. Analysis of the product was obtained by GLC using a 20 ft 8% Apiezon L column. Products were identified by comparing the retention times with authentic samples. In some cases, melting points, NMR specta, and mass spectra were also employed for identification of the products. Yields were corrected by using internal standards for GLC analyses.

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Registry No.—$LiAlH_4$, 16853-85-3.

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Oxidative Dehydrogenation of Pyrazolines with Cobalt(II) and Oxygen

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Synthesis of pyrazoles can be accomplished in several ways, including the dehydrogenation of pyrazolines.[1-5] A number of dehydrogenating agents have been employed for this purpose. However, none except tetrachloro-1,2-benzoquinone qualifies as a truly general reagent. They either require too severe a reaction condition or their use is accompanied by products of decompositions and ring scission.

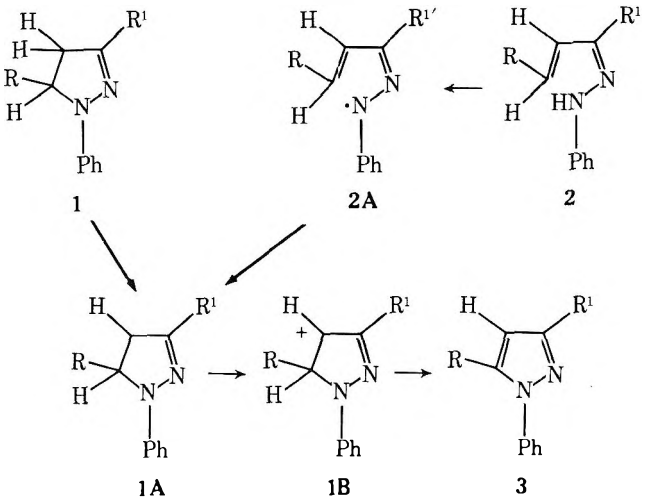
We now wish to report a mild general route for the oxidative dehydrogenation of *N*-phenyl-3,5-disubstituted-2-pyrazolines to the corresponding pyrazoles using catalytic amounts of cobalt soap of fatty acids (C_6–C_{10}). The reactions proceed smoothly and in high yields under fairly mild conditions compared to the methods reported previously. For example, 1,3,5-triphenylpyrazoline on treatment with catalytic amounts of cobalt soap and oxygen at 1 atm in refluxing benzene yielded 1,3,5-triphenylpyrazole (**3**, R, R′ = Ph) in quantitative yield in less than 30 min. The generality of the method is evident from the fact that a wide variety of substituted pyrazolines underwent smooth oxidation in good yields. The results are summarized in Table I.

We propose that Co(III) ions are responsible for the oxidative dehydrogenation reaction. The Co(III) ions may be formed by the interaction of the Co(II) soap with traces of peroxides present in solution under the conditions of reaction.[7-9]

The pyrazolines are converted to a cyclic radical intermediate (**1A**, see Scheme I) by a hydrogen abstraction by Co(III) followed by further oxidation of the radical to a carbenium ion (**1B**). Loss of a proton from the carbenium ion intermediate leads to the pyrazole **3**. The reduced Co(II) ions formed during this oxidation are reoxidized to Co(III) under the conditions of the reaction. Thus, only a catalytic amount (50–100 ppm) of Co(II) ions is required for the completion of the reaction. The proposed scheme is analogous to the mechanism of liquid-phase oxidation of hydrocarbons using Co(II) ions and oxygen as catalyst.[7-9]

It occurred to us that the cyclic radical intermediate **1A** could also be generated from chalcone phenylhydrazones (**2**) through the intermediary of a nitrogen radical (**2A**) (see Scheme I). Accordingly we oxidized benzalacetophenone phenylhydrazone (**2**, R, R′ = Ph) and *m*-nitrobenzalacetophenone phenylhydrazone (**2**, R = *m*-$NO_2C_6H_4$; R′ = Ph) using reaction conditions identical with those used previously for pyrazolines and could realize 90 and 60% yields of the corresponding pyrazoles.

Scheme I



Experimental Section

All melting points are uncorrected. IR spectra were determined on a Perkin-Elmer Infracord spectrometer in Nujol and UV spectra on a Perkin-Elmer Coleman Model 55 spectrophotometer in ethanol.

All pyrazolines were prepared by the reaction of the appropriate substituted chalcones with phenylhydrazine in refluxing acetic acid[4] and were fully characterized prior to use.

Preparation of Cobalt Soap. To a solution of sodium hydroxide (4.2 g) in water (100 mL) was added fatty acids with 6–10 carbons (23.5 mL) without allowing the temperature to rise above 25 °C. The pH of the solution was then set to 7 either by adding fatty acids or alkali. Benzene (350 mL) was added followed by a solution of $CoSO_4 \cdot 2H_2O$ (19 g) in water (75 mL). The organic layer was separated, washed, dried (Na_2SO_4), the concentration of cobalt in catalyst solution was estimated.

The experimental procedure can be simplified by a single dilution with benzene. The cobalt concentration is then estimated and the requisite volume to give 96 ppm of cobalt(II) is added to the reaction mixture. This change implies that 16 g/L of cobalt catalyst concentration as mentioned previously is not the only suitable catalyst concentration for this reaction.

Dehydrogenation of 2-Pyrazolines (General Procedure). The reaction assembly consisted of a flask fitted with a gas disperser and a reflux condenser connected to the flask through a Dean and Stark water separator. The top of the condenser was attached to a pressure gauge, and the pressure was regulated using an exit valve. Pyrazoline (0.01 mol) was dissolved in anhydrous benzene (150 mL), and the catalyst [96 ppm Co(II)] was added to this solution. The reaction vessel was pressurized to 1 atm at room temperature by bubbling oxygen into the reaction flask. The reactants were then brought to reflux and maintained for 30 min at an oxygen pressure of 1 atm.[10] The organic layer was then washed with 2% hydrochloric acid and water and dried, and the solvent was evaporated. The residue was purified by crystallization or by chromatography on silica gel, eluting with benzene–diethyl ether (98:2 v/v). When treated similarly for 3 h, chalcone phenylhydrazone gave pyrazole. The UV and IR spectra of all pyrazoles were in agreement with those reported in the literature.[3-6]

Table I. Yields of Products from the Oxidation of *N*-Phenyl-3,5-disubstituted-2-pyrazolines

Pyrazole	Registry no.	R	R¹	Yield, %	Mp, °C	Lit. mp, °C
3a	2183-27-9	Ph	Ph	100	139	140[4]
3b	16860-55-2	*m*-$NO_2C_6H_4$	Ph	60	130	130[5]
3c	16860-68-7	α-Furyl	Ph	88	71	64[5]
3d	16860-69-8	α-Thienyl	Ph	92	113	112[5]
3e	10252-53-6	Ph	PhCH=CH	95	141	141[4,5]
3f	16901-34-1	Ph	*p*-BrC_6H_4	92	157	159[5]
3g	21159-63-7	α-Furyl	*p*-ClC_6H_4	65	83	
3h	33045-42-0	α-Thienyl	*p*-ClC_6H_4	95	133	134[6]
3i	21159-60-4	α-Furyl	*p*-$OMeC_6H_4$	80	86	
3j	58950-01-9	α-Thienyl	*p*-$OMeC_6H_4$	94	91	
3k	1128-54-7	H	Me	89	33	33[4]

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Registry No.—**1A**, 742-01-8; **1B**, 6969-04-6; **1C**, 2755-71-7; **1D**, 2755-72-8; **1E**, 2515-62-0; **1F**, 19429-34-6; **1G**, 4035-38-5; **1H**, 5204-27-3; **1I**, 4035-37-4; **1J**, 20264-73-7; **1K**, 10252-46-7.

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(10) It was found that bubbling in oxygen through an open system was less efficient, requiring about 5 h to complete the reaction. Use of a slight positive pressure is expected to increase the dissolved oxygen content, thereby accelerating the oxidation reaction.

Deoxygenation of Amine *N*-Oxides or *C*-Nitroso Compounds by Dialkyl Sulfoxylates

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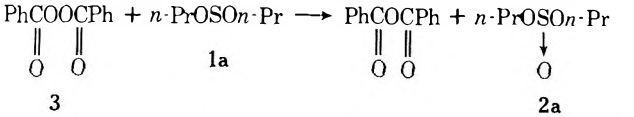
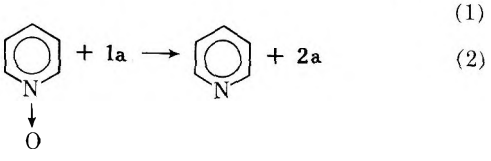
Deoxygenation reactions of a variety of organic compounds by trivalent phosphorus compounds are well known. For example, dibenzoyl peroxide,[1] pyridine *N*-oxide,[2] or nitrosobenzene[3] is deoxygenated by triphenyl phosphine or triethyl phosphite to give benzoic anhydride, pyridine, or azoxybenzene, respectively. Sulfoxylates (**1**) are readily oxidized,[4] yielding sulfites (**2**) upon exposure to air; nevertheless, little attention has been paid to the deoxygenation reactions by **1**. Thus it seemed reasonable that a similar deoxygenation reaction could be carried out by **1**. Di-*n*-propyl sulfoxylate (**1a**) and diethyl sulfoxylate (**1b**) were used in the present study; the former was more accessible and stable than the latter.

First, dibenzoyl peroxide (**3**) was allowed to react with **1a**. The reaction took place violently even at room temperature and benzoic anhydride and di-*n*-propyl sulfite (**2a**) were obtained in almost quantitative yields (eq 1). The result is in contrast to the reaction of dioxetane, a cyclic peroxide, and **1** which affords tetraalkoxysulfurane instead of oxirane.[5]

Pyridine *N*-oxide (**4a**) also reacted with **1a** at room temperature to give pyridine and **2a** in yields of 96 and 85%, respectively (eq 2). Similarly, 2-picoline *N*-oxide (**4b**), 3-picoline



3 **2a** (1)

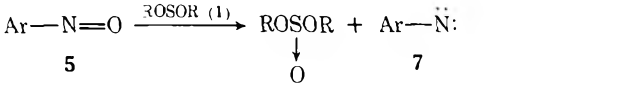


4a (2)

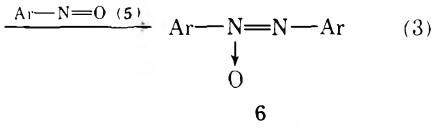
N-oxide (**4c**), or 4-picoline *N*-oxide (**4d**) reacts with **1a** at room temperature or in refluxing benzene to give amine and **2a** as shown in Table I. 4-Nitropyridine *N*-oxide (**4e**) did not react with **1a** under similar conditions, but, upon heating in the absence of solvent a vigorous exothermic reaction occurred with the evolution of nitric oxide. The only product isolated from the reaction mixture was di-*n*-propyl sulfite (**2a**). The deoxygenation of pyridine *N*-oxide (**4a**) or its homologues by triphenyl phosphine must be carried out under drastic conditions (heating above 200 °C).[2]

Reactions of *C*-nitroso compounds with sulfoxylates (**1**) gave a variety of products. When equimolar quantities of nitrosobenzene (**5a**) and **1a** or **1b** were refluxed in benzene or CCl_4, the solution gradually turned from green to reddish brown and azoxybenzene (**6a**) was obtained in 61–76% yields (eq 3). *p*-Nitrosotoluene (**5b**) or *o*-nitrosotoluene (**5c**) similarly reacted with **1a** to give 4,4′-dimethylazoxybenzene (**6b**) or 2,2′-dimethylazoxybenzene (**6c**). The sulfite (**2**) was not isolated in these cases but its formation was confirmed by an infrared spectrum.

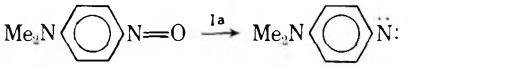
In addition, we examined the reaction of **1a** and *p*-dimethylaminonitrosobenzene (**5d**) and found that *p*-dimethylamino-*N*-sulfinylaniline (**8**) was formed together with 4,4′-bis(dimethylamino)azoxybenzene (**6d**) and 4,4′-bis(dimethylamino)azobenzene (**9**). The mechanism of the formation of **8** is not obvious. Bunyan and Cadogan[3] proposed the mechanism of formation of **6** by assuming arylnitrene (**7**) to be a transient intermediate. Accordingly, the reaction presumably proceeds through the intermediate **10** generated by the attack of nitrene **7d** on **1a**.[6]



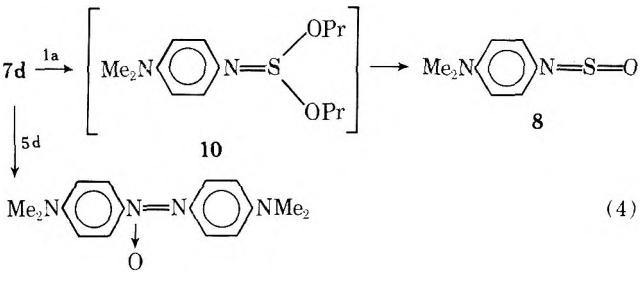
5 **2** **7**



6 (3)



5d **7d**

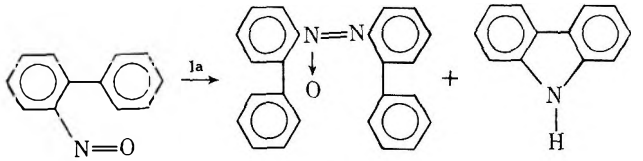


10 **8** (4)

6d

The path of the formation of **9** also cannot be elucidated. However, the dimerization of **7d** to give **9** is excluded as has been pointed out by Bunyan and Cadogan,[3] and our separate experiment confirmed that both the deoxygenation of **6d** to **9** by **1a** and the reaction of **8** with **5d** to form **9** did not occur under similar conditions.

o-Nitrosobiphenyl (**5e**) reacted with **1a** to give o-azoxybiphenyl (**6e**) (34%) and carbazole (**11**) (20%). In the case of the reaction with phosphine or phosphite, only **11** was obtained in high yield.[3]



5e **6e** **11** (5)

Finally, reactions of sulfoxylates and other compounds such as sulfoxides, sulfones, aromatic nitro compounds, or *N*-nitroso compounds were examined. However, deoxygenation

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Table I

Amine *N*-oxide	Registry no.	Solvent	Reaction temp, °C	Time, h	Yield of product, % Amine	Sulfite (2a)
(4a) Pyridine	694-59-7	$CHCl_3$	Room temp	3	96	85
(4b) 2-Picoline	931-19-1	Benzene	Reflux	1	78	75
(4c) 3-Picoline	1003-73-2	CH_2Cl_2	Room temp	2	94	72
(4d) 4-Picoline	1003-67-4	Benzene	Reflux	0.5	70	71
(4e) 4-Nitropyridine	1124-33-0	None	110–120	1	0	18

did not take place even by refluxing in benzene for a long time and the starting materials were recovered.

Experimental Section

IR spectra were measured with a Hitachi EPI-G2 spectrometer. NMR spectra were determined in CCl_4 or $CDCl_3$ solution with a JEOL JNM-PMX-60 spectrometer. Mass spectra were obtained on a Hitachi Double Focusing Mass Spectrometer RMU-7M at 70 eV. Di-*n*-propyl sulfoxylate (**1a**),[7] diethyl sulfoxylate (**1b**),[4] and o-nitrosobiphenyl (**5e**)[8] were prepared by the methods of the literature, respectively. All other reagents were obtained commercially.

Reaction of Dibenzoyl Peroxide (3) with 1a. A solution of 4.5 g (0.03 mol) of **1a** in 20 mL of benzene was added to a stirred solution of 7.3 g (0.03 mol) of **3** in 30 mL of benzene at room temperature during 1 h. The reaction is exothermic and proceeded violently unless controlled by addition of **1a**. The stirring was continued for an additional 1 h. The solvent was removed and the residue was distilled to give 3.8 g (77%) of di-*n*-propyl sulfite (**2a**),[9] bp 65 °C (6 mm). The oily residue was chromatographed on silica gel using ether–hexane (1:2) as eluent to give 6.7 g (99%) of benzoic anhydride, mp 40–42 °C. Di-*n*-propyl sulfite (**2a**) was identified by spectral data, IR (neat) ν(S→O) 1200 cm^{-1}; NMR (CCl_4) δ 3.90 (m, 2 H) 1.71 (m, 2 H) 0.99 (t, 3 H).

Reaction of Amine *N*-Oxides (4) with 1a. A solution of 4.5 g (0.03 mol) of **1a** in 20 mL of $CHCl_3$ was added to a stirred solution of 2.9 g (0.03 mol) of pyridine *N*-oxide (**4a**) in 30 mL of $CHCl_3$ at room temperature during 1 h. The stirring was continued for an additional 2 h. The solvent and pyridine were removed by evaporation and the residue was distilled to give 4.0 g (85%) of **2a**. Amount of pyridine was estimated as its hydrochloride, 3.3 g (96%). Similarly, 2-picoline *N*-oxide (**4b**), 3-picoline *N*-oxide (**4c**), or 4-picoline *N*-oxide (**4d**) was allowed to react with **1a** and 2-picoline (bp 56–58 °C (50 mm)), 3-picoline (bp 62–65 °C (24 mm)), or 4-picoline (bp 65 °C (29 mm)) and **2a** were obtained by fractional distillation. 4-Nitropyridine *N*-oxide (**4e**) (5.6 g 0.04 mol) and **1a** (6 g 0.04 mol) were heated at 110–120 °C for 1 h; the mass turned to dark brown with evolution of nitric oxide. Di-*n*-propyl sulfite (**2a**) (1.2 g) was obtained by distillation of the reaction mixture.

Reaction of Nitrosobenzene (5a), *p*-Nitrosotoluene (5b), or o-Nitrosotoluene (5c) with Sulfoxylate (1). A solution of 1.6 g (0.015 mol) of **5a** and 2.3 g (0.015 mol) of **1a** in 25 mL of benzene was refluxed under nitrogen atmosphere. The green solution turned reddish brown gradually. After 10 h, the solvent was removed and the residue was chromatographed on alumina using hexane–benzene (1:1) as eluent to give 0.9 g (61%) of azoxybenzene (**6a**) as yellow crystals: mp 33–36 °C; IR (neat) ν(N→O) 1475 cm^{-1}. Similarly, **6a** was obtained in 76% yield by the reaction of **1b** and **5a** in CCl_4 solution. *p*-Nitrosotoluene (**5b**) or o-nitrosotoluene (**5c**) was allowed to react with **1a** under similar conditions and 4,4′-dimethylazoxybenzene (**6b**) (48%) [mp 70 °C; IR (KBr) ν(N→O) 1465 cm^{-1}] or 2,2′-dimethylazoxybenzene (**6c**) (56%) [mp 58 °C; IR (KBr) ν(N→O) 1475 cm^{-1}] was obtained by column chromatography on silica gel using hexane–benzene (3:2) as eluent.

Reaction of *p*-Dimethylaminonitrosobenzene (5d) with 1a. A solution of 2.0 g (0.0133 mol) of **5d** and 4.0 g (0.0266 mol) of **1a** in 20 mL of benzene was refluxed for 20 h under nitrogen atmosphere. The solvent was removed and the residue was chromatographed on silica gel using benzene as eluent to give 1.1 g (45%) of *p*-dimethylamino-*N*-sulfinylaniline[10] (**8**) as red crystals: mp 72 °C (lit. 72 °C); IR (nujol) ν(S→O) 1140 cm^{-1}; NMR (CCl_4) δ 7.78 (d, 2 H) 6.52 (d, 2 H) 3.06 (s, 6 H). Further elution with chloroform gave 0.2 g of 4,4′-bis(dimethylamino)azobenzene (**9**) as reddish brown crystals [mp 270–273 °C (lit.[3] 271–273 °C); NMR ($CDCl_3$) δ 7.83 (d, 4 H) 6.78 (d, 4 H) 3.10 (s, 12 H)] and 0.25 g of 4,4′-bis(dimethylamino)azoxybenzene (**6d**) as reddish orange crystals [mp 245–246 °C (lit.[3] 257–259 °C); IR (KBr) ν(N→O) 1455 cm^{-1}; NMR ($CDCl_3$) δ 8.30 (d, 2 H) 8.17 (d, 2 H) 6.77 (d, 2 H) 6.72 (d, 2 H) 3.10 (s, 12 H)].

Reaction of *o*-Nitrosobiphenyl (5e) with 1a. A solution of 1.8 g (0.01 mol) of **5e** and 1.5 g (0.01 mol) of **1a** in 25 mL of toluene was refluxed for 10 h under nitrogen atmosphere. The solvent was removed and the residue was chromatographed on silica gel using benzene–hexane (2:1) as eluent to give 0.33 g (20%) of carbazole as colorless plates [mp 242 °C (lit. 245 °C); IR (KBr) ν(N–H) 3410 cm^{-1}] and 0.60 g (34%) of *o*-azoxybiphenyl (**6e**) as light yellow crystals [mp 157 °C (lit. 157–158 °C); IR (KBr) ν(N→O) 1450 cm^{-1}; mass *m/e* 350 (M^+), 349 ($M^+ - H$), 334 ($M^+ - O$), 333, 184, 168, 167, 166, 153, 152].

Registry No.—**1a,** 3359-70-4; **2a,** 623-98-3; **3,** 94-36-0; **5a,** 586-96-9; **5b,** 623-11-0; **5c,** 611-23-4; **5d,** 138-89-6; **5e,** 21711-71-7; **6a,** 495-48-7; **6b,** 955-98-6; **6c,** 956-31-0; **6d,** 794-95-6; **6e,** 7334-103; **8,** 13066-26-7; **9,** 6257-64-3; 2-picoline, 109-06-8; 3-picoline, 108-99-6; 4-picoline, 108-89-4.

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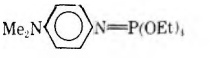
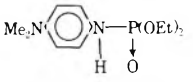
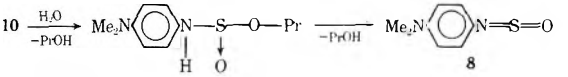


was obtained by the reaction of **5d** and triethyl phosphite and this phosphorimidate was readily hydrolyzed during chromatography to give diethyl *N-p*-dimethylaminophenylphosphoramidate



Presumably, the labile intermediate **10** is likewise hydrolyzed during chromatographic separation to form the aminosulfinate, which decomposes into **8** and *n*-propyl alcohol.



Aminosulfinates, RNHS(O)OR′, are known as very unstable compounds which decompose into *N*-sulfinylamines and alcohols immediately. G. Zinner, *Chem. Ber.*, **91**, 966 (1958).
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Structure of Tirotundin[1]

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Tirotundin, the main sesquiterpene lactone of *Tithonia rotundifolia* (Mill.) Blake, was assigned[2] the gross structure and stereochemistry depicted in formula **1a** (R = H), although formula **2** could not be excluded with certainty. Because of this ambiguity and because the substance exhibited some anti-

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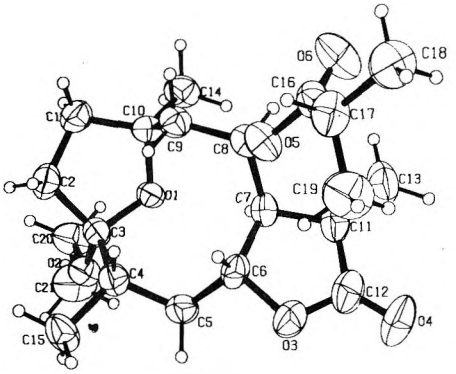


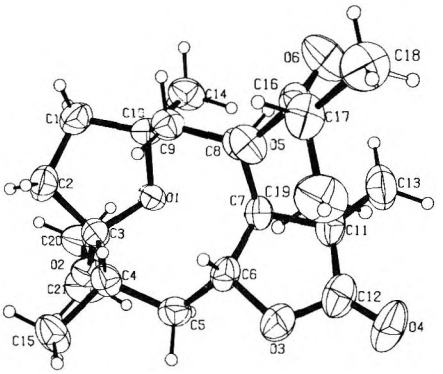
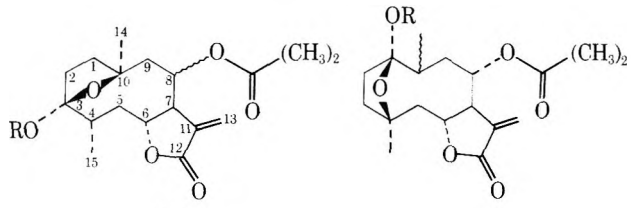


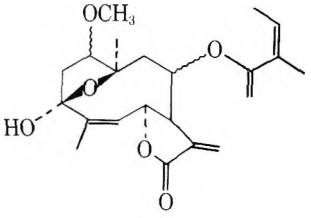
Figure 1. Stereoscopic view of **1b** (R = Et).

tumor activity,[3] single crystals of its ethyl ether (R = Et) were examined by x-ray crystallography. The results led to structure **1b** (R = Et), thus confirming the earlier deduction with exception of the configuration at C-8.

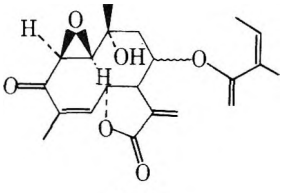


1a, b

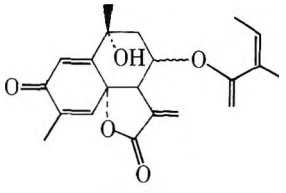
2



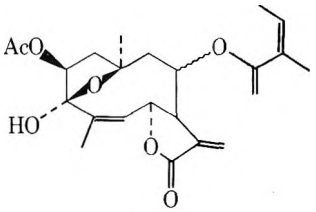
3a, b



4a, b



5a, b



6a, b

a, ester side chain α; b, ester side chain β

Crystal data for **1b** (R = Et) are listed in Table I. Figure 1 is a stereoscopic drawing of the molecule which represents the absolute configuration if H-7 is α in all sesquiterpene lactones of authenticated stereochemistry.

This is in harmony with the observation[2] of a negative Cotton effect associated with the n $\rightarrow$ π^* transition of a trans-fused lactone closed to C-6 of a germacranolide ring system.[4] The lactone torsion angles listed in Table II show that although the carbonyl and α,β-unsaturated methylene groups deviate only slightly from coplanarity, the sign of the C=C—C=O torsion angle (ω_2) indicating the chirality of this chromophore which has been related to the Cotton effect[5] is paired with the sign of the C(α)–C(β)–C(γ)–O torsion angle (ω_3), as has been noted previously for other sesquiterpene lactones.[6]

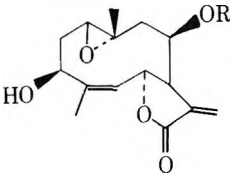
The results of the x-ray analysis require reexamination of the arguments used previously[2] for deducing the stereochemistry of tirotundin at C-8. The earlier conclusion that the side chain was α oriented was based on the similarity of the chemical shifts of H-7 and H-8 in the NMR spectra of tirotundin, on the one hand, and **3a**, related to tifruticin (presumably **4a**) and deoxytifruticin (presumably **5a**),[2] and woodhousin (presumably **6a**)[7] on the other. In turn assignment of α orientation to the ester side chains of tifruticin and woodhousin was based on NMR evidence that hydrolysis of the ester functions attached to C-8 was accomplished by lactone ring reorientation toward C-8[8] and on differences in the values of $J_{7,8}$ and $J_{8,9}$ between derivatives of erioflorin (**7b**)

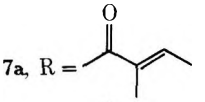
Table I. Crystal Data for 1b (R = Et)

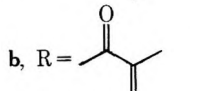
Formula	$C_{21}H_{32}O_6$ monoclinic
Space group	$P2_1$ (Z = 2)
a, Å	10.199 (3)
b, Å	13.262 (5)
c, Å	7.725 (3)
β, deg	95.80 (3)
d_{calcd}, gcm^3	1.215

Table II. Lactone Ring Torsion Angles of 1b (R = Et)

C(6)–O(3)–C(12)–C(11)	ω_1	−4.5°
C(13)–C(11)–C(12)–O(4)	ω_2	−4.1°
C(11)–C(7)–C(6)–O(3)	ω_3	−8.2°
C(5)–C(6)–C(7)–C(8)	ω_4	+107.4°







and woodhousin that were thought to be appropriate models. It is not clear whether the assumed analogy between tirotundin and **3a** and **6a** was unjustified or whether the C-8 stereochemistry of tifruticin, deoxytifruticin, woodhousin, and related compounds also requires revision (to **4b**, **5b**, **6b**, etc.). a decision between the two possibilities must await reisolation of tifruticin and woodhousin.

Experimental Section

Single crystals of ethyl tirotundin were prepared by Dr. R. Murari by recrystallization from ethyl acetate–hexane. Intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu K_α radiation, θ–2θ scans, pulse height discrimination). Of the 1477 inde-

pendent reflections for $\theta < 57$, 1459 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple solution procedure[13] and was refined by full matrix least squares to $R = 0.046$ and $R_w = 0.067$ (heavier atoms anisotropic, hydrogen atoms isotropic and not refined). The final difference map has no peaks greater than ±0.3 eA^{-3}.

Registry No.—**1b**, (R = H), 56377-67-4; **1b** (R = Et), 56377-68-5.

Supplementary Material Available: Tables III, IV, and V listing bond distances, bond angles, and torsion angles of compound **1b** (R = Et) (3 pages). Ordering information is given on any current masthead page.

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(8) Germacranolides containing α orientated lactonizable groups at C-6 and C-8 preferentially lactonize toward C-8.[9] The general applicability of this rule to *cis*-$\Delta^{4,5}$-germacranolides has not been tested but heliangin (**7a**)[10] and erioflorin (**7b**)[11,12] of authenticated stereochemistry (ester side chain β) do not undergo reorientation of the lactone group on hydrolysis with base.
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Benzamidomethyl Group as a Thiol Protecting Group for Cysteine, *N*-Methylcysteine, and Corresponding *N-tert*-Butyloxycarbonyl Derivatives

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New protecting groups for the thiol function of cysteine are of current interest.[1] The acetamidomethyl (Acm) group[2] has been reported for use with cysteine in peptide synthesis. In our laboratory, attempted use of the Acm group for protection of the thiol function in *N*-methyl-L-cysteine[3] gave noncrystalline material that was shown by TLC analysis to be a mixture of products. We therefore investigated use of the related benzamidomethyl (Bam) group and report this group to be a convenient thiol protective group for cysteine and *N*-methylcysteine.

The benzamidomethyl group was conveniently incorporated into L-cysteine and *N*-methyl-L-cysteine by treatment of equimolar ratios of *N*-hydroxymethylbenzamide[4] and the respective amino acid in anhydrous trifluoroacetic acid (F_3AcOH) at room temperature. Upon removal of F_3AcOH under reduced pressure, the S-protected derivatives **1** and **2** were isolated in good yield as the trifluoroacetate salts. By analogy with the procedure for introduction of the S-trityl group,[5] we have found the use of F_3AcOH as solvent and acid catalyst to be effective and convenient.

$$Cl^-H_2^+\text{-Cys-OH} + C_6H_5CONHCH_2OH \rightarrow F_3AcO^-\ H_2^+\text{-Cys(Bam)-OH}$$

1

$$\text{H-MeCys-OH} + C_6H_5CONHCH_2OH \rightarrow F_3AcO^-\ H_2^-\text{-MeCys(Bam)-OH}$$

2

The *S*-benzamidomethyl group was found to be stable to a wide variety of reaction conditions commonly used in peptide synthesis (Table I). Removal of the Bam group was effected by treatment at pH 4 and room temperature with 2 equiv of Hg(II).

Table I. Studies on Stability of Bam Group to Various Deblocking Conditions

Reagents–solvents–temp	Reaction time (h)	Stability of Bam group
1 N NaOH–H_2O–25 °C	5	Stable
1 N HCl–H_2O–25 °C	5	Stable
6 N HCl–H_2O–110 °C	24	Not stable
N_2H_4·H_2O–MeOH–25 °C	24	Stable
Zn–90% AcOH–0 °C	5	Stable
Anhydrous F_3AcOH–25 °C	5	Stable

The *N-tert*-butyloxycarbonyl (Boc) derivatives **3** and **4** were prepared in good yield by treatment of the respective S-protected derivatives **1** and **2** with 2 equiv of *tert*-butylazidoformate[6] in the presence of tetramethylguanidine. The Boc derivative **4** was isolated as the crystalline dicyclohexylammonium salt. Compound **3** was converted into the *N*-hydroxysuccinimido active ester **5** by reaction with *N,N'*-dicyclohexylcarbodiimide and *N*-hydroxysuccinimide.[7]

Boc-Cys(Bam)-OR

3, R = H

5, R = NSu

$$\text{Boc-MeCys(Bam)-}O^-\ H_2N^+(C_6H_{11})_2$$

4

Experimental Section

Melting points are uncorrected. TLC analysis was carried out on silica gel plates (Quanta gram) in the following solvent systems: A, *n*-BuOH–AcOH–H_2O (10:2:3); B, $CHCl_3$–95% EtOH (8:2). Spots were located by ninhydrin spray, iodine, and ultraviolet light. NMR spectra were recorded on a Varian EM360 spectrometer using Me_4Si as an internal standard.

***S*-Benzamidomethyl-L-cysteine Trifluoroacetate (1).** A mixture of L-cysteine hydrochloride (3.61 g, 10.0 mmol) and *N*-hydroxymethylbenzamide[4] (4.53 g, 10.0 mmol) in anhydrous F_3AcOH (30 mL) was stirred at room temperature for 45 min. The solvent was removed in vacuo, the residue was dissolved in absolute ethanol (30 mL), and the solution was evaporated to dryness in vacuo. This process was repeated twice, and the residue obtained was triturated with ether, filtered, washed with ether, and dried under vacuum over NaOH and P_2O_5. The product[8] was recrystallized from 95% ethanol to yield 6.6 g (60%) of **1**: mp 169–171 °C; $[\alpha]^{25}_D$ −33.3° (*c* 1.0, H_2O); R_f 0.32 (A); NMR (Me_2SO-d_6) δ 3.45 (m, 2 H, Cys methylene), 4.24 (m, 1 H, α-H), 4.77 (d, 2 H, Bam methylene), 7.50–8.80 (m, 9 H, aromatic and NH).

Anal.[9] Calcd for $C_{11}H_{14}N_2O_3S$·CF_3COOH: C, 42.39; H, 4.08; N, 7.61. Found: C, 42.43; H, 4.14; N, 7.53.

***S*-Benzamidomethyl-*N*-methyl-L-cysteine Trifluoroacetate (2).** *N*-Methyl-L-cysteine (5.0 g, 37 mmol) and benzamidomethanol (5.6 g, 37 mmol) in anhydrous F_3AcOH (50 mL) was treated as described above for **1**. The crude product[8] (mp 166–168 °C) was recrystallized from 95% ethanol to yield 12.5 g (88%) of **2**: mp 169–170 °C; $[\alpha]^{25}_D$ +34.5° (*c* 1, H_2O); R_f 0.29 (A); NMR (Me_2SO-d_6) δ 2.60 (s, 3 *H*, *N*-methyl), 3.27 (m, 2 H, Cys methylene), 4.27 (m, 1 H, α-H), 4.50

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(m, 2 H, Bam methylene), 7.10–8.30 (m, 9 H, aromatic plus exchangeable protons).

Anal.[9] Calcd for $C_{12}H_{16}N_2O_3S \cdot CF_3COOH$: C, 43.97; H, 4.45; N, 7.32. Found: C, 44.05; H, 4.61; N, 7.52.

***N*-*tert*-Butyloxycarbonyl-*S*-benzamidomethyl-L-cysteine (3).** A mixture of 1 (4.10 g, 11.1 mmol) and tetramethylguanidine (2.39 g, 22.3 mmol) in 30 mL of anhydrous dimethylformamide was stirred in an ice bath. To the cold reaction mixture was added dropwise and simultaneously *tert*-butyloxycarbonyl azide[6] (2.90 g, 22.3 mmol) and tetramethylguanidine (2.39 g, 22.3 mmol). The mixture was stirred at room temperature for 48 h, and the solvent was removed in vacuo. The residue was dissolved in water (60 mL) and extracted with ether (2 × 20 mL), and the aqueous phase was acidified, with cooling, by the addition of solid citric acid. The oil that separated was extracted with ethyl acetate (100 mL), and the organic phase was washed with water and dried over anhydrous $MgSO_4$. Upon removal of solvent, the product was obtained as a viscous oil that crystallized from ether: 3.75 g (95%); mp 141–142 °C; $[\alpha]^{25}_D$ −28.5° (c 1, methanol); R_f 0.8 (A); NMR ($CDCl_3$–Me_2SO-d_6, 5:1) δ 1.46 (s, 9 H, *t*-Bu), 3.16 (m, 2 H, Cys methylene), 4.30–4.80 (m, 3 H, Bam methylene and α-H), 6.40 (m, 1 H, NH), 7.35–8.32 (m, 6 H, aromatic and NH), 8.90 (m, 1 H, carboxyl hydrogen).

Anal. Calcd for $C_{16}H_{22}N_2O_5S$: C, 54.24; H, 6.22; N, 7.70. Found: C, 54.12; H, 6.34; N, 7.56.

***N*-*tert*-Butyloxycarbonyl-*N*-methyl-*S*-benzamidomethyl-L-cysteine Dicyclohexylammonium Salt (4).** Compound 4 was prepared by treatment of a mixture of **2** (12.3 g, 32.2 mmol) and tetramethylguanidine (6.88 g, 64.4 mmol) in 80 mL of dry dimethylformamide with *tert*-butyloxycarbonyl azide (8.36 g, 64.4 mmol) and tetramethylguanidine (6.88 g, 64.4 mmol) as described above for the preparation of **3**. The product 4 was isolated as an oil, which was taken up in cold ether and treated with dicyclohexylamine (5.98 g). The dicyclohexylammonium salt, which crystallized, was collected by filtration, washed with ether (15 mL), and dried to yield 17.2 g (97%) of 4: mp 147–148 °C; $[\alpha]^{25}_D$ −95° (c 1, methanol); R_f 0.77 (A) 0.57 (B); NMR ($CDCl_3$) δ 0.9–2.1 (br m, 31 H, *t*-Bu and cyclohexyl), 2.9 (m, 5 H, *N*-methyl and Cys methylene), 4.3–4.9 (m, 3 H, Bam methylene and α-H), 7.4–8.2 (m, 6 H, aromatic and NH), 8.5–8.9 (br m, 2 H, ammonium NH).

Anal. Calcd for $C_{17}H_{24}N_2O_5S \cdot C_{12}H_{23}N$: C, 63.38; H, 8.56; N, 7.65. Found: C, 63.52; H, 8.66; N, 7.81.

***N*-*tert*-Butyloxycarbonyl-*S*-benzamidomethyl-L-cysteine *N*-Hydroxysuccinimide Ester (5).** A mixture of **3** (1.05 g, 3.0 mmol), *N*-hydroxysuccinimide (0.36 g, 3.0 mmol), and *N*,*N*′-dicyclohexylcarbodiimide (0.63 g, 3.0 mmol) in dry tetrahydrofuran (10 mL) was stirred at 0 °C for 2 h and then allowed to stand overnight in a refrigerator. The dicyclohexylurea was removed by filtration and the solvent removed in vacuo. The residue was taken up in ethyl acetate (30 mL), washed with 10% $NaHCO_3$ and water, and dried over $MgSO_4$. Removal of the solvent in vacuo gave an amorphous solid that was crystallized from 2-propanol to yield 0.97 g (72%) of ester **5**: mp 145–146 °C; $[\alpha]^{25}_D$ −117.5° (c 1, chloroform); R_f 0.86 (A); NMR ($CDCl_3$) δ 1.49 (s, 9 H, *t*-Bu), 2.90 (s, 4 H, succinimido protons), 3.30 (m, 2 H, Cys methylene), 4.83 (m, 3 H, Bam methylene and α-H), 5.78 (m, 1 H, NH), 7.33–8.28 (m, 6 H, aromatic and NH).

Anal. Calcd for $C_{20}H_{25}N_3O_7S$: C, 53.22; H, 5.54; N, 9.31. Found: C, 53.11; H, 5.64; N, 9.41.

Removal of the *S*-Benzamidomethyl Group. Compound 1 (37 mg, 0.1 mmol) was dissolved by warming in 5 mL of methanol–water (1:1). The clear solution was treated at room temperature with mercuric acetate (32 mg, 0.1 mmol) and the mixture was stirred for 1 h. Hydrogen sulfide was passed into the reaction mixture for 10 min and the precipitate was removed by filtration. TLC analysis (solvent A) showed that complete deblocking of 1 had occurred and that the product formed was cysteine as shown by comparison with an authentic sample.

Acknowledgment. Appreciation is expressed to the U.S. Public Health Service (National Cancer Institute, Grant CA 10653) for support of this work.

Registry No.—**1**, 64840-21-7; **2**, 64840-23-9; **3**, 33375-72-3; **4**, 64840-25-1; 4 free acid, 64840-24-0; **5**, 64852-94-4; L-cysteine hydrochloride, 52-89-1; *N*-hydroxymethylbenzamide, 6282-02-6; *N*-methyl-L-cysteine, 4026-48-6; *tert*-butyloxycarbonylazide, 1070-19-5; dicyclohexylamine, 101-83-7; *N*-hydroxysuccinimide, 6066-82-6.

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(8) The crude product was found to be reasonably pure and could be used to prepare the corresponding Boc derivatives without further purification.
(9) The analytical sample was prepared by recrystallization of 0.5 g of crystalline product from a minimum volume of water.

Reaction of Singlet Oxygen with Nitronate Salts, Conversion of Nitro Compounds into Carbonyls

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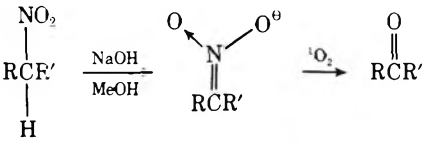
Methods for the conversion of nitro compounds to carbonyls have recently been summarized by McMurray and co-workers.[1] These workers reported that the ozonolysis of nitronate salts produces aldehydes and ketones in good yields. Unfortunately, this method uses ozone, which can react with other functional groups in a substrate, and also involves a relatively long workup procedure. Since singlet oxygen, like ozone, is an electrophilic species, it should also react very rapidly with nitronate results, but may react differently with the rest of the molecule. For example, ozone will react with a monosubstituted olefin,[2] whereas it is inert to singlet oxygen.[3]



Reaction of the nitronate salt with singlet oxygen, generated in situ using dye-sensitized photooxygenation, afforded the corresponding carbonyl compound rapidly and in good yield. Some of our results are given in Table I. When the nitronate salt of 5-nitro-1-hexene was treated with this procedure, 5-keto-1-hexene was obtained, whereas using ozone a ketoozonide would have been produced. To confirm that singlet oxygen was indeed the reactive species involved, 1,4-diazabicyclo[2.2.2]octane (Dabco), a known singlet oxygen quencher, was added.[4] In all cases there was no formation of ketone, indicating Dabco had quenched all the singlet oxygen produced.

In summary, singlet oxygen provides a more facile alternative procedure to the use of ozone for the preparation of carbonyl compounds from nitronate salts. Recently, a very convenient dry method was reported for the conversion of nitro groups into carbonyls.[5]

Experimental Section

General Reaction Procedure. A water-cooled immersion irradiation apparatus similar to the one described by Gollnick and Schenck was used.[6] O_2 was recirculated by a Cole-Parmer Masterflex Tubing Pump. The solutions were irradiated with a Sylvania Q/CL 500-W tungsten–halogen lamp operating at 110 V for 1 h. Oxygen uptake was measured by a gas burette.

The nitro compound (5.0 mM) in 10 mL of methanol with 1 mg of rose bengal added was treated with 1.1 equiv of NaOH (0.55 mL, 10 N) to form the nitronate salt. The solution was then cooled to 0 °C

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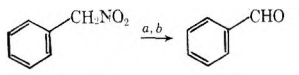
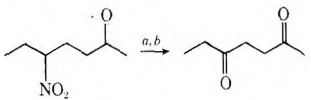
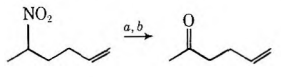
Table I. Oxidation of Nitronate Salts

Reaction	% yield with singlet oxygen	% yield with ozone[1]
 1 → 2	49	68
 3 → 4	60	83
$CH_3(CH_2)_7NO_2$ (5) → $CH_3(CH_2)_6CHO$ (6)	67	65
 7 → 8	66	

[a] OH^-. [b] Rose Bengal, $h\nu$, O_2.

and a stream of oxygen was bubbled through during the irradiation. After warming to room temperature, the solvent was removed in vacuo. The residue was dissolved in chloroform, washed with water, and dried over sodium sulfate. After removal of the solvent, the product was purified by distillation under reduced pressure in a Rinco Kugelrohr. Products were identified by spectral and gas chromatographic comparison with authentic samples. Quenching experiments were done as above adding 4.821 g (42.98 mM) of Dabco to the initial mixture. Gas chromatography of the worked up reaction indicated the absence of any carbonyl products.

Benzaldehyde (2) was prepared from α-nitrotoluene[7] 1 and identified by spectral comparison with an authentic sample: 49% yield.

Heptane-2,5-dione (4) was prepared from 5-nitroheptan-2-one[8] (3) and identified by spectral comparison with an authentic sample: 60% yield.

Octanal (6) was prepared from 1-nitrooctane[9] (5) and identified by spectral comparison with an authentic sample: 67% yield.

5-Nitro-1-hexene (7). Sodium borohydride reduction of 5-hexene-2-one afforded 5-hydroxy-1-hexene: bp 138 °C (lit.[10] bp 140 °C); NMR ($CDCl_3$) δ 3.78 (sextet, 1, J = 6.4 Hz, C-5) and 1.17 (d, 3, J = 6.4 Hz, C-6). Bromination of the alcohol with phosphorus tribromide gave 5-bromo-1-hexene: bp 100 °C (30 mm); NMR ($CDCl_3$) δ 4.14 (sextet, 1, J = 6.5 Hz, C-5), 1.68 (d, 3, C-6). Nitration of the bromohexene with sodium nitrite in dimethyl sulfoxide[9] afforded 5-nitro-1-hexene (7): bp 105 °C (30 mm); IR (film) 3020, 2925, 2850 (CH), 1630 (C=C), 1530, (NO_2), 1340, 990 ($CH=CH_2$), 915 ($C=CH_2$), 857 cm^{-1}; NMR ($CDCl_3$) δ 6.0–5.55 (m, 1, C-2), 5.2–4.9 (m, 2, C-1), 4.58 (br sextet, 1, J = 6.5 Hz, C-5), 2.3–1.6 (m, 4, C-3,4), 1.51 (d, 3, J = 6.5 Hz, C-6). Anal. Calcd for $C_6H_{11}NO_2$: C, 55.79; H, 8.58. Found: C, 55.72; H, 8.52.

5-Hexen-2-one (8) was prepared from 5-nitro-1-hexene (7) and identified by spectral comparison with an authentic sample: 66% yield.

Acknowledgment. This investigation was supported by Grant No. CA-15348 awarded by the National Cancer Institute, DHEW, and in part by the National Science Foundation through Grant No. CHE 76-05757.

Registry No.—5-Hydroxy-1-hexene, 626-94-8; 5-bromo-1-hexene, 4558-27-4.

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Alkyl Inductive Effects: New-Model Systems for Defining Intrinsic Polar Substituent Effects by Fluorine-19 and Carbon-13 Nuclear Magnetic Resonance

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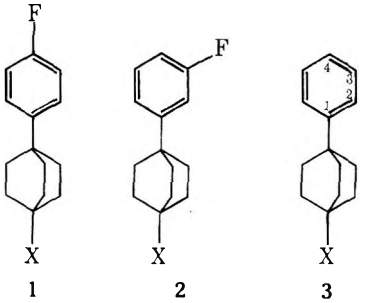
The inductive effects of alkyl substituents continue to attract interest. According to Taft and Levitt,[1] alkyl induction is significant and, together with polarizability effects, is quantitatively reflected by new σ_1 values (Me, −0.046; Et, −0.057; *i*-Pr, −0.065; *t*-Bu, −0.074) derived from a statistical analysis of gas-phase ionization potential data and polarizability "models".[2] The new scale parallels the inductive order of electron release (*t*-Bu > i-Pr > Et > Me) previously quantified (σ^*) from the rates of acid- and base-catalyzed hydrolyses of esters, such as RCO_2Et, by utilizing the Ingold–Taft relationship.[3] On the other hand, Charton[4] has recently concluded from a successful correlative analysis of rate data for base-catalyzed hydrolyses of such esters with steric parameters[5] that the σ^* scale is invalid and that it arises from an incomplete cancellation of steric effects in the Ingold–Taft relationship. The corollary of this conclusion is that the electrical effects of alkyl groups are unimportant in these reactions. A similar viewpoint has been expressed previously by Ritchie and Sager[6] on the basis that in many systems Taft correlations are as good when hydrogen and the aforementioned alkyl groups (and others) are all assigned $\sigma^* = 0$. However, this analysis has been, in the main, unaccepted by authors of modern physical organic texts[7] except for Hine[8] and Ritchie.[9]

Although Charton's analysis has been strongly criticized,[10,11] Bordwell and Fried[12] have presented equilibrium acidity data of carboxamides, $RCONH_2$, in dimethyl sulfoxide solution which offer strong experimental support for the beliefs expressed by Ritchie and Charton.

Recently, in connection with other studies,[13] we have had occasion to examine the effect of substituents on the ^{19}F chemical shifts of model systems 1 and 2, as well as the ^{13}C chemical shifts of C-4 in system 3, which indicate that these



1 2 3

phenylbicyclo[2.2.2]octyl skeletal frameworks are eminently suited for resolving whether or not alkyl inductive effects are significant, as well as testing the validity of the new σ_I values. In this regard, there are several beneficial aspects of these models. (i) They are stereochemically well-defined model systems in which the polar field effect emanating from substituent–substrate polarity can be assessed quantitatively in total isolation of other electronic mechanisms. Obviously, hyperconjugation involving the alkyl substituents is completely excluded by the rigid saturated framework intervening between the substituent and the phenyl ring, while polarizability effects should be negligible on the basis of distance dependency (r^{-6}).[14] These latter two phenomena are always

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Table I. Substituent Chemical Shifts (SCS) [a] for Systems 1, 2, and 3

Substituent (X)	^{19}F SCS Cyclohexane 1	Cyclohexane 2	DMF 1	DMF 2	^{13}C SCS,[b] Cyclohexane 3
Me	0.09	0.00	0.07	0.00	0.00
Et	0.07	0.00	0.07	0.00	0.00
i-Pr	0.05		0.05		0.03
t-Bu	0.03		0.02		0.03

[a] Chemical shifts (ppm) referenced to parent compound (X = H); a positive sign denotes deshielding. [b] X = H (c-C_6D_{12}, relative to Me_4Si): 125.73 (C-4).[28]

concomitant effects to be dubiously disentangled from inductive perturbations when assessing alkyl substituent effects in other model systems. (ii) Steric and solvation effects, problems associated with chemical reactivity studies, are completely excluded. (iii) ^{19}F and ^{13}C chemical shifts can be readily measured in a nonpolar solvent such as cyclohexane; hence, the substituent chemical shifts (SCS) can be considered *intrinsic* measures of substituent induction applicable to the gas phase. (iv) DSP correlations[15] of good precision are obtained between the SCS of **1** (eq 1a and 1b), **2** (eq 2a and 2b), and **3** (eq 3) and available substituent parameters[15,16] for a basis set of substituents, which indicate that the sensitivity of these systems to polar effects (ρ_I values) is more than adequate to assess the question of alkyl induction.

$$SCS = 2.49\sigma_I + 0.18\sigma_R^0 \text{ (cyclohexane; } f = 0.13; \text{ SD} = 0.13, n = 14) \quad (1a)$$

$$SCS = 1.50\sigma_I + 0.02\sigma_R^0 \text{ (DMF; } f = 0.09; \text{ SD} = 0.05; n = 13) \quad (1b)$$

$$SCS = 1.49\sigma_I + 0.14\sigma_R^0 \text{ (cyclohexane; } f = 0.07; \text{ SD} = 0.05; n = 8) \quad (2a)$$

$$SCS = 0.63\sigma_I + 0.11\sigma_R^0 \text{ (DMF; } f = 0.11; \text{ SD} = 0.03; n = 7) \quad (2b)$$

$$SCS = 1.34\sigma_I + 0.23\sigma_R^0 \text{ (cyclohexane; } f = 0.07; \text{ SD} = 0.04; n = 8) \quad (3)$$

Accordingly, we have synthesized a number of appropriate alkyl derivatives of **1**, **2**, and **3**[17] and measured their NMR spectra (^{19}F and ^{13}C). A scrutiny of the data listed in Table I leads to two important conclusions. First, it can be seen that the expected SCS,[18] based on the polar sensitivity parameters (ρ_I) for **1**, **2**, and **3** and the new σ_I scale, are not realized in these model systems. Surprisingly, for **1**, the most sensitive system to polar effects, all the alkyl ^{19}F SCS are *positive*, implying, if taken at face value, *electron withdrawal* in the order Me > Et > *i*-Pr > *t*-Bu! This result is dramatically exemplified by the spectrum (Figure 1) of a mixture in cyclohexane of all the alkyl derivatives of **1** as well as the parent compound (X = H). The compounds were present in the ratio 1:1:1.5:2:1 (total concentration did not exceed 10%, w/w). However, since polar effects in system **1** are greatly attenuated by changing the solvent from cyclohexane to DMF (see eq 1a and 1b), the observed constancy of the shifts in **1** (cyclohexane and DMF) indicates unambiguously that their origin is definitely *not* polar in nature and, moreover, that polar effects for all the alkyl groups attached to an sp^3-hybridized carbon must be *zero*.[19] This conclusion is strongly reinforced by the observed SCS for systems **2** and **3** (Table I). Note that, within experimental error, they are all *zero*. The inescapable conclusion, therefore, is that the new σ_I scale (and the old σ^* scale) is invalid as a measure of intrinsic inductive effects of alkyl groups, as suggested by Ritchie,[9] Charton,[4] and Bordwell.[12] Undoubtedly, the new σ_I scale for alkyl groups embodies predominantly the effects of hyperconjugation and polarizability, both having fairly similar structural dependencies with regards to branching.[20] It is important to note that Houk and co-workers[20] have recently presented correlations of data from various model systems which reveal the importance of alkyl hyperconjugation on the ionization potentials of species employed for deriving the new σ_I scale.[2] There may also be a small polar contribution to the σ_I values when the alkyl groups are attached to an sp^2-hybridized carbon center.[1,19]

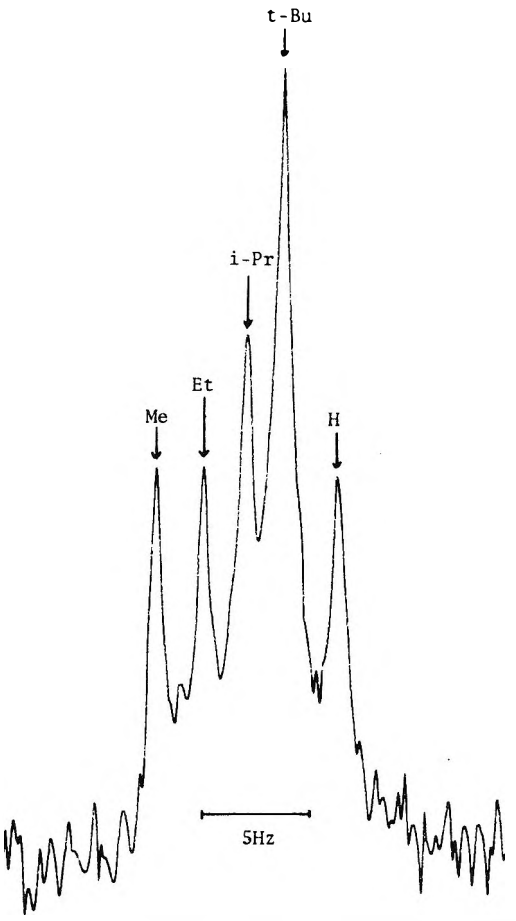

Figure 1. The 84.66-MHz ^{19}F NMR proton-decoupled spectrum of a mixture of **1** (X = H, Me, Et, *i*-Pr, and *t*-Bu) in cyclohexane.

Secondly, we believe that the "anomalous" downfield shifts induced by alkyl substitution in system **1**, but not observed in **2** and **3**, reflect small but significant changes in the hyperconjugative interaction between the phenyl and bicyclo[2.2.2]octyl moieties due to substitution at the bridgehead. Several considerations lead to this conclusion. (i) In **1**, the para orientation of the fluorophenyl tag is extremely sensitive to mesomeric effects which are relatively *constant* with respect to solvent changes (ρ_R = 31.0 and 31.85 for cyclohexane and DMF, respectively).[21] Hence, even a change of 0.005 in the σ_R^0 value[22] of the bicyclo[2.2.2]octyl group on bridgehead substitution would produce a chemical-shift perturbation of ~0.15 ppm in **1**. (ii) In **2**, the meta orientation of the fluorophenyl tag ($\rho_R \approx 0$) is virtually insensitive to mesomeric effects.[23] (iii) In **3**, although the carbon monitor (^{13}C SCS of C-4) is para orientated and, therefore, quite sensitive to resonance effects (ρ_R = 20.7 for cyclohexane),[21] sensitivity considerations (^{13}C SCS are ca. one-half the magnitude of ^{19}F SCS for a given electronic perturbation)[24] suggest that any mesomeric perturbation here should be approximately one-third of that observed in **1**. Hence, "anomalous" shifts similar to those observed in **1** are not detected in **3**, since their magnitude are

within the limits of experimental error for measuring the ^{13}C chemical shifts (see Experimental Section).

The only possible corollary which follows from this conclusion is that the angular relationship of the C–C bonds with respect to the π electron system at the point of attachment of the bicyclo[2.2.2]octyl moiety, an important factor determining the magnitude of σ–π interactions,[25] can be perturbed by substituent-induced structural changes of the saturated skeletal framework. The fact that this phenomenon is observed in a bicyclo[2.2.2]octyl framework made considerably rigid by phenyl group "anchoring", together with other noted apparent manifestations of substituent-induced structural distortions of caged systems,[26] suggests that strong reservations must be held concerning the use of fairly flexible model systems for precisely defining *weak* intrinsic polar effects. In particular, this applies to the quinuclidine system which has been heralded as a source of such information.[27] Here the probe is an integral part of the skeletal framework and, thus, is probably responsive to structural changes. Interestingly, although the ionization of 4-substituted quinuclidinium perchlorates indicates that the effects of alkyl substituents adhere to the σ^* scale,[10,27a] it should be noted that, according to this model system, Me and Et are electron withdrawing while *i*-Pr and *t*-Bu are electron donating! The disclosures in this paper suggest that these results are anomalous and, moreover, are probably a consequence of changes in the ionization potential of the nitrogen lone pair electrons due to hybridization adjustments effected by substituent-induced structural changes. Solvation factors may also be an important contributing factor.

Experimental Section

Compounds. 1-Methyl-4-*p*-fluorophenylbicyclo[2.2.2]octane (1, X = CH_3). A solution of 1 (X = Cl; 1.0g; 0.0042 mol)[28] and trimethylaluminum[29] (0.60 g; 0.0084 mol) in 1,2-dichloroethane[30] (5 mL) was stirred under a nitrogen atmosphere for 24 h at 50 °C. The reaction mixture was then cooled to −70 °C before methanol (10 mL) was added carefully to destroy excess trimethylaluminum. The mixture was then allowed to come to room temperature and quenched with dilute sulfuric acid before workup in the usual manner. Sublimation afforded 1 (X = CH_3; 0.8 g; 87%): mp 43.5–47 °C; ^1H NMR ($CDCl_3$) δ 0.84 (3 H, s, aliphatic), 1.18–2.00 (12 H, m, aliphatic), 6.78–7.43 (4 H, m, aromatic).

Anal. Calcd for $C_{15}H_{19}F$: C, 82.5; H, 8.8. Found: C, 82.8; H, 8.9.

1-Ethyl-4-*p*-fluorophenylbicyclo[2.2.2]octane (1, X = C_2H_5). 1 (X = Cl; 1.0 g; 0.0042 mol)[28] was treated with excess triethylaluminum under the same conditions described above for alkylation with trimethylaluminum. Similar workup procedures afforded a white solid (90%) after sublimation. A quantitative analysis by a combination of GLC and mass spectral determinations indicated that the product was a mixture of 1 (X = C_2H_5; *m/e* 232) and 1 (X = H; *m/e* 204) in the ratio of 7:3, respectively. Since the latter compound is the appropriate parent compound employed as an internal reference in the measurement of ^{19}F SCS, no attempt was made to purify the compound.

1-Isopropyl-4-*p*-fluorophenylbicyclo[2.2.2]octane [1, X = $CH(CH_3)_2$]. A solution of 1 (X = $COCH_3$; 3 g; 0.012 mol)[28] in ether (25 mL) was added dropwise to an ether solution of methyllithium (2 M; 0.013 mol) at −70 °C. The reaction mixture was allowed to come to room temperature and stirred for 1 h before workup in the usual manner. The crude alcohol [1, X = $C(CH_3)_2OH$; 3.0 g; 94%] was treated with hydrogen chloride in the manner described by Brown and Rei[31] to afford 1 [X = $C(CH_3)_2Cl$; 3.2 g; 81%]. A mixture of the crude chloride [1, X = $C(CH_3)_2Cl$; 0.8 g; 0.0029 mol] and tri-*n*-butyltin hydride[32] (1.2 g; 0.0041 mol) was irradiated with a Hanovia 500-W UV lamp. After 1 h, the suspension changed into a clear homogeneous liquid. The reaction mixture was dissolved in hexane (5 mL) and then treated with bromine until the solution was reddish-brown in color. The mixture was then passed through a column of alumina to remove organotin salts. The hexane was removed under reduced pressure to yield a residue which was recrystallized from aqueous ethanol to afford fine white needles of 1 [X = $CH(CH_3)_2$; 0.53 g; 75%]: mp 53.5–55 °C; ^1H NMR ($CDCl_3$) δ 0.82 (6 H, d, aliphatic, J_{HH} = 6 Hz), 1.04–1.99 (13 H, m, aliphatic), 6.77–7.41 (4 H, m, aromatic).

Anal. Calcd for $C_{17}H_{23}F$: C, 82.9; H, 9.4. Found: C, 82.9; 9.5.

1-*tert*-Butyl-4-*p*-fluorophenylbicyclo[2.2.2]octane [1, X = $C(CH_3)_3$]. A solution of crude 1 [X = $C(CH_3)_2Cl$; 1.0 g; 0.0036 mol] in methylene chloride (10 mL) at −70 °C was treated with an excess of trimethylaluminum according to the procedure described by Kennedy and co-workers.[29] After standard workup, sublimation of the residue and then recrystallization from methanol afforded white needles of 1 [X = $C(CH_3)_3$; 0.7 g; 76%]: mp 103.5–106.5 °C; ^1H NMR ($CDCl_3$) δ 0.83 (9 H, s, aliphatic), 1.34–1.99 (12 H, m, aliphatic), 6.78–7.47 (4 H, m, aromatic).

Anal. Calcd for $C_{18}H_{25}F$: C, 83.0; H, 9.7. Found: C, 82.7; H, 9.7.

1-Methyl-4-*m*-fluorophenylbicyclo[2.2.2]octane (2, X = CH_3). Prepared from 2 (X = Cl)[28] by the same procedure described above for 1 (X = CH_3). Distillation afforded a colorless oil: bp 120 °C (1 mm); $n^{22}D$ 1.5185; ^1H NMR ($CDCl_3$) δ 0.85 (3 H, s, aliphatic), 1.20–2.05 (12 H, m, aliphatic), 6.65–7.35 (4 H, m, aromatic).

Anal. Calcd for $C_{15}H_{19}F$: C, 82.5; H, 8.8. Found: C, 82.7; H, 8.8.

1-Ethyl-4-*m*-fluorophenylbicyclo[2.2.2]octane (2, X = C_2H_5). Prepared from 2 (X = Cl)[28] by the same procedure described above for 1 (X = C_2H_5). The mixture of 2 (X = C_2H_5 and H), shown to be in the ratio of 7:3, respectively, by a combination of GLC and mass spectrometry, was not separated for the reasons cited above for 1 (X = C_2H_5).

1-Methyl-4-phenylbicyclo[2.2.2]octane (3, X = CH_3). Prepared from 3 (X = Cl)[28] as described above for 1 (X = CH_3). The compound was sublimed and recrystallized from methanol to afford white needles: mp 47.5–49.5 °C (lit.[33] 50–52 °C); ^1H NMR ($CDCl_3$) δ 0.83 (3 H, s, aliphatic), 1.29–2.02 (12 H, m, aliphatic), 7.07–7.42 (5 H, m, aromatic).

Anal. Calcd for $C_{15}H_{20}$: C, 89.9; H, 10.1. Found: C, 90.0; H, 10.2.

1-Ethyl-4-phenylbicyclo[2.2.2]octane (3, X = C_2H_5). Prepared from 3 (X = $COCH_3$)[28] by the Wolf–Kishner[34] reduction procedure in 88% yield. The compound was recrystallized from aqueous methanol to afford white needles: mp 33.5–34 °C (lit.[33] 36–38 °C); ^1H NMR ($CDCl_3$) δ 0.59–2.06 (17 H, m, aliphatic), 7.06–7.43 (5 H, m, aromatic).

1-Isopropyl-4-phenylbicyclo[2.2.2]octane [3, X = $CH(CH_3)_2$]. 3 (X = $COCH_3$; 4.5 g; 0.02 mol)[28] was converted to the tertiary alcohol 3 [X = $C(CH_3)_2OH$; 3.9 g; 81%] and then the chloride 3 [X = $C(CH_3)_2Cl$; 86%] by the same procedures described above for the corresponding derivatives of 1. The crude chloride was treated with lithium/*tert*-butyl alcohol[34] in tetrahydrofuran and then workedup in the usual manner. Sublimation of the product afforded 3 (X = $CH(CH_3)_2$; 78%): mp 63–65 °C (lit.[33] mp 60–62 °C); ^1H NMR ($CDCl_3$) δ 0.82 (6 H, d, aliphatic; J_{HH} = 6 Hz) 1.04–2.02 (13 H, m, aliphatic), 7.02–7.42 (5 H, m, aromatic).

1-*tert*-Butyl-4-phenylbicyclo[2.2.2]octane [3, X = $C(CH_3)_3$]. Prepared from crude 3 [X = $C(CH_3)_2Cl$] in the same manner outlined above for 1 [X = $C(CH_3)_3$]. The product was sublimed and recrystallized from methanol to afford white needles of 3 [X = $C(CH_3)_3$; 88%]: mp 108–111.5 °C; ^1H NMR ($CDCl_3$) δ 0.82 (9 H, s, aliphatic), 1.34–1.99 (12 H, m, aliphatic), 7.06–7.42 (5 H, m, aromatic).

Anal. Calcd for $C_{18}H_{26}$: C, 89.2; H, 10.8. Found: C, 89.2; H, 10.6.

Spectra. The ^{19}F and ^{13}C NMR spectra were obtained at 84.66 and 67.89 MHz, respectively, on Bruker spectrometers. The proton broad-band decoupled ^{19}F NMR spectra (spectral width of 2.5 Hz/cm) were obtained for cyclohexane and DMF solutions containing 5% (w/w) of 1 or 2 and 2% (w/w) of the appropriate parent compound (X = H).[28] The ^{19}F SCS can be considered accurate to better than 0.01 ppm. The samples for proton-decoupled ^{13}C NMR spectra were prepared in deuteriocyclohexane (5 mol %) with $(CH_3)_4Si$ as an internal standard. A sweep of 15 000 Hz was used, and 16K data points were collected and transformed to 8K real data points. The ^{13}C chemical shifts are considered to be accurate to ±0.03 ppm.

^1H NMR spectra were measured with a Varian A-60 spectrometer. Gas chromatographic analysis was performed on a Varian 1740 gas chromatograph using a 10-ft column of 5% SE-30 on 100/120 Chromosorb W. Mass spectra were recorded on an AEI MS30 spectrometer.

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Registry No.—1 (X = CH_3), 64872-36-2; 1 (X = C_2H_5), 64872-37-3; 1 [X = $CH(CH_3)_2$], 64872-38-4; 1 [X = $C(CH_3)_3$], 64872-39-5; 1 (X = Cl), 61541-33-1; 1 (X = $COCH_3$), 64872-40-8; 1 [X = $C(CH_3)_2OH$],

64872-41-9; **1** [X = $C(CH_3)_2Cl$], 64872-42-0; **2** (X = CH_3), 64872-43-1; **2** (X = C_2H_5), 64872-44-2; **2** (X = Cl), 64872-45-3; **3** (X = CH_3), 23062-66-0; **3** (X = C_2H_5), 23062-67-1; **3** [X = $CH(CH_3)_2$], 23102-73-0; **3** [X = $C(CH_3)_3$], 64872-46-4; **3** (X = Cl), 33732-68-2; **3** (X = $COCH_3$), 64872-47-5; **3** [X = $C(CH_3)_2OH$], 64872-48-6; **3** [X = $C(CH_3)_2Cl$], 64872-49-7; trimethylaluminum, 75-24-1; triethylaluminum, 97-93-8; tributyltin hydride, 688-73-3.

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Regiospecificity and Conformational Specificity in Oxime Alkylation of a Geometrical Enantiomeric Isomer[1a]

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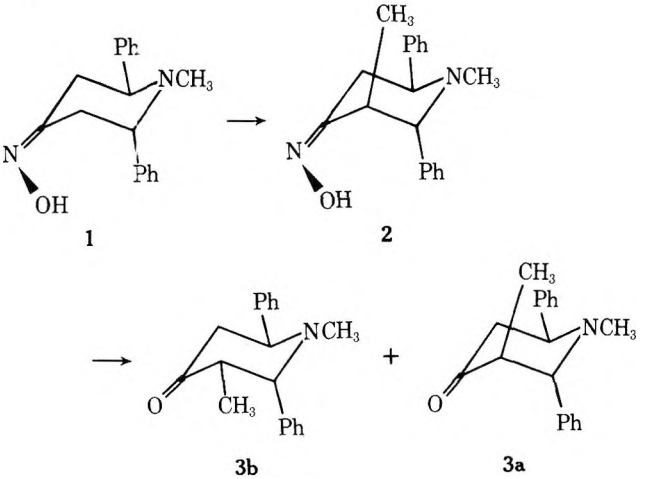
The reactions of electrophiles with the anions of oximes,[1] oxime ethers,[2] dialkylhydrazones,[3] and nitrosamines[1a,4] have been shown to occur with bond formation on the cisoid carbon and perpendicular to the plane of the functional group. This suggests that a cisoid arrangement of four overlapping p orbitals having six electrons produces more stable molecular orbitals than the transoid arrangement. These conclusions are based on structural assignments of the product of electrophilic reactions with the anion, and, although undoubtedly correct, do not provide absolute evidence for the stereochemistry of the reaction pathway. Recently, the dimethylhydrazone anion was shown to be formed by initial removal of the transoid proton with subsequent rearrangement of the stereochemistry to the cisoid anion before alkylation. This observation requires some reevaluation of the stereochemical specificity of the reactions of oximes. A process involving rotation about the carbon–nitrogen bond or inversion at nitrogen prior to or during alkylation could be proposed similar to that of the dimethylhydrazones.[5] To answer this question about the mechanistic sequence of the anion formation and electrophilic reaction, we report the results obtained on anion formation and methylation of the single geometrical enantiomeric isomer,[6] (*Z*)-(−)-1-methyl-2,6-diphenyl-4-piperidone oxime (**1**).[7]



A sample of **1** ($[\alpha]^{25}_D$ +26.34° (*c* 0.331 g/100 mL); EtOH 95%) was shown to be 87% optically pure by ^1H NMR analysis of the NCH_3 in the presence of the chiral shift reagent Eu(tfc)$_3$.[10] The dianion of **1** was prepared with *n*-butyllithium and alkylated with methyl iodide to give 88% of (*Z*)-(2*R*,3*R*,6*S*)-1,3-dimethyl-2,6-diphenyl-4-piperidone oxime (**2**) ($[\alpha]^{25}_D$ −30.76° (c 0.331 g/100 mL); EtOH 95%). The optical purity of **2** was shown to be 86% based on the integration of the NMe signals or 80% based on the CMe signals. Since the singlet of the NCH_3 probably gave a more accurate analysis,

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the alkylation must have occurred with little or no loss of optical purity.

That the reaction of anion formation and alkylation occurred at the syn carbon was demonstrated by determining the absolute configuration of the (−)-1,3-dimethyl-2,6-diphenyl-4-piperidone (**3**) formed by hydrolysis of **2**. Reaction of **2** with pyridinium chlorochromate[11] gave a 56% yield of 1:1 mixture of the two epimers of **3a** and **3b**. This mixture gave a negative Cotton effect at 296 nm which by the ketone sector rule[12] confirmed the absolute configuration to be (−)-(2*R*,3*R*,3*S*,6*S*)-1,3-dimethyl-2,6-diphenyl-4-piperidone (**3a** and **3b**). The optical purity of the ketones was estimated to be 75% by ^{1}H NMR analysis using Eu(Tfc)$_3$.[10] The loss in chirality on hydrolysis of the oxime probably reflects the error in the determination of optical purity of the ketones (**3a** and **3b**).

These results clearly show the regiospecificity of the alkylation of the oximino dianion to be syn to the oximino oxygen and conformationally specific giving an axially substituted oxime. This series of reactions also provides a unique approach to stereochemical control of synthesis of substituted ketones via a chiral oxime.

Experimental Section

Stereospecific Alkylation of (*Z*)-2,6-Diphenyl-1-methyl-4-piperidone Oxime (1). A 0.5 M solution of 1.658 g (5.92 mmol) of (*Z*)-(+)-2,6-diphenyl-1-methyl-4-piperidone oxime, $[\alpha]_D$ +26.34°,[6] in anhydrous tetrahydrofuran was cooled to −80 °C under a stream of dry nitrogen. To the solution was added rapidly 5.918 mL (13.02 mmol) of 2.2 M *n*-butyllithium in hexane. The resulting solution was stirred under nitrogen at −10 °C for 45 min. The solution was cooled again to −80 °C, followed by the rapid addition of 0.379 mL (6.1 mmol) of iodomethane, and stirred between 0 and 5 °C for 2 h. The reaction mixture was hydrolyzed with 20 mL of water, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were dried over sodium sulfate and filtered through magnesium sulfate. Evaporation of the solvent furnished 1.8 g of **1** as a yellow solid. The product was recrystallized from aqueous ethanol to give 1.5 g (88%) of (*Z*)-(−)-(2*R*,3*R*,6*S*)-1,3-dimethyl-2,6-diphenyl-4-piperidone oxime (**2**): mp 187.9 °C; IR ($CHCl_3$) 3750, 3300, 1650, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (d, 3 H), 1.85 (s, 3 H), 2.30 (q, 1 H), 2.56 (t, 1 H), 3.5 (br, 1 H), 3.1–3.3 (m, 2 H); $[\alpha]^{25}_D$ −30.76° (*c* 0.331 g/100 mL, 95% EtOH). Only the product containing the axially oriented 3-methyl was observed.

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.68; H, 7.82; N, 9.55.

(−)-(2*R*,3*R*,3*S*,6*S*)-1,3-Dimethyl-2,6-diphenyl-4-piperidone (3a and 3b). To a suspension of 582 mg (2.7 mmol) of pyridinium chlorochromate in 6 mL of methylene chloride was added finely powdered sodium acetate and a solution of **2** in 15 mL of methylene chloride. The mixture started to turn black within a few seconds, but stirring was continued at room temperature for 35 h. The mixture was diluted with 100 mL of ether and filtered through Florisil. Evaporation of the solvent gave 200 mg of an oily residue. The crude product was chromatographed through silica gel to give 168 mg (56%) of 1:1 **3a** and **3b** as a yellow oil which crystallized: mp 131–132 °C; IR (neat) 1710^{-1}; NMR ($CDCl_3$) δ 0.74 (d, axial C-Me), 1.08 (d, equatorial C-Me), 1.75 (s) and 1.85 (s) (3 H, *N*-methyl), 2.3–3.6 (m, 5 H, Ar), 7.4 (m, 10 H); $[\alpha]^{25}_D$ −34.8° (*c* 0.775 g/100 mL; 95% ethanol), CD [θ] −853° cm^2/g at 296 nm (c 0.00755 g/cm^3 in 95% EtOH).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 82.07; H, 7.66; N, 5.00.

The picrate was prepared in ethanol to give a yellow solid, mp 170–171 °C.

Anal. Calcd for $C_{25}H_{24}N_4O_8$: C, 58.99; H, 4.82; N, 11.00. Found: C, 58.25; H, 4.72; N, 11.01.

Determination of the Optical Purity of 1, 2, and 3. To 51 mL of a 0.5 M solution (0.17 mmol) of the amine in deuteriochloroform was added 0.05 mL (0.005 mmol) of tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III), Eu(tfc)$_3$, as a 0.1 M solution of deuteriochloroform. The NMR spectra of these solutions exhibited an NCH_3 singlet for the one isomer at δ 2.19 and a singlet at δ 2.00 for the other isomer. The intensities of the peaks showed a composition of 87 and 13% for **1** and 86 and 14% for **2**. The 3-methyl group for the (−)-isomer of **2** appeared as a doublet at δ 1.65 and a doublet at δ 1.85 for the (+)-isomer at a ratio of 80:20% (−:+). The original solution of oxime (**2**), now with 0.2 mL (0.002 mmol) of Eu(tfc)$_3$ in $CDCl_3$ (0.1 M), gave a broad singlet at δ 2.7 for the 3-methyl group of the (−)-isomer and a similar absorption at δ 3.1 for the (+)-isomer. A ratio of 4:1 (−:+) was calculated. The two *N*-methyl groups had collapsed into one broad singlet.

The NMR of the mixture of **3a** and **3b** showed no separation of the signal for the N methyl and the C methyl of **3b**. The axial methyl groups of the isomers of **3a** separated into two collapsed doublets at about δ 0.8. The optical purity was estimated from this ratio to be about 75%. This value is subject to considerable error due to problems in integration. Since **3b** was formed from **3a**, the optical purity of **3b** must be the same as **3a**.

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Registry No.—**1**, 64912-36-3; (−)-**2**, 64912-37-4; (+)-**2**, 64912-38-5; **3a**, 64912-39-6; **3b**, 64912-40-9; **3** picrate, 57162-51-3.

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Reactions of Dichlorobenzenes with Solvated Electrons in Liquid Ammonia[1a]

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Halobenzenes and other monosubstituted benzenes react with solvated electrons from alkali metals in liquid ammonia to give a phenyl radical and the anion of the leaving group.[2] Phenyl radicals can react with another electron and be further reduced to phenyl anions, which upon abstracting protons from ammonia gives, ultimately, benzene.[3]

Dichlorobenzenes were expected to react with solvated electrons step by step as halobenzenes do, and that would imply the formation of *o*-, *m*-, and *p*-chlorophenyl anions at some stage of the reaction. The *o*-chlorophenyl anion generated by other means in liquid ammonia has been shown to eliminate the chloride ion leading to benzyne, but no similar elimination of the chloride ion from the *m*- or *p*-chlorophenyl

Table I. Reaction of Halobenzenes with Alkali Metals in Liquid Ammonia

Expt no.	Halobenzene	Concn, M	Metal	Concn, M[a]	Benzene	Aniline yield, %[b]	Solid products
1	C_6H_5Cl[p]	0.11	K	0.24	79	11	
2	C_6H_5Cl[p]	0.11	Na	0.26	80	12	
3	C_6H_5Cl[p]	0.16	Li	0.43	86	2	
4[c]	C_6H_5Cl[p]	0.070	Na	0.21	96		
5[d]	o-$C_6H_4Cl_2$[q]	0.053	K	0.24	70	11	
6[d]	o-$C_6H_4Cl_2$[q]	0.080	Na	0.39	54	19	
7[d]	o-$C_6H_4Cl_2$[q]	0.076	Li	0.38	86	7	
8[d,e]	o-$C_6H_4Cl_2$[q]	0.040	Na	0.23	88	1	
9[f]	o-$C_6H_4Cl_2$[q]	0.20	Li	0.14	21[g]	1	
			Li	0.36	69[h]	2	
			Li	0.55	72[i]	5	
			Li	0.70	80[j]	6	
10	m-$C_6H_4Cl_2$[r]	0.070	K	0.11	23	27	32
11	m-$C_6H_4Cl_2$[r]	0.053	Na	0.22	22	18	44
12	m-$C_6H_4Cl_2$[r]	0.070	Li	0.36	27		53
13[d]	p-$C_6H_4Cl_2$[s]	0.019	K	0.11	25	10	54
14[d]	p-$C_6H_4Cl_2$[s]	0.056	Na	0.26	27	4[k]	51
15[d]	p-$C_6H_4Cl_2$[s]	0.059	Li	0.36	37		52
16[l]	p-$C_6H_4Cl_2$[s]	*0.041*	Na	*0.19*	*80*		5
17[m]	p-$C_6H_4Cl_2$[s]	0.028	Na	0.09	74		3
18[n]	p-$C_6H_4Cl_2$[s]	0.032	Na	0.14	41	o	58

[a] The metal was added bit by bit, and the concentration is stated as if it had not reacted. [b] Benzene and aniline were determined by GLC and the solid products by weighing. Biphenylamine and 2- and 4-aminobiphenyls were detected in small yields but were not quantified. [c] 0.35 M water was added. [d] The yield is the average of two concordant runs. [e] 0.33 M water was added. [f] Samples were taken after each addition of metal. [g] 78% of the unreacted o-DCB was determined. [h] 22% of the unreacted o-DCB was determined. [i] 9% of the unreacted o-DCB was determined. [j] Biphenylamine and 2- and 4-aminobiphenyls in ca. 10% yield. [k] In another run aniline was distilled and isolated (6.5% yield by weighing). [l] 0.40 M water was added. [m] 0.20 M methanol was added. [n] 0.14 M toluene was added. [o] Not quantified. [p] Registry no.: 108-90-7. [q] Registry no.: 95-50-1. [r] Registry no.: 541-73-1. [s] Registry no.: 106-46-7.

anion has been reported, although these anions have been generated in several solvents.[4,5]

Results and Discussion

The reaction of chlorobenzene (CB) with Na or K metal in liquid ammonia gives benzene (ca. 80%) as the major product, together with aniline (ca. 12%), and very small amounts of diphenylamine and aminobiphenyls (experiments 1 and 2). These results can be explained by the reaction of CB with a solvated electron to give the phenyl radical,[2] which does not react with ammonia to give benzene, at least in competitive reactions with nucleophiles or solvated electrons.[6] As the reaction proceeds, the concentration of amide ions builds up, and the amide ions can react with phenyl radicals by the $S_{RN}1$ mechanism to give, ultimately, aniline.[7] Some aniline could also be formed via benzyne by the reaction of CB with amide ions.

When Li metal was used as the electron source, the yield of aniline dropped to 2% (experiment 3). This result is attributed to the low solubility of $LiNH_2$ in liquid ammonia[8] which severely limits the rate of reaction with the phenyl radical.

When CB reacted with Na metal in liquid ammonia containing water as the proton source to neutralize amide ions, benzene was the only product formed (experiment 4).

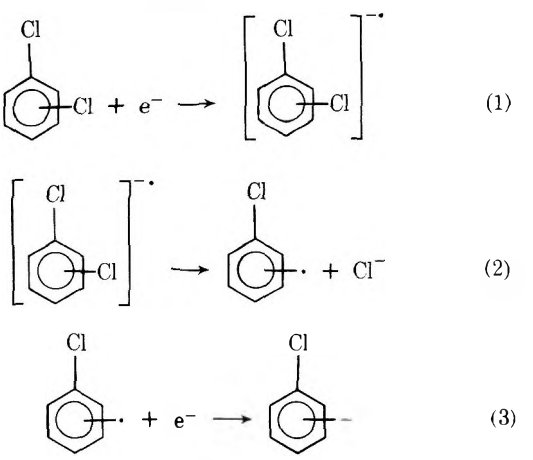
The reaction of o-dichlorobenzene (o-DCB) with Na or K metal in liquid ammonia yielded benzene (54–70%) and aniline (19–11%). With Li metal as the electron source, there was a slight decrease in the yield of aniline (experiment 7).

The reactions of m-dichlorobenzene (m-DCB) and p-dichlorobenzene (p-DCB) with Na or K metal in liquid ammonia gave small yields of benzene and aniline (experiments 10–14).[9] The remaining organic product was a complex mixture of saturated, unsaturated, and aromatic hydrocarbons. Attempts to isolate a pure fraction by column chromatography, GLC, TLC, or recrystallization were unsuccessful because the products decomposed during the process. NMR analyses of the crude product or samples obtained by column chromatography or by recrystallization indicated the presence of $-CH_2-$ and $=CH-$ absorption, together with aromatic protons. The relative amount of each was highly dependent upon the metal used. After catalytic hydrogenation over Pt/C, the product from the reaction with any of the three metals showed only aromatic and $-CH_2-$ protons in a ratio of ca. 1:1.4.

Our results can be explained as shown in Scheme I. Steps 1 and 2 are straightforward in analogy with the reaction of CB. Inasmuch as the phenyl radical does not abstract hydrogen from ammonia, it is reasonable to assume that o-, m-, and p-chlorophenyl radicals do not abstract hydrogen either. However, they can take another electron, giving the corresponding o-, m-, and p-chlorophenyl anions (step 3).

o-Chlorophenyl anion has been generated by other means, and it has been shown to eject chloride ion, giving benzyne.[11] The o-chlorophenyl anion can also be protonated, giving CB, and the ratio of protonation–elimination is 7.6 in 60% ammonia–40% diethyl ether.[12] Benzyne can further react with

Scheme I



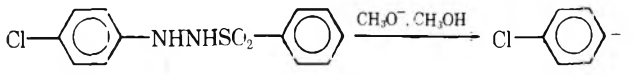
electrons and protons to be reduced to benzene, or it can react with ammonia or amide ion, forming aniline.

In order to see whether any CB can be obtained from the reaction of o-DCB with Li metal when there are electrons in deficiency, we carried out an experiment in which we took samples after each small addition of the metal to the reaction solution and analyzed the reaction mixture by GLC (experiment 9). Even when large amounts of o-DCB remained unreacted, CB could not be detected. In order to have an estimate of the relative reactivities of CB and o-DCB, equimolecular amounts of each substrate were treated with Na metal in liquid ammonia, and it was found that both reacted at about the same rate, in agreement with similar results found earlier with related substrates.[13]

The fact that no CB was found may be attributed to the reaction of CB with electrons in an electron-rich zone (electrons in high local concentration, with the rate of reaction being greater than the rate of mixing).

Similar pathways can be expected for *m*- and *p*-chlorophenyl radicals, which can take an electron giving *m*- and *p*-chlorophenyl anions. However, protonation of these anions seems not to be the main reaction pathway, because in such a case the ultimate product should be benzene as with CB. The reaction of *p*-DCB in the presence of good proton donors led mainly to benzene (experiments 16 and 17).

It is known that the *p*-chlorophenyl anion is an intermediate in the basic decomposition of 1-(*p*-chlorophenyl)-2-benzenesulfonyl hydrazide in methanol[4,5] (eq 4).



(4)

When we treated this substrate with KCH_3O in liquid ammonia, we found 25–30% of the chloride elimination, together with 30–40% of CB, and therefore estimate the ratio of the proton capture rate to the chloride elimination rate to be 1–1.4.[14]

Elimination of the chloride ion from *m*- and *p*-chlorophenyl anions should form *m*- and *p*-benzyne-like intermediates, which may give rise to the polymeric material; *m*- and *p*-benzynes have been postulated as intermediates in several reactions.[15]

In the reaction of *p*-DCB with solvated electrons from Na metal in liquid ammonia containing toluene as hydrogen donor, the yield of benzene was slightly increased (experiment 18). In the same reaction in the presence of methanol (experiment 17) or water (experiment 16) as proton donors, a large increase in the benzene yield was found.

These results are consistent with the mechanism sketched in Scheme I and indicate that the rate of hydrogen abstraction of the *m*- and *p*-chlorophenyl radicals from toluene does not compete with its reaction with electrons; however, protonation of the *m*- and *p*-chlorophenyl anions is the major reaction pathway in the presence of good proton donors such as water or methanol.

Experimental Section

General. Reagents were all commercially available materials except for 1-(*p*-chlorophenyl)-2-benzenesulfonyl hydrazide, which was prepared by the procedure of Hoffmann,[16] mp 136–137 °C dec, from aqueous ethanol (lit.[4] 136–137 °C dec). Solvents were purified by standard procedures. NMR spectra were recorded on a Varian T-60 nuclear magnetic resonance spectrophotometer with CCl_4 as solvent, and all spectra are reported in parts per million relative to Me_4Si (δ). Potentiometric titrations were carried out with a Metrohm Herisau pH Meter Model E 396 B, using a combined silver–calomel electrode (Metrohm Herisau). TLC was performed on silica gel plates. Column chromatography was performed on neutral aluminum oxide (Merck). Gas chromatographic analyses were performed on a Varian Aerograph Series 2400 with a flame ionization detector. Peak areas were corrected by the detector response using internal standards (toluene to quantify benzene, biphenyl to quantify aniline, anthracene to quantify aminobiphenyls and diphenylamine, and bromobenzene to quantify chlorobenzene). A 1.8 × 3 mm column packed with 10% Carbowax 20M on Chromosorb P was used. Alkali metals were cut in small pieces and washed free of oil with dried diethyl ether or pentane immediately before addition to the reaction mixtures. Liquid ammonia was dried over sodium metal and distilled, under nitrogen, into the reaction flask.

Reaction of Chlorobenzene and Alkali Metals. A procedure for the reaction of Na metal with CB is representative. The reaction was performed in a three-neck round-bottom flask fitted with a dry ice–isopropyl alcohol condenser, stirred by a magnetic stirrer, and constantly swept by a slow stream of dry nitrogen. To distilled liquid ammonia (220 mL), CB (0.025 mol) was added, and then Na metal (0.057 mol) was added bit by bit. In the reactions in which water (or another proton donor) was used, it was added before the alkali metal. After all the alkali metal had been introduced, solid ammonium chloride was added to quench the reaction, followed by 150 mL of diethyl ether with the internal standards, and the ammonia was allowed to evaporate. The ether extract was washed with water, dried over anhydrous Na_2SO_4, and analyzed by GLC.

Reaction of o-Dichlorobenzene with Alkali Metals. The procedure was the same that as for CB. In experiment 9, where samples were taken after each addition of metal, a J-shaped tube was used to take liquid ammonia from the reaction flask and added to water, extracted with ether, and analyzed by GLC.

Reaction of *m*- and *p*-Dichlorobenzenes with Alkali Metals. The reactions were performed as before. When the ether from the ether extract was evaporated in vacuo, a waxy solid was found. With Na or K metal as the electron source, and after removal of aniline by distillation in vacuo, the NMR spectrum had peaks centered at δ 1.2, a complex group of peaks in δ 1.3–3.2, a small multiplet at δ 5.6, and a peak at δ 7.2. With Li metal as the electron source, all these peaks remained, but aniline was not formed. After catalytic hydrogenation (atmospheric pressure with 10% Pt/C, 48 h), only the olefinic peaks disappeared (δ 5.6).

Reaction of 1-(*p*-Chlorophenyl)-2-benzenesulfonyl Hydrazide with Potassium Methoxide. After the addition of 1.24 g of K metal (31.8 mmol) to 100 mL of distilled liquid ammonia, 1.29 mL of anhydrous methyl alcohol (31.8 mmol) was slowly added dropwise. A crystal of ferric chloride was added to catalyze the formation of $KOCH_3$, and then solid 1-(*p*-chlorophenyl)-2-benzenesulfonyl hydrazide (1.45 mmol) was added slowly. After 30 min the reaction was quenched with excess redistilled water and then processed as in the previous experiments. The water layer was acidified with nitric acid and diluted to standard volume, and aliquots of the dilute solution were titrated potentiometrically with silver nitrate to quantify the chloride ion. In a blank reaction with everything the same but without the 1-(*p*-chlorophenyl)-2-benzenesulfonyl hydrazide, the chloride ion yield was determined to be less than 1%.

Acknowledgment. We thank Professor Joseph F. Bunnett for helpful suggestions and critical reading of the manuscript.

Registry No.—Benzene, 71-43-2; aniline, 62-53-3; ammonia, 7664-41-7; biphenylamine, 122-39-4; 2-aminobiphenyl, 90-41-5; 4-aminobiphenyl, 92-67-1; 1-(*p*-chlorophenyl)-2-benzenesulfonyl hydrazide, 21857-36-3.

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A Stereospecific Route to Trisubstituted Olefins via Organoboranes

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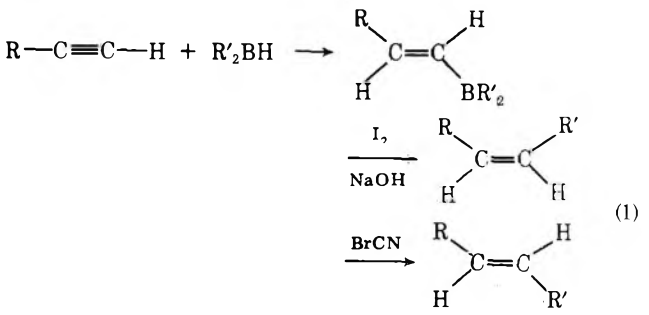
The Zweifel syntheses of cis[1] and trans[2] olefins (eq 1) via vinylboranes have found limited applications in organic

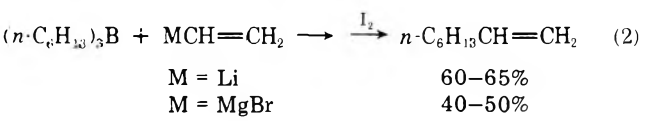


(1)

synthesis in large part because of the limited availability of stable dialkylboranes.[3] A further limitation is the requirement imposed by hydroboration that a hydrogen be cis to boron in the initial borane, thus limiting the applicability of this reaction to cis and trans disubstituted olefins.

Since the common intermediate in these reactions appears to be a vinyl-substituted borate salt, it appeared reasonable to investigate alternative methods of obtaining the intermediates. In analogy with the lithium alkynyltrialkylborate complexes,[4] formation of a vinyltrialkylborate complex[5] from a vinyllithium and a trialkylborane followed by iodination should lead to olefins. Herein, we report the utility of this sequence in the synthesis of stereospecifically defined trisubstituted olefins[6,7] and the somewhat surprising stereochemistry of this reaction.

Initially, we found that treatment of tri-*n*-hexylborane with vinyllithium or vinylmagnesium bromide followed by iodination gives moderate yields of 1-octene[8] (eq 2). In order to

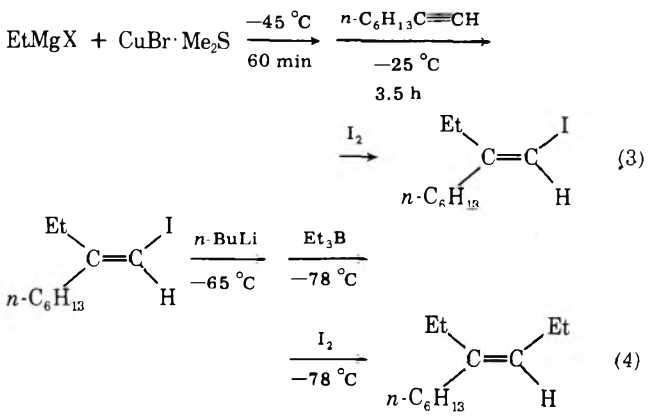


(2)

M = Li	60–65%
M = MgBr	40–50%

ascertain the overall stereochemistry and the potential synthetic applications to stereospecifically defined olefins, we undertook a systematic study of this reaction using 2,2-disubstituted vinyl iodides as precursors of stereospecifically defined vinyllithiums.

Reaction of ethylmagnesium bromide in the presence of CuBr·Me_2S with 1-octyne leads upon iodination to a 63% yield of (*E*)-2-ethyl-1-iodo-1-octene (eq 3).[9] Sequential treatment of the iodide with *n*-butyllithium, triethylborane, and iodine at low temperature leads to a 75% yield of (*E*)-4-ethyl-3-decene (eq 4).[10] In view of these encouraging results, a number

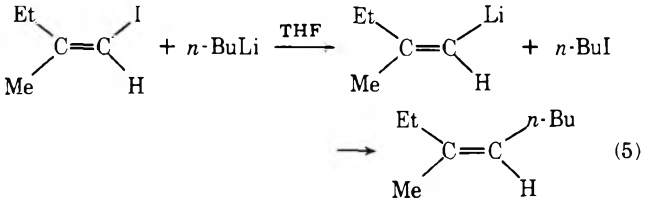


(3)

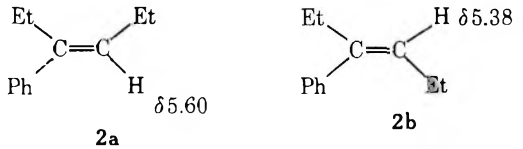
(4)

of the iodides were synthesized by the Normant procedure. From these derivatives the corresponding trisubstituted olefins **1a–j** were prepared. The results are summarized in Table I.

Comparison of the proton-decoupled ^{13}C NMR spectra of *Z* and *E* isomers **1g** and **1h** clearly indicates that the two isomers are different. The stereochemistry of the products was determined in two ways. Treatment of (*Z*)-2-methyl-1-iodo-1-butene with *n*-butyllithium in THF at −78 °C leads to halogen–metal exchange. Subsequent displacement of the iodide with retention at the vinyl carbon[11] gives (*Z*)-3-methyl-3-octene (eq 5), identical in all respects with **1i**. Further support for this stereochemical assignment comes from the proton NMR spectrum of **1j**. Comparison of the vinyl proton's adsorption at δ 5.56 in **1j** with those reported for (*Z*)- and (*E*)-3-phenyl-3-hexene[12] (**2a,b**) confirms the stereochemical assignment of **1j** as the *E* isomer.



(5)



2a **2b**

The stereochemical purity of the resultant trisubstituted olefins remains a difficult problem. In all cases, by proton-decoupled ^{13}C NMR spectroscopy we appear to have only one isomer. In the case of **1g** and **1h**, each isomer is clearly different, uncontaminated by detectable amounts of the opposite isomer. Furthermore, in the proton NMR of **1j** we cannot detect any of the opposite isomer. Based on careful NMR analysis of **1j**, we have determined this isomer to be at least 97% stereochemically pure. Unfortunately, preliminary attempts to analyze **1g** and **1h** by capillary gas chromatography have failed to separate the isomers.[13] However, the ^{13}C NMR spectra indicate each isomer to be at least 95% stereochemically pure.

Presumably, this reaction involves a mechanism similar to the halogenation reactions of vinylboranes. Initial complexation of the vinyllithium with the trialkylborane gives an "ate" complex (eq 6). Subsequent formation of the iodonium ion

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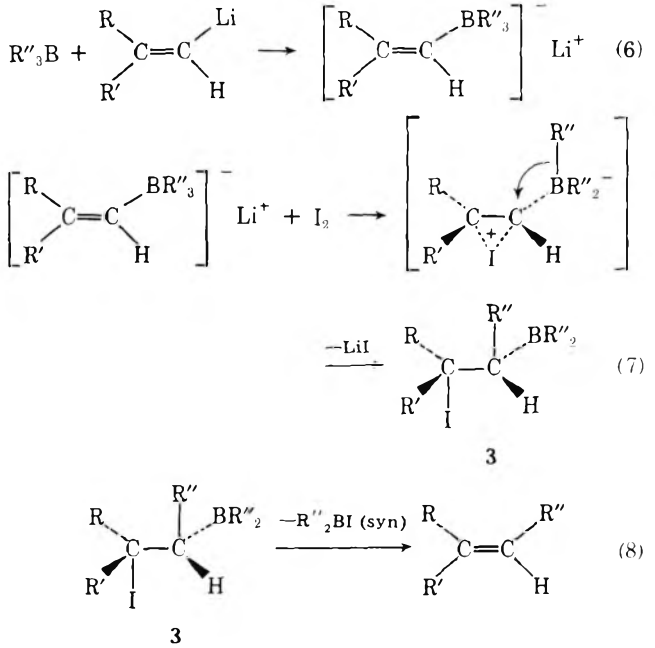
Table I. Iodination of Lithium Trialkylvinylborates to Give Trisubstituted Olefins

Vinyl iodide[a] R	Vinyl iodide[a] R′	Registry no.	R''_3B,[b,c] R″ =	Registry no.	Product	Registry no.	Yield,[d,e] %
Ethyl	*n*-Hexyl	64705-58-4	Ethyl	97-94-9	(*E*)-4-Ethyl-3-decene (**1a**)	64705-61-9	75 (61)
			n-Butyl	122-56-5	(*E*)-6-Ethyl-5-dodecene (**1b**)	64705-62-0	82
			Isobutyl	1116-39-8	(*E*)-5-Ethyl-2-methyl-4-undecene (**1c**)	64705-63-1	72
			sec-Butyl	1113-78-6	(*E*)-5-Ethyl-3-methyl-4-undecene (**1d**)	64705-64-2	66
			Cyclohexyl	1088-01-3	(*E*)-1-Cyclohexyl-2-ethyl-1-octene (**1e**)	64705-65-3	76
			Cyclopentyl	23985-40-2	(*E*)-1-Cyclopentyl-2-ethyl-1-octene (**1f**)	62134-95-6	82
n-Propyl	Ethyl	64705-59-5	Ethyl		(*Z*)-4-Ethyl-3-heptene (**1g**)	64705-66-4	80
Ethyl	*n*-Propyl	64705-60-8	Ethyl		(*E*)-4-Ethyl-3-heptene (**1b**)	64705-67-5	87
Ethyl	Methyl	52812-57-4	*n*-Butyl		(*Z*)-3-Methyl-3-octene (**1i**)	34213-99-5	79
Ethyl	Phenyl	64245-21-2	Ethyl		(*E*)-3-Phenyl-3-hexene (**1j**)	39857-50-6	38

[a] 5.0 mmol of the iodide treated with 5.0 mmol of *n*-BuLi at −80 °C in 5.0 mL of ether and stirred for 15 min at −60 °C. [b] 5.0 mmol added dropwise at −80 °C and stirred for 10 min. [c] 5.0 mmol of I_2 added in 3 mL of THF. [d] Analysis by GLPC (isolated yields in parentheses). [e] All compounds exhibited spectral data in accordance with their structure and gave satisfactory elemental composition by high-resolution mass spectrometry and/or elemental analysis.

followed by migration of an alkyl group from boron to carbon with concurrent anti opening of the iodonium ion leads to **3** (eq 7). β-Haloboranes similar to **3** are known to eliminate R_2BX in an anti manner in the presence of excess base.[1] In the absence of base, a thermal syn elimination similar to that previously reported for the cyanobromination of vinylboranes[2] must occur, leading directly to the trisubstituted olefin **1** (eq 8).



These results are in sharp contrast to the recent report of Evans and co-workers[5a,b] wherein the reaction of a vinyllithium with an alkylboronate ester followed by iodination leads to net inversion of the carbon originally bearing iodine. Presumably, the change in mechanism is due to the increased electrophilicity of **3** vs. the borinate and boronate intermediates investigated by Zweifel and Evans and to the absence of nucleophiles such as sodium methoxide or sodium hydroxide present in their reactions.

In summary, the present development provides a convenient stereospecific route to trisubstituted olefins in two steps from a terminal acetylene, a Grignard reagent, and a trialkylborane. While alternative procedures are available for the synthesis of olefins from vinyl iodides, the ready availability of trialkylboranes via hydroboration and the known limitation of other reactions to relatively unhindered alkyl derivatives suggest that his procedure may be the method of choice in many cases. To enhance the utility of this sequence, work is in progress to develop a "blocked" borane for use in this reaction[14] and to apply this sequence to the synthesis of naturally occurring compounds.

Experimental Section

Infrared spectra were recorded on a Pye Unicam SP 1000 using a thin film on sodium chloride. ^1H NMR spectra were determined on a Varian EM-360 or a Varian PFT-80 spectrometer using $CDCl_3$ as solvent and Me_4Si as an internal standard. ^{13}C NMR data were obtained on a Varian CFT-20 instrument in $CDCl_3$ solvent and using Me_4Si as an internal standard. Low-resolution mass spectra were recorded on a Hewlett-Packard 5980A mass spectrometer. High-resolution data were obtained on an AEI MS-30 instrument.

GLC analyses were carried out on a Varian 1400 chromatograph equipped with a flame detector and a Hewlett-Packard 3380 integrating recorder using 6 ft × 0.125 in. stainless steel columns filled with 10% loaded packing on AW-DMCS treated 80–100 Chromosorb W. Either Se-30 or Xe-60 liquid phases were used. All yields based on GLC were determined using an internal standard. Preparative gas chromatography was carried out on a Varian 920 instrument equipped with 6 ft × 0.5 in. stainless steel columns filled with 20% loaded packing on AW-DMCS treated 40–60 Chromosorb W. Either Se-30 or Xe-60 liquid phases were employed.

Air-sensitive materials were handled via the standard techniques described in Chapter 9 of ref 3c. All glassware was dried at 150 °C for 4 h, assembled hot, and allowed to cool under a nitrogen purge. The reaction flasks were fitted with a side arm capped with a rubber septum. All reactions were carried out under a static pressure of nitrogen.

Materials. Triethyl- and triisobutylborane were obtained from Callery Chemical Co. and used without further purification. Tri-*n*-butyl-, tricyclopentyl-, and tricyclohexylborane were prepared by hydroboration with borane methylsulfide in THF.[3c] Tri-*sec*-butylborane was obtained from Aldrich Chemical Co. and standardized by oxidation with alkaline hydrogen peroxide. The *n*-alkanes (Phillips) employed as internal standards were used as received. All solvents were distilled from benzophenone ketyl under nitrogen. The vinyl iodides were prepared by the method of Normant using CuBr·Me_2S as the source of copper. The solvent used was a 50:50 mixture of ether and dimethyl sulfide. All other conditions are identical with those reported.[9] The iodides were consistently isolated in ca. 60% yields using this procedure. The lithium reagents were prepared by the method of Normant.[15]

(*E*)-4-Ethyl-3-decene (1a). A dry 250-mL flask equipped with a septum-capped inlet, reflux condenser, and magnetic stirring bar was flushed with nitrogen. The flask was charged with 60 mL of ether and 15.96 g (60 mmol) of (*E*)-2-ethyl-1-iodo-1-octene and cooled to −80 °C. To this mixture 25.64 mL of *n*-butyllithium (2.34 M) was

added. The solution was placed in a −60 °C bath ($CHCl_3/CO_2$) for 30 min and cooled to −80 °C. Triethylborane (5.87 g, 60 mmol) was added, and the solution was stirred for 10 min. Finally, 15.24 g (60 mmol) of iodine dissolved in 60 mL of THF was added over a 15-min period. The solution was stirred for 1 h at −80 °C and then allowed to warm to room temperature. The reaction was hydrolyzed with 75 mL of 3 N NaOH under nitrogen. The residual borane was washed three times with 50 mL of 3 N NaOH then oxidized in the presence of 75 mL of 3 N NaOH by the slow dropwise addition of 15 mL of 30% hydrogen peroxide. The organic layer was washed with water and dried, and the solvent was removed by distillation through a 6-in. Vigreux column. Subsequent distillation through a Teflon-coated microspinning band column at 77 mmHg gave 6.43 g of *n*-butyl iodide. The pressure was reduced to 15 mmHg and further distillation gave 6.19 g (61%) of analytically pure (*Z*)-4-ethyl-3-decene; bp 81–83 °C (15 mm); IR 1378, 1465, 2860, 2940, 2970, 3040 cm^{-1}; NMR ($CDCl_3$) δ 0.8–1.6 (m, 17 H), 1.98 (m, 6 H), 5.08 (t, 1 H); high-resolution mass spectrum; *m/e* 168.1881 ($M^{+\cdot}$) ($C_{12}H_{24}$ requires 168.1913).

General Procedure for the Preparation of Olefins 1b–j. A dry 50-mL round-bottom flask equipped with a septum-capped side arm and reflux condenser was connected to an oil bubbler. The system was purged with nitrogen and maintained under nitrogen until after the oxidation. To this flask was added 5 mL of THF and 5.0 mmol of the iodide. The solution was cooled to −80 °C, and 5.5 mmol of *n*-butyllithium was added. The solution was stirred at −60 °C for 30 min and cooled to −80 °C, and 5.0 mmol of the appropriate borane was added. The solution was stirred for 10 min, and then 1.26 g (5 mmol) of I_2 in 5 mL of THF was added. The solution was stirred for 1 h at −80 °C and allowed to warm to room temperature. The residual borane was washed three times with 5 mL of 3 N NaOH then oxidized by addition of 2 mL of 3 N NaOH followed by the dropwise addition of 2 mL of 30% hydrogen peroxide. The organic layer was separated and dried, and the trisubstituted olefin content was measured by GLC vs. an internal standard. Purification by preparative gas chromatography afforded essentially pure (<98%) trisubstituted olefins.

(*E*)-6-Ethyl-5-dodecene (1b). Isolation by preparative gas chromatography gave 0.61 g of pure material; IR 1465, 2840, 2940, 2965 cm^{-1}; NMR ($CDCl_3$) δ 0.6–1.75 (m, 21 H), 2.0 (m, 6 H), 5.10 (t, 1 H); high-resolution mass spectrum, *m/e* 196.2213 ($M^{+\cdot}$) ($C_{14}H_{28}$ requires 196.2190).

(*E*)-5-Ethyl-2-methyl-4-undecene (1c). Isolation by preparative gas chromatography gave 0.53 g of pure material; IR 1370, 1385, 1470, 2960, 2980, 3060 cm^{-1}; NMR ($CDCl_3$) δ 0.70–2.30 (m, 27 H), 5.10 (t, 1 H); high-resolution mass spectrum, *m/e* 196.2202 ($M^{+\cdot}$) ($C_{14}H_{28}$ requires 196.2190).

(*E*)-5-Ethyl-3-methyl-4-undecene (1d). Isolation by preparative gas chromatography gave 0.49 g of pure material; IR 1378, 1465, 2865, 2940, 2975 cm^{-1}; NMR ($CDCl_3$) δ 0.60–1.68 (m, 22 H), 1.8–2.4 (m, 5 H), 4.82 (d, 1 H); high-resolution mass spectrum, *m/e* 196.2179 ($M^{+\cdot}$) ($C_{14}H_{28}$ requires 196.2190).

(*E*)-1-Cyclohexyl-2-ethyl-1-octene (1e). Isolation by preparative gas chromatography gave 0.61 g of pure material; IR 1450, 2860, 2935, 2965 cm^{-1}; NMR ($CDCl_3$) δ 0.5–2.5 (m, 29 H), 4.96 (d, 1 H); high-resolution mass spectrum, *m/e* 222.2327 ($M^{+\cdot}$) ($C_{16}H_{30}$ requires 222.2346).

(*E*)-1-Cyclopentyl-2-ethyl-1-octene (1f). Isolation by preparative gas chromatography gave 0.51 g of pure material; IR 1380, 1460, 2870, 2950; NMR ($CDCl_3$) δ 0.5–3.0 (m, 27 H), 4.98 (d, 1 H); high-resolution mass spectrum, *m/e* 208.2190 ($M^{+\cdot}$) ($C_{15}H_{28}$ requires 208.2214).

(*Z*)-4-Ethyl-3-heptene (1g). Isolation by preparative gas chromatography gave 0.22 g of pure material; IR 855, 875, 900, 1390, 1465, 2880, 2940, 2975, 3020 cm^{-1}; NMR ($CDCl_3$) δ 0.50–1.65 (m, 11 H), 1.70–2.30 (m, 6 H), 5.16 (t, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.98, 14.12, 14.66, 21.03, 21.74, 29.64, 32.37, 125.63, 140.48; high-resolution mass spectrum, *m/e* 126.1422 ($M^{+\cdot}$) (C_9H_{18} requires 126.1408).

(*E*)-4-Ethyl-3-heptene (1h). Isolation by preparative gas chromatography gave 0.178 g of pure material; IR 1390, 1465, 2880; 2940, 2975, 3020 cm^{-1}; NMR ($CDCl_3$) δ 0.5–1.67 (m, 11 H), 1.70–2.40 (m, 6 H), 5.10 (t, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.28, 13.86, 14.75, 20.90, 21.44, 23.11, 38.89, 126.13, 140.49; high-resolution mass spectrum, *m/e* 126.1417 ($M^{+\cdot}$) (C_9H_{18} requires 126.1408).

(*Z*)-3-Methyl-3-octene (1i). Isolation by preparative gas chromatography gave 0.32 g of pure material; IR 1378, 1460, 2860, 2940, 2970; NMR ($CDCl_3$) δ 0.60–1.50 (m, 10 H), 1.68 (d, 3 H), 1.80–2.40 (m, 4 H), 5.17 (t, 1 H); high-resolution mass spectrum, *m/e* 126.1420 ($M^{+\cdot}$) (C_9H_{18} requires 126.1408).

(*E*)-3-Phenyl-3-hexene (1j). Isolation by preparative gas chromatography gave 0.18 g of pure material; IR 700, 765, 865, 1038, 1075, 1380, 1460, 1600, 2880, 2940, 2980, 3040, 3065; NMR (CCl_4) δ 0.7–1.3 (m, 6 H), 2.0–2.7 (m, 4 H), 5.57 (t, 1 H), 7.23 (s, 5 H); high-resolution mass spectrum, *m/e* 160.1244 ($M^{+\cdot}$) ($C_{12}H_{16}$ requires 160.1251).

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(7) Biologically active compounds of this class include insect pheromones and insect juvenile hormone.
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(9) The addition of the organocopper reagent to a terminal acetylene is highly dependent on the purity of the copper salt used. We find CuBr·Me_2S to be the method of choice using a 1:1 mixture of dimethyl sulfide–diethyl ether as solvent. All other conditions are identical to those of Normant and coworkers: J. F. Normant, G. Cahiez, C. Chuit, and J. Villieras, *J. Organomet. Chem.*, **77**, 269. 281 (1974).
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(13) Preliminary attempts involved the use of 50 ft SCOT columns using Apiezon L or OV-1 as liquid phase and 150 ft wall-coated capillary columns using squalane or OV-101 as the liquid phase.
(14) In accordance with Suzuki,[5d] our preliminary results suggest that *B*-alkyl-9BBN's undergo this reaction in good yields with the same overall stereochemistry described herein.
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Communications

Synthesis and Thermal Rearrangement of exo-Tetracyclo[4.3.0.0^{2,4}.0^{5,7}]non-8-ene, a σ-Homosemibullvalene. A Novel Entry into the C_9H_{10} Energy Manifold

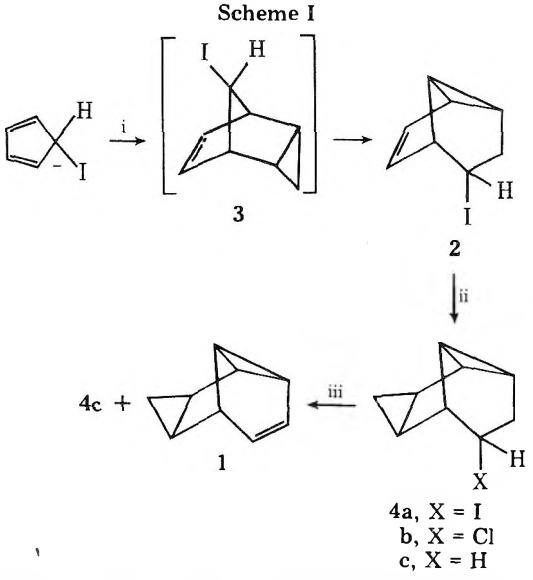
Summary: *exo*-Tetracyclo[4.3.0.0^{2,4}.0^{5,7}]non-8-ene (σ-homosemibullvalene, **1**) has been conveniently synthesized in two steps from the 5-iodocyclopenta-1,3-diene–cyclopropene cycloadduct and its thermal chemistry examined.

Sir: Recent interest in the chemistry and σ,π-isomerizations of σ-homobenzene[1] and σ-homotropilidene[2] derivatives, including fluxional behavior of the latter, has focused attention on further homologues related to these systems. We now report the synthesis and thermal rearrangement of the *cis*-σ-bishomotropilidene, *exo*-tetracyclo[4.3.0.0^{2,4}.0^{5,7}]non-8-ene (**1**), a σ-homosemibullvalene which unlike its next lower homologue, semibullvalene,[2b,c] is surprisingly resistant to thermal σ,π-valence isomerization.

Treatment of 5-iodocyclopenta-1,3-diene[3] with excess cyclopropene at −78 °C, followed by intermittent warming to 0 °C, afforded the tricyclooctenyl iodide **2** as a colorless oil in variable (40–90%) yield.[4] The structure and stereochemistry of **2** was readily established by its characteristic NMR spectrum that includes the expected doublet of doublets for the C-4 exo proton.[5] This one-step entry into the dihydrosemibullvalene ring system is most obviously a consequence of the facile rearrangement,[5,6] perhaps with thallium ion catalysis, of the initial (4 + 2) adduct, *anti*-8-tricyclo[3.2.1.0^{2,4}]oct-6-enyl iodide (**3**). Cyclopropanation of **2** (see Scheme I) gave in 90% yield the tetracyclic iodide **4a** [δ (CCl_4) 4.05 (ddd, 1 H), 1.0–3.1 (br m, 8 H), 0.55 (m, 1 H), 0.02 (m, 1 H); M^+ (70 eV) *m/e* 245.9895 (weak), 119 (66), 91 (100)].[7] The stereochemistry of the newly incorporated cyclopropane ring follows from the highly selective steric preference for exo cyclopropanation of norbornene type double bonds.[8]

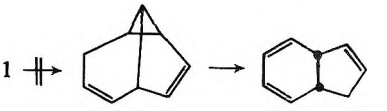
Quantitative conversion of **4a** to a 2:3 mixture of **1** and **4c**, respectively, was accomplished using a slight molar excess of KO-*t*-Bu in dimethylformamide at 110 °C for 2.5 h under nitrogen. The two-component mixture was cleanly separated by preparative GLC to yield the desired **1** [δ (CCl_4) 5.54 (m, 2 H), 3.25 (br d, 1 H), 0.9–2.1 (m, 5 H), −0.1–0.1 (m, 2 H); M^+ (70 eV) *m/e* 118 (40), 117 (100), 91 (40); M^+ + 1 (30 eV) 119.0817, M^+ 118.0766,[9] M^+ − 1 117.0704][10] and its dihydro derivative **4c**. The structure of **4c** was confirmed by comparison with authentic material prepared by sodium metal reduction of **4a** in refluxing THF–*t*-BuOH).

Scheme I



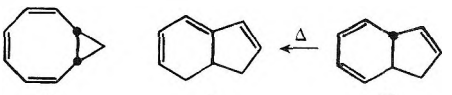
Reagents: i, c-C_3H_4, −78 to 0 °C; ii, CH_2N_2–CuCl, CH_2Cl_2; iii, KO-*t*-Bu–DMF, 110 °C.

At the outset investigation of the thermal behavior of **1** was largely prompted by consideration of its potential for homo-Cope rearrangement to the known[11] π-homosemibullvalene isomer **6**. Indeed a completely analogous 6π-electron reor-



ganization has been recently proposed to account for the rearrangement and eventual fragmentation of a pentacyclic $(CH)_{12}$ hydrocarbon.[12] Initial thermolysis studies of **1** indicated complete recovery after heating in a static system at 140–150 °C for 12.5 h. On the basis of the reasonable assumption that the isomerization **1** → **6** is exoergic and assuming <10% conversion to the π isomer at these temperatures, the activation energy (E_a) for the homo-Cope rearrangement of **1** is estimated to be >35 kcal/mol, a value at least 30 kcal/mol higher than the similar activation barrier for the degenerate Cope rearrangement in semibullvalene.[2c]

On pyrolysis in a glass packed Vycor tube flow system (10 Torr, N_2; contact time ~1 s) at 400–520 °C **1** undergoes rearrangement to a mixture of hydrocarbons reminiscent of that obtained from the thermolysis of other isomeric C_9H_{10} systems,[11,13,14] most notably bicyclo[6.1.0]nona-2,4,6-triene (**7**),[13] with one significant difference. Thus at 520 °C **1** was converted (99.2%) to a six or seven component mixture of hydrocarbons, the major components of which were identified as 7,7a-dihydroindene (**8**; 55.2%),[15] indane (21.2%), indene (6%), and *cis*-3a,7a-dihydroindene (**9**; 10–12%).[16] Analogy to the previously reported[13d,f,g] interconversions of alkylated dihydroindene isomers suggested that **8** must arise by 1,5-sigmatropic isomerization of *trans*-3a,7a-dihydroindene (**10**). Indeed pyrolysis of an enriched sample of **10** (77.8% **10**, 18.1% **8**)[17] under the identical conditions (520 °C, 10 Torr, N_2) afforded a similar product distribution to that obtained from **1**.[18] By contrast *cis*-dihydroindene **9** was largely (>97%) unaffected by these flow pyrolysis conditions.



The striking conclusion from the above results is that thermal isomerization of **1** leads to predominantly *trans*- rather than *cis*-dihydroindene, which is the customary molecular sink for thermal isomerizations of C_9H_{10} systems.[14] Therefore substantial rearrangement by the homo-Cope pathway is ruled out since **6** has been previously shown[11] to rearrange quantitatively to *cis*-dihydroindene **9**. The most plausible precursor to **10** is either *cis*,[3] *trans*- or *cis*,[2] *trans*,-

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cis-cyclonona-1,3,5,7-tetraene (or both). Both of these highly reactive tetraenes have been implicated as intermediates, along with the all *cis*-cyclononatetraene, in the thermal isomerization of the bicyclononatriene **7**, although the mode of their formation is still a matter of conjecture.[13] It is clear, however, that **7**, in its normal state, cannot be an intermediate in the isomerization of **1**, since under the above flow pyrolysis conditions it gave, as expected, *cis*-dihydroindene **9** as the major (80%) thermal product.

While further mechanistic studies are required we would suggest the intriguing possibility of retro Diels–Alder cleavage of **1** to vibrationally excited **7** in its extended conformation, which thereupon suffers immediate symmetry-allowed electrocyclic opening to *cis*,[3] *trans*-cyclononatriene.[19]

References and Notes

(1) H. Prinzbach and R. Schwesinger, *Angew. Chem.*, **84**, 988 (1972); H. Prinzbach, H. Fritz, H. Hagemann, D. Hunkier, S. Kagabu, and G. Philippossian, *Chem. Ber.*, **107**, 1971 (1974), and references cited therein.

(2) (a) W. von E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963); (b) H. E. Zimmerman, R. W. Binkley, R. S. Givens, G. L. Grunewald, and M. A. Sherwin, *J. Am. Chem. Soc.*, **91**, 3316 (1969); (c) A. K. Cheng, F. A. L. Anet, J. Mioduski, and J. Meinwald, *ibid.*, **96**, 2887 (1974), and references cited therein.

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(4) The yield of **2** appeared to be enhanced when a slight excess of thallium cyclopentadienide was used in the preparation of 5-iodocyclopenta-1,3-diene.

(5) K. Henrick and B. L. Johnson, *Aust. J. Chem.*, **25**, 2263 (1972); see also J. S. Haywood-Farmer and R. E. Pincock, *J. Am. Chem. Soc.*, **91**, 3020 (1969), and C. L. Deyrup, Ph.D. Dissertation, Boston University, 1970.

(6) H. Tanida, T. Tsuji, and T. Irie, *J. Am. Chem. Soc.*, **89**, 1953 (1967); M. A. Battiste, C. L. Deyrup, R. E. Pincock, and J. Haywood-Farmer, *ibid.*, **89**, 1954 (1967).

(7) A low intensity ion in the mass spectrum of **4a** at *m/e* 154 was attributed to trace contamination by chloride **4b**, presumably formed through halide exchange with the catalyst CuCl.

(8) Cf. J. Haywood-Farmer, R. E. Pincock, and J. I. Wells, *Tetrahedron*, **22**, 2007 (1966); M. A. Battiste and M. E. Brennan, *Tetrahedron Lett.*, 5857 (1966).

(9) The measured parent ion (M^+) mass is slightly beyond acceptable error limits due to interference by the ^{13}C isotope peak of the intense (base) $M^+ - 1$ ion; however, the flanking *m/e* 119 and 117 ions gave the correct accurate masses for the assigned structure.

(10) After the studies reported in this paper were concluded our attention was directed to a report by T. Kumagai and T. Mukai [*Chem. Lett.*, 1187 (1975)] in which these authors propose the structure **1** for the 30% component isolated from the acetone-sensitized photolysis of tricyclo[3.2.2.$0^{2,4}$]-nona-6,8-diene (homobarrelene). Structure assignment by the Japanese workers was largely based on analysis of the NMR (100 MHz) spectrum, which we find to be essentially identical with the spectrum (60 MHz, briefly annotated in the text) of our synthetic material, thus confirming their assignment.

(11) J. A. Berson, R. B. Boettcher, and J. J. Vollmer, *J. Am. Chem. Soc.*, **93**, 1540 (1971).

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(14) For a brief summary of the thermal isomerizations of a variety of C_9H_{10} systems, see J. M. Brown, *MTP Int. Rev. Sci.: Org. Chem., Ser. One*, **5**, 196–200 (1973).

(15) To our knowledge **8** has not been previously reported. Its identity follows from its NMR [($CDCl_3$) complex multiplets from δ 1.6–3.0 (allylic) and 5.5–6.4 (vinyl) in 1:1 area ratio] and UV [λ_{max} (CCl_4) 300 nm (ϵ 8000)] spectra, its extreme sensitivity to oxygen and partial conversion to indene on exposure to air, and its alternative generation on pyrolysis of **10**. In addition, the vinyl proton pattern in the NMR spectrum of **8** is essentially identical with that for 1,1-dimethyl-7,7a-dihydroindene.[13d] We thank Professor S. W. Staley for copies of the NMR and IR spectra of the latter hydrocarbon taken from the Ph.D. Thesis of T. J. Henry, University of Maryland, 1971. Indane and indene were identified by preparatiye GLC isolation and comparison of NMR spectra with those of authentic samples.

(16) Allylbenzene, an anticipated secondary pyrolysis product, was also detected by NMR as a minor product, but was inseparable from *cis*-dihydroindene **9** under the capillary GLC conditions utilized for product analysis. In a later run NMR analysis of the *cis*-dihydroindene component after preparative GLC collection showed <10% contamination by allylbenzene.

(17) The enriched sample of *trans*-dihydroindene **10** was secured by preparative GLC collection of the minor (15%) dihydroindene isomer obtained on pyrolysis of **7** at 75 °C. Under the GLC conditions **10** is partially isomerized to **8**.

(18) One difference noted in the pyrolysis of **10** is that the relative yield of *cis*-dihydroindene **9** is considerably reduced (<5%). We estimate the allylbenzene/**9** ratio in this case to be essentially equal from NMR analysis of the crude pyrolysis mixture.

(19) We wish to thank the National Science Foundation for financial support of this work (Grant GP-38630X) and Dr. Roy King for his assistance with the aquisition and interpretation of the mass spectrometric data.

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Aryl Selenocyanates and Aryl Thiocyanates: Reagents for the Preparation of Activated Esters

Summary: Treatment of carboxylic acids with phenyl selenocyanate and phenyl thiocyanate in the presence of tri-*n*-butylphosphine affords benzeneselenol esters and benzenethiol esters, respectively.

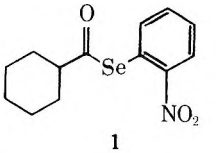
Sir: As a result of current interest in the synthesis of naturally occurring macrocyclic lactones and lactams,[1] considerable attention has been focused on the preparation of activated esters.[2,6] We wish to report a new method for the preparation of selenol esters (eq 1) and thiol esters (eq 2) which proceeds

$$\mathrm{RCOOH} \xrightarrow[\mathrm{Bu_3P}\ \mathrm{CH_2Cl_2}]{\mathrm{ArSeCN}} \mathrm{RCOSeAr} \qquad (1)$$

$$\mathrm{RCOOH} \xrightarrow[\mathrm{Bu_3P}\ \mathrm{CH_2Cl_2}]{\mathrm{ArSCHN}} \mathrm{RCOSAr} \qquad (2)$$

under mild conditions. During the course of examining the reaction of aryl selenocyanates with alcohols[7] and aldehydes,[8] we observed that carboxylic acids dissolved in methylene chloride or tetrahydrofuran reacted with aryl selenocyanates in the presence of tri-*n*-butylphosphine. We also demonstrated that substitution of aryl thiocyanates for aryl selenocyanates results in the formation of thiol esters.

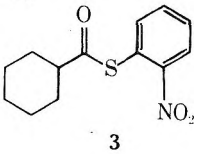
In the case of selenol esters, the reaction is best carried out employing 1.0 equiv of aryl selenocyanate and 2.0 equiv of tri-*n*-butylphosphine. The reaction can be performed on a variety of alkyl and aryl carboxylic acids (Table I) employing phenyl selenocyanate.[9] Cyclohexanecarboxylic acid, upon treatment with phenyl selenocyanate and tri-*n*-butylphosphine in methylene chloride, gave rise to an 88% yield of pure activated ester. Yields of pure isolated benzeneselenol esters are generally high (Table I). Reaction of *p*-chlorobenzoic acid with phenyl selenocyanate under the conditions described above gave rise to only a 36% yield of product, with the major product (54%) being diphenyl diselenide. Utilization of o-



1

$BrCH_2(CH_2)_5COSC_6H_5$

2



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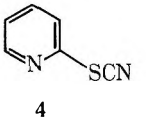

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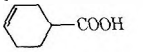
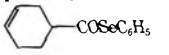
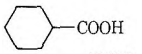
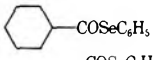
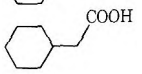
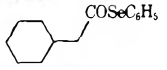
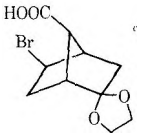
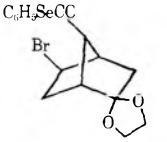
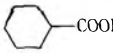
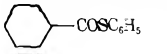
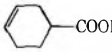
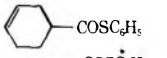
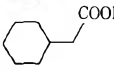
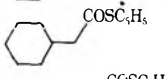
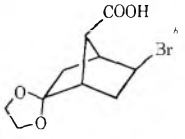
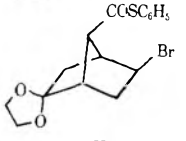
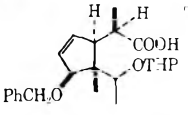
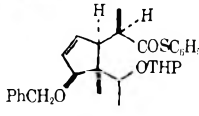
Table I. Synthesis of Benzeneselenol Esters[a]

Starting acid	Time, h	Selenol ester	Isolated yield, %	Mp, °C [Bp, °C (mm)]
CH_3COOH[b]	2.5	$CH_3COSeC_6H_5$	79	[80 (0.5)]
C_6H_5COOH	2.0	$C_6H_5COSeC_6H_5$	84	37–38
$CH_3(CH_2)_6COOH$	3.0	$CH_3(CH_2)_6COSeC_6H_5$	78	[140–143 (1.0)]
p-$CH_3OC_6H_4COOH$	0.5	p-$CH_3OC_6H_4COSeC_6H_5$	83	62–63
p-ClC_6H_4COOH	0.3	p-$ClC_6H_4COSeC_6H_5$	36[d]	83.5–84.5
	3.5		84	[119–124 (0.16)]
	2.0		88	[118–123 (0.12)]
	3.0		78	[148 (1.0)]
	3.0		46	123–125

[a] All reactions were carried out at room temperature in methylene chloride, using 1.0 equiv of phenyl selenocyanate and 2.0 equiv of tri-n-butylphosphine, unless stated otherwise. [b] This reaction was performed in tetrahydrofuran. [c] 2 equiv of phenyl selenocyanate were utilized. [d] A 54% yield of diphenyl diselenide was isolated.

Table II. Synthesis of Benzenethiol Esters[a]

Starting acid	Thiol ester	Isolated yield, %	MP, °C [Bp, °C (mm)]
CH_3COOH	$CH_3COSC_6H_5$	92	[52–54 (0.16)]
C_6H_5COOH	$C_6H_5COSC_6H_5$	96	55–56
$C_6H_5CH_2COOH$	$C_6H_5CH_2COSC_6H_5$	94	33.0–33.5
$CH_3(CH_2)_6COOH$	$CH_3(CH_2)_6COSC_6H_5$	81	[118–119 (0.1)]
p-$CH_3OC_6H_4COOH$	p-$CH_3OC_6H_4COSC_6H_5$	96	94–95
p-ClC_6H_4COOH	p-$ClC_6H_4COSC_6H_5$	92	79.5–81.5
$BrCH_2(CH_2)_5COOH$	$BrCH_2(CH_2)_5COSC_6H_5$	80	[149–153 (0.07)]
		91	[106–107 (0.07)]
		92	[117–118 (0.07)]
		96	[114–116 (0.14)]
		86	127–128
		43	

[a] All reactions were carried out at room temperature for 30 min in methylene chloride employing 1.0 equiv of phenyl thiocyanate and 1.1 equiv of tri-n-butylphosphine, unless stated otherwise. [b] C_6H_5SCN (1 equiv), Bu_3P (1.5 equiv), 3.0 h. [c] C_6H_5SCN (1.5 equiv), Bu_3P (1.5 equiv), 3.0 h.

nitrophenyl selenocyanate led to disappointingly low yields of product. For example, cyclohexanecarboxylic acid provided only a 30% yield of ester **1**.

With respect to aryl thiocyanates, the conversion of carboxylic acids into thiol esters was best performed employing 1.0 equiv of thiocyanate and 1.1 equiv of trialkylphosphine. As illustrated in Table II reaction of 7-bromoheptanoic acid with phenyl thiocyanate and tri-n-butylphosphine gave an 80% yield of thiol ester **2**. Unlike our experience above with o-nitrophenyl selenocyanate, o-nitrophenyl thiocyanate (1.2 equiv) reacted with cyclohexanecarboxylic acid in tetrahedrofuran (4 h, 25 °C) in the presence of tri-n-butylphosphine (1.2 equiv) and triethylamine (1.2 equiv), providing after workup an 86% yield of thiol ester **3**. The preparation of the 2-pyridinethiol ester of cyclohexaneacetic acid utilizing thiocyanate 4[10] was not successful.

General Procedure for the Preparation of Benzenethiol Esters. To a solution of tri-n-butylphosphine (1.11 g, 5.5 mmol) and carboxylic acid (5.0 mmol) in 20 mL of dry methylene chloride under an atmosphere of nitrogen was added in one portion phenyl thiocyanate[11] (676 mg, 5.0 mmol) dissolved in 10 mL of methylene chloride. Upon addition the reaction mixture turns pale yellow. After anywhere from 0.5 to 3.0 h at room temperature, the solvent was removed in vacuo and the residue was chromatographed on silica gel to remove tributylphosphine oxide and minor impurities. Isolated yields of products are given in Table II for several examples.

Acknowledgment. This research was supported by the National Cancer Institute DHEW (CA 13689-06).

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(12) Fellow of the Alfred P. Sloan Foundation.

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Favored Reduction of α-Chlorosilanes vs. α-Chloroalkanes with Tri-*n*-butyltin Hydride

Summary: The reduction of 1-chloro-2,2-dimethyl-2-silapropane, neopentyl chloride, and 1,6-dichloro-2,2,5,5-tetramethyl-2-silahexane with tri-*n*-butyltin hydride under free-radical conditions is described.

Sir: In 1965 it was suggested that α-silyl radicals may be specially stabilized compared to their all-carbon analogues, possibly by vicinal (d–p) π overlap.[1] Such stabilization was invoked to explain the absence of rearrangement in α-silyl radicals.[2] Although ESR studies appear to confirm this stabilization,[3] it seemed desirable to investigate it further. We describe here external and internal competition studies that show the heretofore unreported *preferential reduction of certain α-chlorosilanes over their all-carbon analogues* with tri-*n*-butyltin hydride. These results strongly suggest that some α-silyl radicals are indeed more stable than their all-carbon congeners.

In the external competition, mixtures of 1-chloro-2,2-dimethyl-2-silapropane ("silaneopentyl chloride", **1**) and neopentyl chloride (**2**) were dissolved in dry benzene, sealed in ampules after degassing, and reduced with tri-*n*-butyltin hydride,[4] using di-*tert*-butyl peroxide as the free-radical initiator. The results are given in Table I.

It may be seen that **1** is nearly two orders of magnitude faster in this reduction than is **2**. Because the chlorine abstraction step (eq 1) determines the rate of these reductions,[5] it would appear that $(CH_3)_3SiCH_2\cdot$ (**1**·) is more easily formed than $(CH_3)_3CCH_2\cdot$ (**2**·) and therefore that **1**· might be more stable than **2**·. External competition experiments can be misleading, however. The competitive rate ratio, which only measures the relative activation barriers, might actually reflect a less stable reactant (i.e., **1**) rather than a more stable intermediate (i.e., **1**·).

Table I. Competitive Reduction of 1 and 2[a]

Ratio 1/2, mM	k_{Si}/k_C[b,c]
1:2[d]	78
1:1.5[d]	81

[a] On a 10–20 mmol scale. In benzene at 151–152 °C for 20 h. Ratio of materials (1 + 2)/tri-*n*-butyltin hydride/di-*tert*-butyl peroxide = 10:3:1. [b] Competitive rate ratio, calculated from calibrated initial and final ^1H NMR spectra by a standard method (M. J. Hutchinson and M. W. Mosher, *J. Chem. Educ.*, 48, 629 (1971)). The results are for several runs and are ±3%. [c] The reductions afforded tetramethylsilane from **1** and neopentane from **2**, each in >90% yield. [d] Excess **2** was employed to increase the precision of the results.

$$(CH_3)_3MCH_2Cl + \cdot Sn(n\text{-}C_4H_9)_3$$
$$\mathbf{1},\ M = Si;\quad \mathbf{2},\ M = C$$
$$\xrightarrow[\text{slow}]{k_{Cl}} (CH_3)_3MCH_2\cdot + ClSn(n\text{-}C_4H_9)_3 \qquad (1)$$
$$\text{fast} \downarrow HSn(n\text{-}C_4H_9)_3$$
$$(CH_3)_3MCH_3$$

Because literature data applicable to the free-energy content of **1** appear to vary significantly,[6] another approach to the selectivity in eq 1 was used, viz., internal competition. Here the problem of possible ground-state-energy differences between reactants disappears. The model chosen was 1,6-dichloro-2,2,5,5-tetramethyl-2-silahexane (**8**). Its synthesis (eq 2) commenced with the oxidation of the chloro alcohol **4** (Aldrich) to the chloro aldehyde **5**: pyridinium chlorochromate in methylene chloride;[12] 80% yield; bp ~100 °C (150 mm) (Kugelrohr); 2,4-DNP, mp 137–138 °C. Anal. Calcd for $C_{11}H_{13}ClN_4O_4$: N, 18.63. Found: N, 18.69. Conversion of aldehyde **5** to olefin **6** was accomplished via the Wittig reaction: dimsyl sodium;[13] methyltriphenylphosphonium bromide (or tosylate[14]); 30% yield; bp 108–109 °C (atm); ^1H NMR (CCl_4) δ 5.83, 5.12, 4.90 ($-CH{=}CH_2$) (ABX, J_{trans} = 18, J_{cis} = 9, J_{gem} = 3 Hz), 3.30 (s, $-CH_2Cl$), 1.10 (s, $-CH_3$); IR (neat) 3110, 1642, 928 ($-CH{=}CH_2$), 1382, 1368 (CH_3) cm^{-1}. Anal. Calcd for $C_6H_{11}Cl$: C, 60.76; H, 9.35. Found: C, 61.08; H, 9.50. Addition of silane **7**[15] to **6** in the presence of chloroplatinic acid afforded **8**: 71% yield, collected by GLC on DC-200 at 150 °C; ^1H NMR (CCl_4) δ 3.33 (s, $>CCH_2Cl$), 2.73 (s, $>SiCH_2Cl$), 1.53—1.17 (m, $>SiCH_2CH_2C<$), 0.97 (s, $>C(CH_3)_2$), 0.70–0.30 (m, $>SiCH_2CH_2C<$), 0.13 (s, $>Si(CH_3)_2$); IR (neat) 1390, 1370 ($>C(CH_3)_2$), 1260 ($>Si(CH_3)_2$) cm^{-1}. Anal. Calcd for $C_9H_{20}Cl_2Si$: C, 47.57; H, 8.87. Found: C, 47.83; H, 8.89.

$$ClCH_2C(CH_3)_2CH_2OH \quad \mathbf{4}$$
$$\xrightarrow[CH_2Cl_2]{pyrH^+\ CrO_3Cl^-} ClCH_2C(CH_3)_2CHO \quad \mathbf{5}$$
$$\downarrow [Ph_3P{=}CH_2]$$
$$ClCH_2C(CH_3)_2CH{=}CH_2 \quad \mathbf{6}$$
$$ClCH_2SiH(CH_3)_2\ (\mathbf{7}) \rightarrow (H_2PtCl_6)$$
$$ClCH_2Si(CH_3)_2CH_2CH_2C(CH_3)_2CH_2Cl \quad \mathbf{8} \qquad (2)$$

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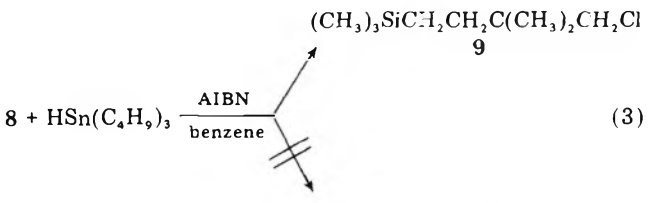
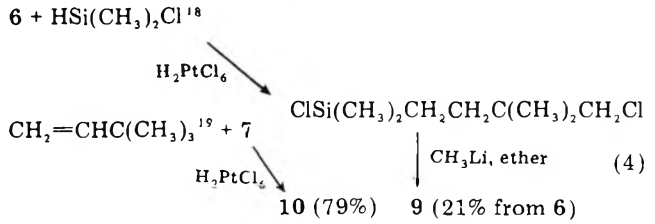
A sample reduction of **8** is described. In an NMR tube were placed **8** (45 mg, 0.198 mmol), tri-*n*-butyltin hydride (freshly prepared,[16] 61 mg, 0.209 mmol), azobisisobutyronitrile (Aldrich, 10 mg), and benzene (distilled Spectrograde material, 300 μL). Nitrogen was bubbled through the material briefly and the tube was capped. The solution was then irradiated in a small irradiation apparatus (Bradford Scientific Co.) at 366 nm and 37 °C (ambient) for 6.5 h. Processing the mixture directly by GLC (DC-200, 150 °C) afforded **9** in essentially quantitative yield based upon consumed reactants (94% reaction), with <5% (if any) of **10**, along with benzene and tri-*n*-butyltin chloride (eq 3).[17] For confirmation of their structures, chlorosilanes **9** and **10** were synthesized by the routes shown in eq 4. Chloro silane **9** was identical (spectra, GLC)



(3)



(4)

with the reduction product: ^{1}H NMR (CCl_4) δ 3.30 (s, $-CH_2Cl$), 1.53–1.17 (m, $>SiCH_2CH_2C<$), 1.0 (s, $>C(CH_3)_2$), 0.67–0.23 (m, $>SiCH_2CH_2C<$), 0.07 (s, $>Si(CH_3)_3$); IR (neat) 1383, 1367 ($>C(CH_3)_2$), 1252, 840–870 ($>Si(CH_3)_3$) cm^{-1}. Anal. Calcd for $C_9H_{21}ClSi$: C, 56.06; H, 10.98, Found: C, 55.72; H, 10.96. Chlorosilane **10** was distinguished from its isomer **9** most readily by its NMR spectrum: ^{1}H NMR (CCl_4) δ 2.73 (s, $-CH_2Cl$), 1.40–1.03 (m, $>SiCH_2CH_2C<$), 0.90 (s, $-C(CH_3)_3$), 0.77–0.32 (m, $>SiCH_2CH_2C<$), 0.12 (s, $>Si(CH_3)_2$); IR (neat) 1392, 1362 ($-C(CH_3)_3$), 1252 ($>Si(CH_3)_2$) cm^{-1}. Anal. Calcd for $C_9H_{21}ClSi$: C, 56.06; H, 10.98. Found: C, 55.67; H, 10.74.

Work is in progress on the reduction of other α-chlorosilanes and α-chloroalkanes, both by external and internal competition techniques, to establish the generality of the present findings.

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(18) Obtained from Silar Laboratories.
(19) Obtained from Aldrich Chemical Co.
(20) A portion of this work comes from the M. S. Thesis of P.M.A., Loyola University of Chicago, 1974.

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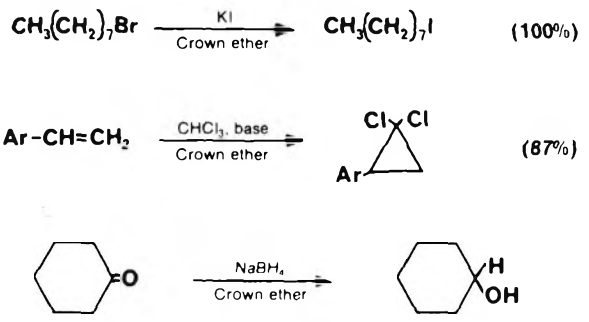
Crown Ethers: Macrocyclic Complexing Agents

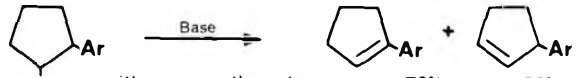
NOW AT GREATLY REDUCED PRICES

Crown ethers have become increasingly valuable tools in organic synthesis as a result of their remarkable ability to solvate alkali, alkaline earth and transition metal cations in nonpolar, aprotic solvents.[1] The selectivity of the crown ethers as complexing agents results from the definite size of the crown cavity, which only admits cations of comparable ionic radii.[2]

When a salt is dissolved in an aprotic solvent using a crown ether, the anion is exposed in such a way that it becomes highly reactive. The nucleophilicities of these exposed ("naked") anions toward organic and inorganic substrates have been the subject of increased research in recent years, as is evident from the following examples involving the use of crown ethers.

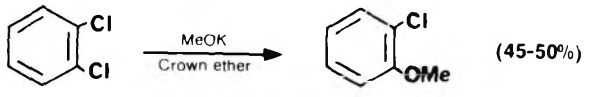


Crown ethers have been found to increase reactivity and influence product geometry.[6]

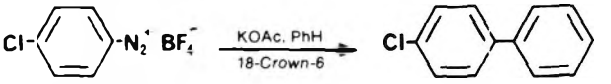


with crown ether, 1 hr	70%	30%
without crown ether, 42 hr	9.3%	90.7%

The use of catalytic amounts of crown ethers has been reported to *decrease* the reaction time of decarboxylations by a factor of 10^5.[7]



Crown ethers have been employed recently to study displacement reactions of alkyldiazonium compounds and the formation of unsymmetrical biaryls.[9]



Michael addition reactions are efficiently catalyzed by KF solubilized in aprotic solvents by **18-crown-6**.[10]

In peptide synthesis, **18-crown-6** was found to function as a catalyst in the quantitative esterification of a chloromethyl resin by the potassium salt of a *t*-Boc amino acid under mild reaction conditions.[11] In contrast to the above reaction the **18-crown-6** complex of potassium cyanide has been reported to cleave protected amino acids and peptides selectively from oxyacyl resins.[12]

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