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VOLUME 43, NUMBER 4 FEBRUARY 17, 1978

BENZYL MERCAPTANS

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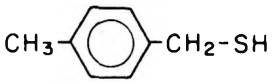
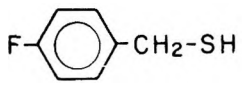


1374
o-Methylbenzyl mercaptan
25g 19.95

1373
m-Methylbenzyl mercaptan
25g 19.95

1375
p-Methylbenzyl mercaptan
25g 17.95



1011
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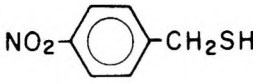
5g 34.85

2819
m-Fluorobenzyl mercaptan
5g 34.85

2914
p-Fluorobenzyl mercaptan
5g 22.50



1377
o-Nitrobenzyl mercaptan (80%)
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1376
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10g 12.50

1378
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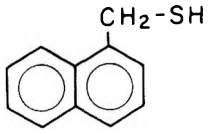
10g 12.50



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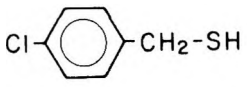

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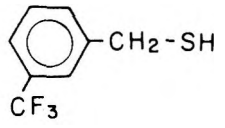
50g 13.25



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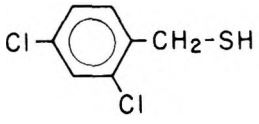

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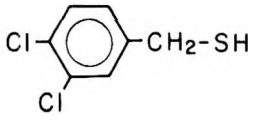

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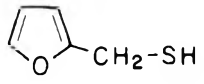
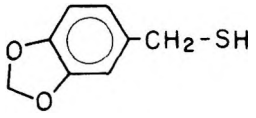


2442
Furfuryl mercaptan
25g 10.00 100g 31.25



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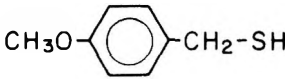

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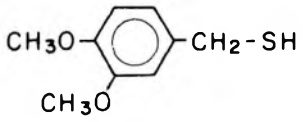

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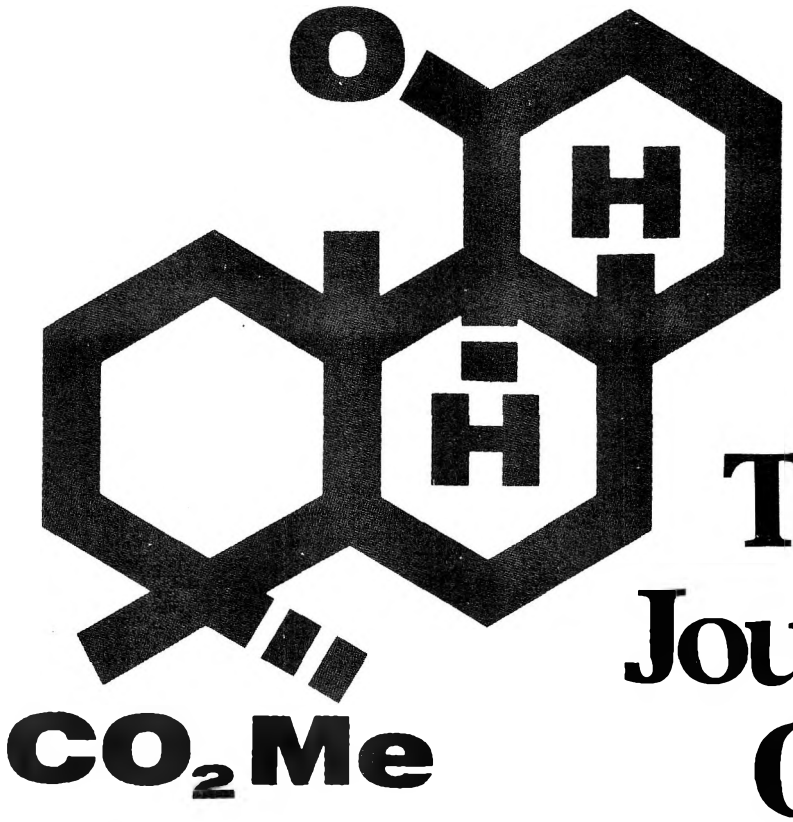

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VOLUME 43, NUMBER 4

FEBRUARY 17, 1978

Introduction of a New 1,3-Electrophilic C–N–C Annulation Reagent in the Synthesis of 2,2′-Anhydrodihydro-5-azathymidine[1]

Wendell Wierenga* and John A. Woltersom

Experimental Chemistry Research, The Upjohn Company, Kalamazoo, Michigan 49001

Received June 28, 1977

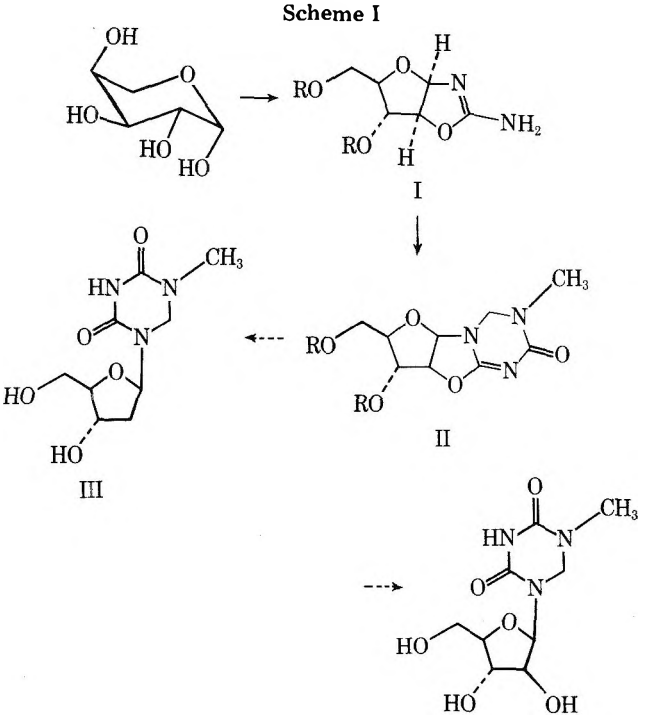
Dihydro-5-azathymidine [1-(2-deoxy-β-D-ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione], isolated from *Streptomyces platensis*, exhibits interesting antibacterial and antiviral properties. As a means of preparing several analogues of this new nucleoside, a synthetic route to the 2,2′-anhydronucleoside analogue was accomplished. The aminooxazoline of arabinose was exploited in a preparation of both possible isomeric triazine anhydronucleosides, II and VI, by direct annulation and a stepwise route, respectively. The conversion to the arabinose analogue is also described.

Recently an unusual nucleoside, III, was isolated from *Streptomyces platensis* (var. clarensis).[2] Besides the antibiotic activity exhibited by this deoxynucleoside, which was the reason for its isolation, interesting antiviral activity was also uncovered. Dihydro-5-azathymidine (1-(2-deoxy-β-D-ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione) demonstrated activity against DNA viruses, particularly against Herpes-type viral infection in vivo, both prophylactically and therapeutically, but was inactive against RNA viruses.[3]

Although no toxicity was noted in rats or mice, aplastic anemia developed in dogs and marrow suppression in cats and rabbits.[4] We initiated efforts to synthesize the 2,2′-anhydronucleoside II in an attempt both to minimize toxicity and maintain antiviral activity as well as to entertain the possibility of also securing the scarce, fermentation-derived nucleoside itself (III).[5] Anhydronucleosides have previously been exploited as key synthons for useful analogues such as ribo-, arabino-, and deoxynucleosides.[6]

As outlined in Scheme I, we envisioned a synthetic route which would exploit the ready availability of the aminooxazoline of arabinose, I. Several of the relevant key features of I are (1) it is prepared in a one-step, base-catalyzed condensation of the inexpensive sugar D-arabinose with cyanamide,[7] (2) it incorporates the prerequisite asymmetric centers for the planned synthesis, and (3) it has latent functionality for the desired triazine ring of II. We wish to report herein the successful utilization of I to prepare, via direct annulation, the anhydronucleoside, II, prefaced by an alternate approach which introduces the requisite three atoms of the isomeric triazine-ring system in a stepwise manner.

Scheme I



Results and Discussion

Our initial endeavors evolved from the concept of a stepwise buildup of the required triazine ring system of II. However, this chemistry required protection of the diol group in I. The primary requirements for acceptable protecting groups were (1) base stability, (2) inability to employ acid removal due to the rapid protonic decomposition of II or III,[8] (3) enhanced lipophilicity for chemical and analytical manipulatability, and (4) the obvious regioselectivity for the 3′,5′-diol. We were pleased to find that the *tert*-butyldimethylsilyl group[9] fulfilled these criteria. The excellent adaptability of this group to nucleosides was concurrently reported by Ogilvie and coworkers.[10]

Treatment of the DMF-insoluble I with *tert*-butyldimethylsilyl chloride under standard conditions afforded the

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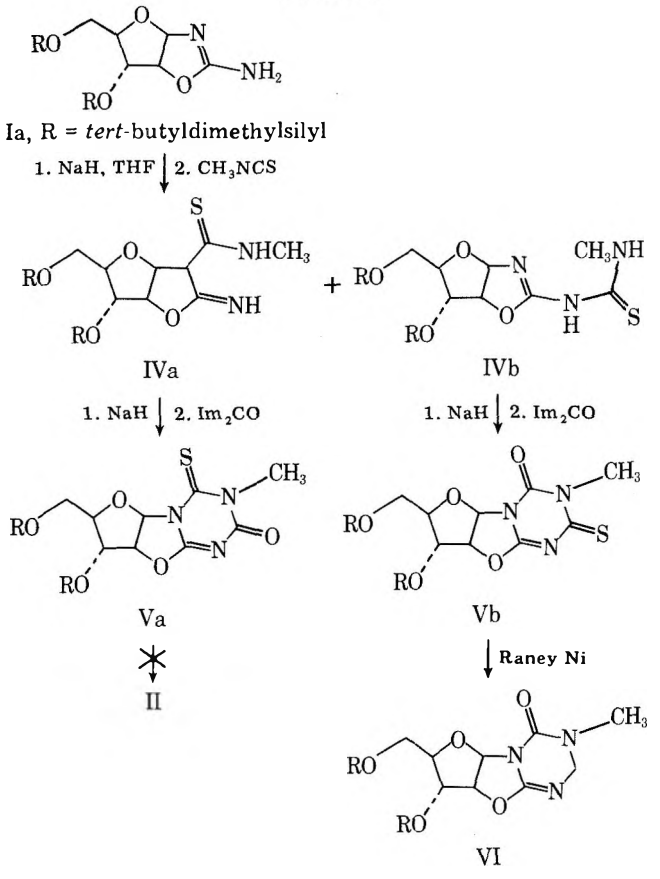
bis(silyl) ether Ia in 85–90% yields recrystallized from hexane. The silyl ether protection allowed a wide range of solvent choices in subsequent chemistry as well as in ready GC and GC–MS analyses.

The aminooxazoline moiety, because of its unsymmetrical, ambident amidine function, has the inherent problem of regioselectivity, both in predicting which nitrogen will be the initial reaction site and then in the structural determination after the fact.[11] When Ia was treated with sodium hydride (NaH) followed by methyl isocyanate, only one product (90%) was produced (Scheme II).[12] However, when methyl isothiocyanate was employed, both isomers (IVa and IVb) were produced in similarly high yield in a 50:50 mixture. Simply heating in THF without base afforded primarily the desired IVa.

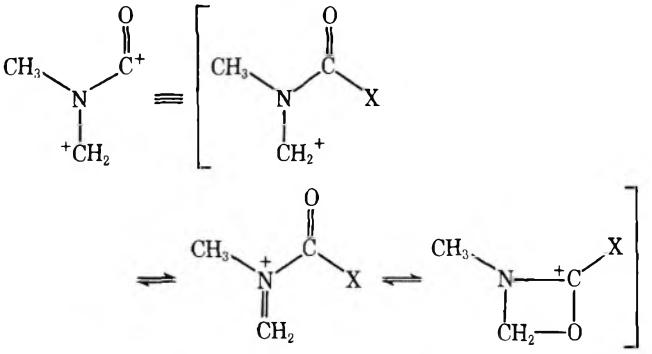
Scheme II



Ring closure with 1,1′-carbonyldiimidazole of either IVa or IVb individually or as a mixture yielded the triazine thiones, Va and Vb, in 95% yield, separable by HPLC (silica gel). Indeed, the conversion of Ia to Va and Vb could be accomplished more efficiently with comparable yields utilizing 1 equiv of base followed by sequential methyl isothiocyanate–carbonyldiimidazole treatment. Unfortunately, we were unable to reductively desulfurize Va to the desired anhydronucleoside II, even though this was readily accomplished with the undesired isomer Vb to yield VI in 65% yield using Raney nickel.[13] Exploring other reduction procedures such as phosphites or borohydrides proved fruitless.

The structure assignments are based on IR, NMR, and UV data with particular emphasis on ^{13}C NMR and lanthanide-shift studies (vide infra) in conjunction with the interrelating chemistry of the isomeric series.

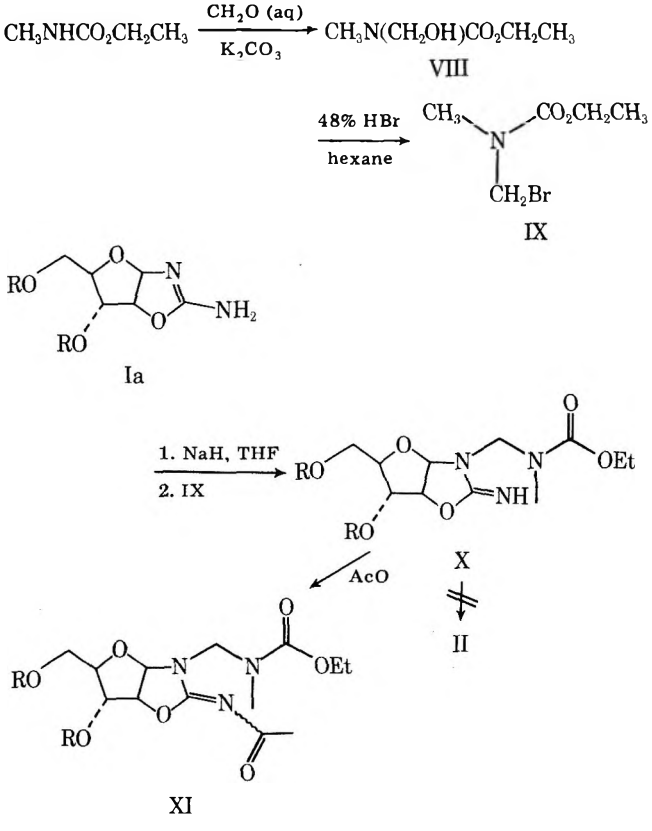
The utility of an approach to nucleoside synthesis based on a three-atom annulation of the aminooxazoline of arabinose has several precedents. These have all involved the three-carbon propriolonitrile (ester) or a functional equivalent to generate the desired regiochemical pyrimidine-ring isomer.[14] As a means of circumventing the problems encountered with the stepwise approach, we initiated efforts to devise an annulation reagent that exhibited the selective alkylation required of the unsymmetrical amidine grouping of the aminooxazoline, that had the desired oxidation state, and that was readily available. Such a species is depicted by VII, wherein X is an appropriate leaving group.



VII

We initially attempted to generate an *N*-carbethoxy-*N*-methyl iminium species via hydride abstraction on ethyl-*N*,*N*-dimethylcarbamate with trityl fluoroborate[15] in chloroform. Even though a high yield of triphenylmethane was realized, the presumed iminium species proved too reactive to utilize directly. A more stable equivalent appeared to be a Mannich-type base such as IX (Scheme III). This was prepared by formaldehyde condensation with methylurethane to yield the hydroxymethylcarbamate, VIII. After a variety of unsuccessful attempts to convert the hydroxyl to a chloro or mesylate group, we found that a two-phase hydrobromic acid system afforded the bromomethylurethane, IX, in 75–80% yield. The reagent is isolated simply by decantation and concentration of the organic phase. It is characterized by a

Scheme III



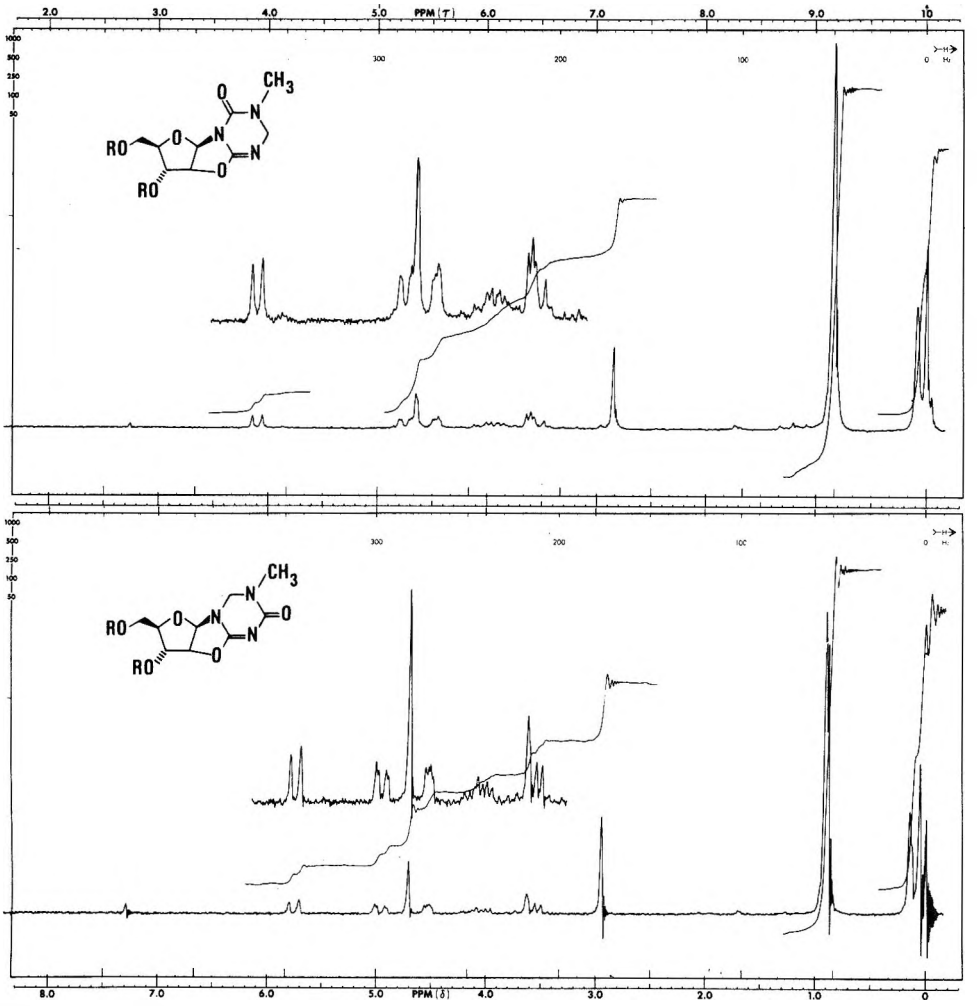


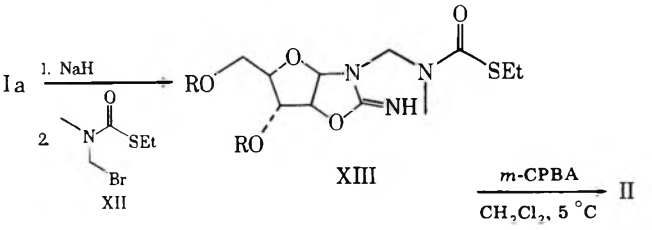
Figure 1. ^{1}H NMR spectra of compounds VI (top) and II (bottom).

shift in the methylene ^{1}H NMR resonance from δ 4.88 to 5.35. Even though it is unstable to standard TLC or column chromatography (silica gel), it can be stored for several weeks in benzene at 0 °C with little decomposition.

Generation of the sodium salt of aminooxazoline Ia followed by addition of the annulation reagent yielded primarily the ring-alkylated derivative X (75% yield). No ring-closed material was detected. That the structure of X is correctly assigned is based not only on spectral characterization and subsequent chemistry but also by acylation with acetic anhydride to XI. The ^{1}H NMR spectrum of XI exhibited two equivalent CH_3CO singlets at δ 2.04 and 2.15, as well as a λ_{max} of 232 nm (ε 9500) in the UV spectrum. If initial alkylation with IX had occurred at the amino nitrogen, the two possible products of acylation would not exhibit these UV characteristics.

Although the annulation reagent, IX, is a potential 1,3 electrophile, the carbamoyl carbonyl proved resistant to intramolecular nucleophilic attack in this system to effect ring closure to the desired 2,2′-anhydronucleoside, II. A variety of conditions (acid, base, neutral, and thermal[16a]) and several leaving groups (OCH_3, OCH_2CH_3, and OCH_2Ph) were tried without success. In attempting to employ better leaving groups, such as phenoxy, we were unable to prepare the annulation reagent under the described conditions.[17a]

To enhance the electrophilicity of the carbamoyl group and still preserve the excellent regioselectivity of IX, we turned to the thiocarbamate system with the idea of modifying the valence of sulfur after alkylation to improve its leaving group capacity with concomitant cyclization. The thiocarbamate reagent, XII,[17b] was prepared analogously to IX, and alkylation proceeded smoothly to XIII (50% yield). Again acylation yielded two isomeric acylimides with a λ_{max} of 233 nm (ε 17 500). Treatment of XIII with 2 equiv of *m*-chloroperoxybenzoic acid (*m*-CPBA) afforded the desired II in 75% yield.



It is presumed that the oxidative cyclization proceeds through the carbamoyl sulfone as an intermediate since 2 equiv of peracid are required.[16b,18] Activation of thioesters to intermolecular nucleophilic substitution by oxidation at sulfur was first reported by Kumamoto and Mukaiyama[19a] and later utilized in an intramolecular application by Masamune and co-workers.[19b]

Now in hand were the two possible anhydronucleoside isomers, VI and II, as indicated by elemental composition and mass spectrometry [characteristic *m/e* 414 (M^+ − *tert*-butyl)]. IR and UV spectra strongly supported the assigned structures with VI exhibiting a C=O at 1750 cm^{-1} and a λ_{max} of 217 nm, whereas II exhibited a C=O at 1665 cm^{-1} and a λ_{max} of 238 nm (ε 4050) in ethanol, with a bathochromic shift to 227 nm (ε 3950) in ether.

Since the ^{1}H NMR spectrum was not definitive in confirming the structural assignments (Figure 1), we investigated

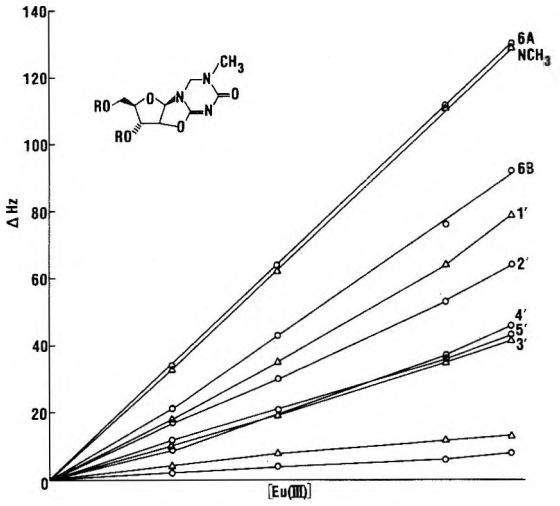


Figure 2. Lanthanide-induced-shift study of compound II using $Eu(dmp)_3$.

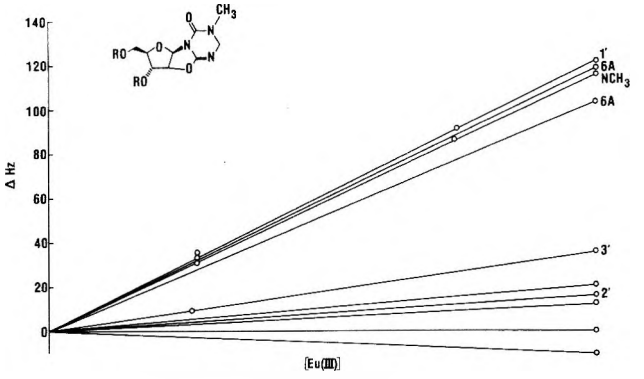


Figure 3. Lanthanide-induced-shift study of compound VI using $Eu(dmp)_3$.

the possible use of a lanthanide-induced-shift study. Although this technique has seen limited application in nucleoside structure determinations due to solubility difficulties in noncomplexing solvents, competing sites for complexation, and often rapid glycosidic bond rotation, we anticipated a possible use since these problems were minimized or nonexistent in II and VI. Indeed, the use of $Eu(dmp)_3$ afforded linear shifts (Figures 2 and 3), suggesting predominate carbonyl complexation over the concentration range investigated. Eu(III) complexation of the C-4 carbonyl isomer (II, Figure 2) exhibited maximal effects on the more proximate N-CH_3 and C-6 hydrogens, whereas the C-6 carbonyl isomer (VI, Figure 3) showed a more pronounced effect on the C-1′ hydrogen relative to the N-CH_3 and C-4 hydrogens.

The calculated values arising from an LISC program generator[20] utilizing x-ray coordinates from dihydro-5-azathymidine (III)[21] allowed for an acceptable fit of the experimental shift data. The results of the computer simulation are summarized in Table I.

Table II denotes the pertinent ^{13}C NMR data for the isomeric series VI, II, Va, and Vb. The assignments are based primarily on the data obtained for similar compounds as detailed in Tables III and IV. Of interest is the trend delineated in Table II, where the carbonyl resonance is shifted downfield 13 ppm when conjugated with the C=N (VI to II) and the thiocarbonyl is shifted 13.8 ppm downfield (Va to Vb). Similarly, the β effect on C-2 is a downfield shift of 0.2–4.4 ppm in proceeding from VI to II, Va, or Vb. Although this phenomenon is opposite to that generally seen with α,β-C=C conjugated carbonyls, it is consistent with other anhydropyrimidine nucleosides.[23-25]

Table I

	II	VI
Computed positional parameter for Eu(III)	2.5 Å	2.3 Å
	107°	90°
	145°	140°
R factors[a]		
Correct	0.079	0.072
Incorrect	0.244	0.222
R-factor ratio	3.09	3.08

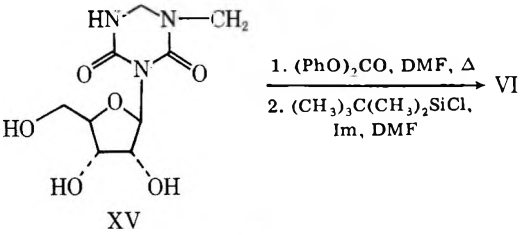
[a] Based on use of six protons in the calculations.

Table II[a]

	VI	II	Va	Vb
C-2	152.8	157.2	153.0	155.9
C-4	64.8	162.8	159.3	187.9
C-6	149.8	59.4	174.1	145.8
N-CH_3	31.0	33.1	34.9	34.9

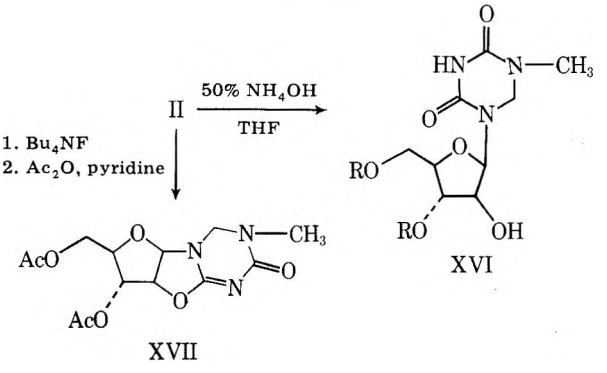
[a] The assignments are given in ppm in $CDCl_3$ (0.1–0.4 M) with a 0.5-s acquisition time. Only the triazine-ring structure is shown, as the bis(silyl)-protected furanose was deleted for simplification.

As an ultimate confirmation for the anhydronucleoside VI, we were able to prepare it by independent chemistry employing the diphenyl carbonate mediated[27] dehydration of riboside XV.[25] This was shown to be identical to VI by TLC, GC, NMR, and mass spectral comparison.



The 2,2′-anhydrodihydro-5-azathymidine (II) exhibited the usual property of facile base hydrolysis to afford the arabinose[6] XVI (Scheme IV), as indicated by the loss of the

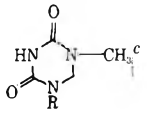
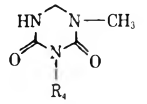
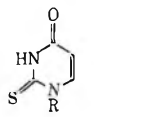
Scheme IV



UV-absorbing chomophore at 233 nm and confirmed by the characteristic upfield shift of the C-2′ hydrogen in the ^1H NMR spectrum.[27] Employing conventional procedures,[6] we were unable to convert II to the parent deoxynucleoside, III.

Removal of the *tert*-butyldimethylsilyl protecting groups

Table III[a]

	R	Registry no.	C-2	C-4	C-6	N–CH_3
	H	64332-47-4	153.3[b]	153.6[b]	56.0	31.2
	R_1	57350-36-4	154.6[b]	155.0[b]	57.0	32.7
	R_2	64332-48-5	152.2[b]	152.5[b]	56.7	32.3
	R_3	64332-49-6	153.9[b]	158.8[b]	57.0	35.1
	R_4[25]	64332-50-9	153.7[b]	55.7	152.0[b]	33.0
	H	141-90-2	175.5	160.5		

[a] The assignments are given in ppm in $CDCl_3$ (0.15–0.2 M), unless otherwise noted, with a 0.5-s acquisition time. R_1 = 2′-deoxy-β-D-ribofuranose, R_2 = triacetyl-β-D-arabinofuranose, R_3 = 3′,5′-bis(*tert*-butyldimethylsilyl)-β-D-arabinofuranose, and R_4 = β-D-ribofuranose. [b] Values may be interchanged. [c] In Me_2SO-d_6. [d] In D_2O.[22]

was readily effected with tetra-*n*-butylammonium fluoride in THF, affording XVII in 84% yield after acetylation. This chemistry worked equally well with VI.

Experimental Section

General. All solvents employed were reagent grade. Tetrahydrofuran was distilled from sodium/benzophenone under N_2 prior to use. All reagents were used as received, and moisture-sensitive materials were stored over indicating calcium sulfate.

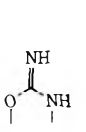
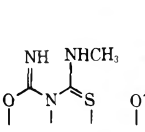
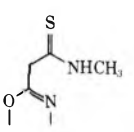
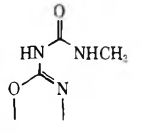
^1H NMR spectra were recorded on either Varian A-60-A or T-60 spectrometers in $CDCl_3$ with internal Me_4Si unless otherwise noted. GC–MS data were recorded on either LKB 9000 or Varian Mat CH-7 instruments. ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer with all values referenced to internal Me_4Si. GC was performed on a Hewlett-Packard 402 instrument with glass columns and He carrier gas.

2-Amino-3′,5′-bis(*O*-*tert*-butyldimethylsilyl)-β-D-arabinofuran[1′,2′:4,5]-2-oxazoline (Ia). To 3.48 g (0.02 mol) of 2-amino-β-D-arabinofuran[1′,2′:4,5]-2-oxazoline[14e] in 50 mL of dry DMF (dimethylformamide, distilled from CaH_2 and stored over activated 4-A molecular sieves) under N_2 in an ice bath was added 3.40 g (0.05 mol) of imidazole, followed by 7.5 g (0.05 mol) of *tert*-butyldimethylsilyl chloride. After 15 min, the now homogeneous solution was allowed to come to room temperature and was stirred for another 2 h. The solution was poured into a stirred, cold 2% sodium carbonate solution (300 mL), filtered after 10 min, washed with 50 mL of cold water, and then allowed to partially dry at room temperature for several hours. The off-white solid was azeotroped once with benzene and then dissolved in hexane (250 mL) with heating, allowed to crystallize, and then filtered and dried at room temperature. Final recovery from the mother liquor yielded a total of 7.0 g (87% yield). An analytical sample recrystallized from hexane had mp 172–173 °C (the product will sublime in vacuo); IR (CCl_4) 1705 cm^{-1} (C=N); NMR δ 5.88 (1 H, d, J = 5.5 Hz, C-1′), 4.50 (1 H, dd, J = 5.5 Hz, C-2′), 4.37 (1 H, m, C-3), 4.3 (2 H, br, NH_2), 3.83 (1 H, m, C-4), 3.62 (2 H, m, C-5), 0.90 (18 H, s, *tert*-butyl), 0.13 and 0.08 (9 H, s, CH_3); TLC, R_f 0.22 (85% EtOAc/hexane); GC, 1.9 min (270 °C, 6 ft, 3.8% UCW-98); GC–MS 402 (no M^+), 387 (2, M – CH_3), 345 (12, M – *tert*-butyl), 261 (29), 97 (35), 89 (100).

Anal. Calcd for $C_{18}H_{38}N_2O_4Si_2$: C, 53.69; H, 9.51; N, 6.96. Found: C, 53.24; H, 9.38; N, 6.78.

3′,5′-Bis(*O*-*tert*-butyldimethylsilyl)-β-D-arabinofuran-[1′,2′:4,5]oxazolo-5-methyl-4-thiono-1,3,5-triazin-6-one (Vb). To 51 mg (1.0 mmol) of 45% NaH (washed twice with hexane) in 10 mL of dry THF at room temperature under N_2 was added 402 mg (1 mmol) of the aminooxazoline Ia in several portions. After 30 min of stirring, the reaction was cooled in an ice bath and 75 μL of CH_3NCS in 125 μL of THF was added dropwise over 10 min. Stirring was continued for 1 h at 5 °C and then for 30 min while warming to room temperature. The solution was taken up in EtOAc, washed with water and brine, and dried over Na_2SO_4. After concentration, the solution was dissolved in 50% EtOAc/hexane and rapidly passed through a 15-g silica gel column with the same solvent. The UV-absorbing material was collected and concentrated, yielding 410 mg (86% yield) of a yellow oil. Separation of the isomers can be achieved by careful column chromatography to ~80% of a single component. NMR (approximately an equal mixture of the two isomers) δ 6.93 and 6.00 (d, J = 5.5 Hz, C-1′), 4.80 and 4.70 (d, J = 5.5 Hz, C-2′), 3.18 and 3.10 (d, J = 5 Hz, N–CH_3); TLC, R_f 0.55 (25% EtOAc/hexane), 0.37 (both UV-active); LC, t_R = 5.0 and 15 min with 2.5% EtOAc/hexane at 1.5 mL/min on a 12-in Lichrosorb SI-60 column.

Table IV[a]

	 Ia	 IVa	 IVb	 XIII
C-2	162.9	155.3	163.2	158.5
C-4			189.8	169.9
C-6		170.8		56.2
N–CH_3		32.1	31.9	34.6

[a] The assignments are given in ppm in $CDCl_3$ (0.1–0.4 M) with 0.5-s acquisition time. Only the triazine-ring structure is shown, as the bis(silyl)-protected furanose was deleted for simplification.

A 410-mg amount of the isomers was treated with 43 mg of hexane-washed NaH (45% oil dispersion) in 5 mL of dry THF at room temperature under N_2 with stirring. After gas evolution ceased, 275 mg of carbonyldiimidazole (1.7 mmol) was added, and the reaction was stirred for 24 h. The heterogeneous solution was worked up as above, including the rapid chromatography, to yield 415 mg (83%) of a yellow solid: IR ($CHCl_3$) 1730 and 1645 cm^{-1} (C=N, C=O) 1100 (C=S); NMR, isomer Va, δ 6.65 (1 H, d, J = 5.5 Hz, C-1′), 5.15 (1 H, d, J = 5.5 Hz, C-2′), 3.66 (3 H, s, N–CH_3); NMR, isomer Vb, δ 6.43 (1 H, d, J = 5.5 Hz, C-1′), 5.23 (1 H, dd, J = 5.5 Hz, C-2′), 3.66 (3 H, s, N–CH_3); TLC, one spot, R_f 0.43 (25% EtOAc/hexane); GC, Va, 7.4 min (55%), Vb, 8.7 min (45%) (265 °C, 4 ft, 3.8% UCW-98); LC, isomer A, t_R = 18 min, isomer B, 21 min (5% EtOAc/hexane at 1.5 mL/min on a 12-in Lichrosorb SI-60 column); (repeated crystallization from ethanol yielded pure isomer Vb with mp 160–161 °C) GC–MS, Va, 501 (no M^+), 444 (23, M^+ – *tert*-butyl), 298 (26), 261 (62), 231 (31), 89 (100); GC–MS, Vb (no M^+), 444 (M^+ – *tert*-butyl), 261 (65), 231 (33), 184 (46), 89 (100).

3′,5′-Bis(*O*-*tert*-butyldimethylsilyl)-β-D-arabinofuran-[1′,2′:4,5]oxazolo-5-methyl-1,3,5-triazin(4,4*H*)-6-one (VI). A 415-mg amount (0.83 mmol) of the ca. 1:1 Va and b isomer mixture was dissolved in absolute ethanol (10 mL) and stirred with 1 mL of Raney nickel (active No. 28, Grace), which had been washed with distilled water extensively and then ethanol likewise. After 1 h at room

temperature, the solution was filtered and concentrated on the rotovapor. GLPC analysis indicated a new peak (6.2 min) with concomitant disappearance of isomer Vb (15.5 min at 250 °C, 4 ft, 3.8% UCW-98; isomer Va still substantially present). The resultant oil was chromatographed employing 60% EtOAc/hexane on a Merck B silica gel column with a 2.0 mL/min flow rate. A 120-mg amount (32% yield) of a colorless oil, which is an overall yield of 20% from Ia, was recovered: IR (CCl_4) 1750 cm^{-1} (C=O), 1720 (C=N); NMR δ 6.18 (1 H, d, J = 5.5 Hz, C-1′), 4.82 (1 H, dd, J = 5.5 Hz, C-2′), 4.72 (2 H, "d" or AB, J < 1 Hz, C-4), 4.55 (1 H, m, C-3′), 3.95 (1 H, m, C-4′), 3.65 (2 H, m, C-5′), 2.90 (3 H, s, N-CH_3), 0.88 (18 H, s, *tert*-butyl), 0.13 and 0.05 (9 H, s, CH_3-Si); UV (EtOH) λ_{min} 265 nm sh (ϵ 350); UV λ_{max} 215–220 nm (ϵ 2000); MS M^+ 471.2560 (calcd for $C_{21}H_{41}N_3O_5Si_2$), 471.2584 (found); GC–MS 471 (no M^+), 456 (2, $M^+ - CH_3$), 414 (14, M^+ – *tert*-butyl), 261 (32), 231 (16), 89 (100); $[\alpha]_D$ −140 ± 14° (EtOH); ORD, $[\phi]_{229}$ −12 400 (trough); CD, $[\theta]_{218}$ −7300 (shoulder); TLC, R_f 0.57 (85% EtOAc/hexane).

3′,5′-Bis(*O*-acetyl)-β-D-arabinofuran[1′,2′:4,5]oxazolo-5-methyl-1,3,5-triazin(4,4*H*)-6-one. To 680 mg (1.45 mmol) of the bis(silyl)-2,2′-anhydro-VI in 20 mL of dry THF under N_2 at room temperature was added with stirring 4.9 mL of tetra-*n*-butylammonium fluoride solution in THF (prepared by the procedure of Pless[28] to a concentration of 0.65 mmol/mL in THF and stored under N_2 over activated 4-Å molecular sieves at 5 °C). After 2 h, the solution was concentrated and placed under 0.01 Torr for 1 h. The resultant gum was taken up in 10 mL of dry pyridine, to which was added, under N_2 with stirring, 3 mL of distilled acetic anhydride. After 4 h at room temperature, the solution was concentrated under high vacuum, taken up in EtOAc, and added to a 100-g silica gel column prepared in the same solvent. After elution with 200 mL of EtOAc, the solvent was changed to 5% MeOH in EtOAc. A 380-mg (80% yield) amount of product was recovered: NMR δ 6.30 (1 H, d, J = 5.5 Hz, C-1′), 5.30 (1 H, m, C-3′), 5.08 (1 H, d, J = 5.5 Hz, C-2′), 4.77 (2 H, J_{AB} = −11 Hz, C-4), 4.0–4.6 (3 H, m, C-4′,5′), 2.91 (3 H, s, N-CH_3), 2.13 and 2.10 (6 H, s, CH_3CO); TLC, R_f 0.49 (10% MeOH/EtOAc); GC, 2.6 min (240 °C, 3.8% UCW-98, 4 ft); GC–MS 327 (3, M^+), 284 (3, $M^+ - CH_3CO$), 225 (12, $M^+ - CH_3 - 2\,CH_3CO$), 183 (22), 128 (100).

Cyclization of 3-β-D-Ribofuranosyl-5-methyl-1,3,5-triazin(4,4*H*)-6-one to the 2,2′-Anhydroarabinofuranosyl. To 300 mg (1.1 mmol) of the riboside XV in 5 mL of dry DMF under N_2 was added 490 mg (2.3 mmol) of diphenyl carbonate and 20 mg of sodium bicarbonate. The stirred solution was heated to 145 °C for 30 min. The resulting brown solution was cooled and poured into 200 mL of ether with stirring. The brown solid was collected by decantation and washed with another 50 mL of ether. It was then taken up in 20 mL of dry DMF, to which was added, under N_2 with stirring, 375 mg (2.5 mmol) of *tert*-butyldimethylsilyl chloride and 173 mg of imidazole. After 3 h at room temperature, the solution was taken up in 100 mL of EtOAc and washed with 50 mL of water, followed by brine. The initial aqueous phase was back-extracted with EtOAc, and this was combined, dried over Na_2SO_4, and concentrated. Chromatography on a Merck silica gel A column employing 40% EtOAc/hexane yielded 20 mg (4% yield) of the anhydro-2,2′-nucleoside. This was identical with VI by TLC (85 and 50% EtOAc/hexane), GC (265 °C, 3.8% UCW-98, 6 ft, 6.0 min), ^1H NMR, and GC–MS.

***S*-Ethyl *N*-Methylthiocarbamate.** To 20 mL of dry ether under N_2 was added 6.0 mL (7.14 g, 0.115 mol) of ethanethiol. The solution was cooled in an ice bath, and 5 mg of a 45% NaH/oil dispersion was added, followed by the rapid dropwise addition of 3.0 mL (4.0 g, 0.07 mol) of methyl isocyanate. Approximately 15 min after the addition was completed, the reaction was taken up in 100 mL of ether, washed with a 50% saturated brine solution (25 mL), dried over $MgSO_4$, and concentrated at reduced pressure to yield 6.3 g (75%): bp 62–68 °C (0.3 mm); NMR δ 6.0 (1 H, brd s, NH), 2.92 (2 H, q, J = 7 Hz, SCH_2), 2.87 (3 H, d, J = 4 Hz, NCH_3), 1.27 (3 H, t, J = 7 Hz, CH_3).

Anal. Calcd for C_4H_9NOS: C, 40.31; H, 7.61; N, 11.75. Found: C, 40.40; H, 7.66; N, 12.64.

S-Ethyl *N*-Hydroxymethyl-*N*-methylthiocarbamate. To 6.3 g (0.053 mol) of the *N*-methylthiocarbamate in 20 mL of water were added 5 mL of 37% formaldehyde, 50 mg of potassium carbamate, and 3 mL of MeOH. The reaction solution was stirred for 2 h at room temperature. Approximately 20 mL of saturated NaCl (aqueous) was added, and the mixture was extracted with 2 × 75 mL of methylene chloride. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. TLC analysis indicated the usual mixture of starting material and desired product. The mixture was resolved by a 200-g silica gel column employing 40% EtOAc/hexane eluant. The product was obtained in 49% yield (3.85 g). The recovered starting material can be recycled. IR (neat) 3400 cm^{-1} (OH), 1650 (C=O); ^1H NMR δ 4.88 (2 H, s, CH_2OH), 4.6 (1 H, brd s, OH), 3.03 (3 H, s, N-CH_3), 2.90 and 1.27 (SCH_2CH_3); ^{13}C NMR 170.05 ppm (C=O), 72.57 (NCH_2O), 33.71 (NCH_3), 24.67 (SCH_2), 15.18 (CH_3); TLC, R_f 0.41 (50% EtOAc/hexane).

Anal. Calcd for $C_5H_{11}NO_2S$: C, 40.24; H, 7.43; N, 9.39. Found: C, 40.01; H, 7.97; N, 9.37. Ethyl *N*-hydroxymethyl-*N*-methylcarbamate is prepared analogously.

S-Ethyl *N*-Bromomethyl-*N*-methylthiocarbamate (XII). To 300 mg (2.0 mmol) of the hydroxymethylthiocarbamate in 15 mL of hexane/1 mL of benzene were added 87 mg (1 mmol) of lithium bromide (anhydrous) and 2.0 mL of 48% hydrobromic acid. The solution was stirred vigorously under N_2 for 2.5 h, following which the organic phase was decanted off. The aqueous phase was washed once with 10 mL of hexane and then combined with the hexane/benzene mixture and concentrated (rotovapor), followed by the addition of 10 mL of benzene and reconcentrating to give 400 mg of a slightly yellow oil. The NMR spectrum ($CDCl_3$) indicated ca. 75–80% bromide (δ 5.38 singlet for CH_2Br and NCH_3 singlet at δ 3.32) and 20–25% starting material. The starting material was also noted by TLC. However, the bromide product appeared to decompose on silica gel TLC. The bromide product was usually utilized immediately after preparation but could be stored in benzene at <0 °C for several months. The yield (NMR-based) was ca. 70%.

1-(*S*-Ethyl *N*-Methyl-*N*-methylenethiocarbamoyl)-3′,5′-bis(*O*-*tert*-butyldimethylsilyl)-β-D-arabinofuran[1′,2′:4,5]-2-oxazolimine (XIII). To 51 mg (1 mmol) of 45% NaH/oil dispersion (washed twice with hexane) in 10 mL of dry THF under N_2 at room temperature was added 402 mg (1 mmol) of the bis(TBDMS)aminooxazoline Ia in several portions. After gas evolution ceased, 400 mg (ca. 1.4 mmol, 75% purity) of the bromomethylthiourethane (XII) was added dropwise (in ca. 1 mL of THF via a glass pipette) with stirring over a 5-min period. After stirring for 1 h, the heterogeneous solution was taken up in EtOAc, washed once with 50% saturated saline, dried over Na_2SO_4, and concentrated. Column chromatography (Merck silica gel B, 5 EtOAc/hexane) afforded 255 mg (48% yield) of the monoalkylated product (usually a smaller amount of slightly higher R_f bis(alkylated)oxazolimine was seen by TLC, depending on how much starting material remained): IR (neat) 3350 cm^{-1} (NH), 1700 (C=N), 1665 (C=O); NMR δ 5.82 (1 H, d, J = 5.5 Hz, C-1′), 5.00 (2 H, dd, J_{AB} = −15 Hz, no collapse with MeOH-d_4 and D_2O, C-6), 4.95 (1 H, s, NH), 4.67 (1 H, d, J = 5.5 Hz, C-2′), 4.48 (1 H, m, C-3′), 4.0 (1 H, m, C-4′), 3.62 (2 H, m, C-5′), 3.13 (3 H, s, N-CH_3), 2.99 (2 H, q, J = 7 Hz, S-CH_2), 1.35 (3 H, t, J = 7 Hz, CH_3), 0.91 (18 H, s, *tert*-butyl), 0.15 and 0.07 (9 H, s, CH_3-Si); TLC, R_f 0.50 (50% EtOAc/hexane); GC, 5.8 min (4 ft, 3.8% UCW-98, 260 °C); GC–MS for *S*-methyl ester, 519 (M^+), 504 ($M^+ - CH_3$), 462 (M^+ – *tert*-butyl), 444 ($M^+ - CO_2Et$), 415 (M^+ – *tert*-butyl – OEt), 261 (100).

3-(*S*-Ethyl *N*-Methyl-*N*-methylenethiocarbamoyl)-1-*N*-acetyl-3′,5′-bis(*O*-*tert*-butyldimethylsilyl)-β-D-arabinofuran-[1′,2′:4,5]-2-oxazolimine. To 53 mg (0.1 mmol) of XIII in 2 mL of distilled acetic anhydride at room temperature under N_2 was added 20 mg of anhydrous sodium acetate. After stirring for 30 min, the reaction solution was concentrated. The resulting oil was taken up in EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated to yield 57 mg (100%): IR ($CHCl_3$) 1610–1670 cm^{-1} [broad C=O (C=N)]; UV (EtOH) λ_{max} 233 nm (ϵ 17 500), OEt analogue – λ_{max} = 232 nm (ϵ 9500); NMR ($CDCl_3$) two equivalent CH_3CO singlets at δ 2.04 and 2.15; TLC, R_f 0.61 (50% EtOAc/hexane).

3′,5′-Bis(*O*-*tert*-butyldimethylsilyl)-β-D-arabinofuran-[1′,2′:4,5]oxazolo-5-methyl-1,3,5-triazin(6,6*H*)-4-one (II). To 25 mL of dichloromethane was added 530 mg (1 mmol) of the thiocarbamoyloxazoline XIII, followed by cooling to 5 °C under N_2. With stirring, 500 mg (2.2 mmol, 81% pure) of *m*-chloroperbenzoic acid was added followed by 130 mg (1 mmol) of sodium carbonate. After 1 h at 5 °C followed by 1 h at room temperature, the solution was taken up in EtOAc, washed with saturated sodium bicarbonate and then brine, dried over Na_2SO_4, and concentrated. Chromatography on a Merck A silica gel column employing 90% EtOAc/hexane afforded 370 mg of a white solid (77% yield). Recrystallization from hexane gave mp 145–147 °C (sublimation noted); IR (CCl_4) 1665 cm^{-1} (C=O, C=N); NMR δ 5.82 (1 H, d, J = 5.5 Hz, C-1′), 4.99 (1 H, d, J = 5.5 Hz, C-2′), 4.72 (2 H, s, C-6), 4.52 (1 H, m, C-3′), 4.07 (1 H, m, C-4′), 3.60 (2 H, m, C-5′), 2.93 (3 H, s, N-CH_3), 0.90 and 0.87 (18 H, s, *tert*-butyl), 0.15 and 0.06 (9 H, s, CH_3Si); UV (EtOH) λ_{max} 238 nm (ϵ 4050); UV (EtO_2) λ_{max} 227 nm (3950); MS 471 (no M^+), 456 ($M^+ - CH_3$), 414 (M^+ – *tert*-butyl); $[\alpha]_D$ −130 ± 16°; ORD, $[\phi]_{258}$ −20 300 (0 at 239 mμ) $[\phi]_{218}$ +17 800; CD, $[\theta]_{241}$ −28 400; TLC, R_f 0.12 (85% EtOAc/hexane).

Anal. Calcd for $C_{21}H_{41}N_3O_5Si_2$: C, 53.47; H, 8.76; N, 8.90. Found: C, 53.54; H, 8.55, N, 8.92.

3′,5′-Di-*O*-acetyl-β-D-arabinofuran[1′,2′:4,5]oxazolo-5-me-

thyl-1,3,5-triazin(6,6*H*)-4-one (XVII). To 155 mg (0.3 mmol) of II in 5 mL of dry THF under N_2 at room temperature was added 1.1 mL of tetra-*n*-butylammonium fluoride/THF solution. After 2 h of stirring, the solution was concentrated and stored at 0.1 Torr for 1 h, subsequent to which it was dissolved in 3 mL of dry pyridine and 1 mL of distilled acetic anhydride. After 4 h of stirring at room temperature, the solution was concentrated in vacuo, applied to two 20 × 20 cm, 2000 μ silica gel plates, and eluted with 3 MeOH/EtOAc. The recovered UV band (R_f 0.23 on TLC, same solvent) yielded 82 mg (84% yield): NMR δ 5.99 (1 H, d, J = 5.5 Hz, C-1′), 5.3 (2 H, m, C-2′,3′), 4.78 (2 H, dd, J_{AB} = −7 Hz, C-6), 3.9–4.6 (3 H, m, C-4′,5′), 2.95 (3 H, s, NCH_3), 2.13 and 2.08 (6 H, s, CH_3CO).

3′,5′-Bis(*O*-*tert*-butyldimethylsilyl)-1-β-D-arabinofuranosyl-5-methyl-1,3,5-triazine-2,4(1*H*,3*H*)-dione (XVI). To 100 mg (0.2 mmol) of II in 2 mL of THF was added 100 μL of 50% ammonium hydroxide, and the mixture was stirred for 48 h. The solution was concentrated and azeotroped in vacuo twice with benzene. After preparative TLC (four 20 × 20 cm, 250 μ silica gel plates) in EtOAc, the product was isolated in 50% yield (50 mg): R_f 0.37 in 85% EtOAc/hexane; no UV; NMR ($CDCl_3$) δ 5.80 (1 H, d, J = 6 Hz, C-1′), 5.2 (2 H, brd s, NH and OH), 4.81 (2 H, dd, $J_{AB} \simeq -10$–12 Hz, C-6), 4.68 (1 H, d, $J \simeq 6$ Hz, C-2′), 3.02 (3 H, s, $N-CH_3$), remainder unchanged from III; GC, 3.6 min (240 °C, 6 ft, 3.8% UCW-98), 2.6 min for II at 255 °C; MS (no M^+) 474 ($M^+ - CH_3$), 433, 432 (M^+ − *tert*-butyl), 261.

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Registry No.—VI, 64332-43-0; II, 64332-44-1; Va, 64332-45-2; Vb, 64332-46-3; Ia, 64332-51-0; IVa, 64332-52-1; IVb, 64332-53-2; XIII, 64332-54-3; I (R = H), 27963-98-0; VIII, 53774-80-4; IX, 64332-55-4; XII, 64332-56-5; 3-*N*-acetyl XIII, 64345-59-1; XVII, 64332-57-6; methylurethane, 105-40-8; *tert*-butyldimethylsilyl chloride, 18162-48-6; 3′,5′-di-*O*-acetyl-β-D-arabinofuran[1′,2′:4,5]oxazolo-5-methyl-1,3,5-triazin(4,4*H*)-6-one, 64332-58-7; *S*-ethyl *N*-methylthiocarbamate, 14128-44-0; ethanethiol, 76-08-1; methyl isocyanate, 624-83-9; *S*-ethyl *N*-hydroxymethyl-*N*-methylthiocarbamate, 64332-59-8.

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Reaction of Santonin with Hydroxylamine[1]

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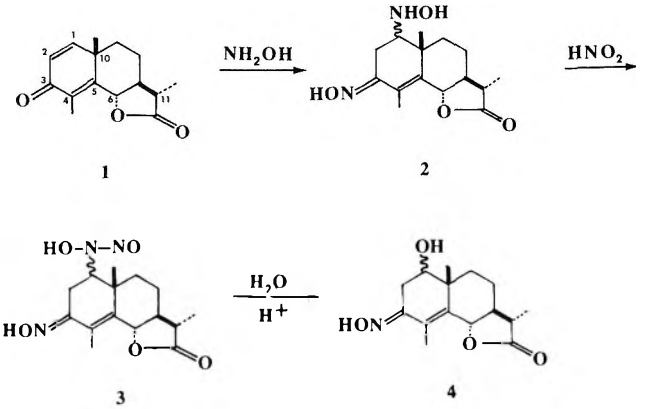
Structures are assigned on the basis of UV, IR, and NMR spectra to the products obtained by Francesconi and Cusmano[2] from the reaction of santonin with excess hydroxylamine. Reaction under approximately neutral conditions affords, in addition to santonin oxime, (1*S*,4*S*,5*R*)-5,1-(epoxyimino)tetrahydrosantonin (*E*)- and (*Z*)-oximes (**6**); under strongly alkaline conditions it affords the 4*R*-*Z*-isomer **5**. These react with benzaldehyde to give isomeric (1*S*, 5*R*)-5,1-[epoxy(phenylmetheno)nitrilo]tetrahydrosantonin (*E*)- and (*Z*)-oximes (**23**), and with nitrous acid to give *N*-nitroso derivatives. The latter decompose in aqueous acetic acid and form (1*R*,4*R*,5*S*,10*S*)- and (1*R*,4*S*,5*S*,10*S*)-3-(*E*)- and -(*Z*)-oximino-5,10-epoxyhexahydrohyposantonin (**9, 10**).

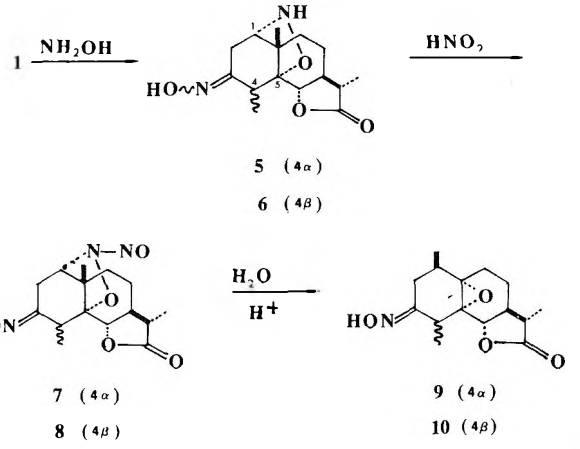
Francesconi and Cusmano[2] observed that (−)-α-santonin (**1**)[3] reacted with an excess of hydroxylamine to give, besides the expected oxime, two isomeric products ("α- and β-hydroxylaminosantonin oximes") containing an additional molecule of hydroxylamine. Many years later, it was suggested[4] that these two compounds had structures (possibly stereoisomeric) represented by **2**, produced by Michael-type addition for which there is ample precedent.[5] On the basis of these structures, the further reactions observed by Francesconi and Cusmano were rationalized as shown in Scheme I. Thus, the nitroso derivatives **3**, on digestion with 50% acetic acid, gave two isomeric compounds ("hydroxysantonin oximes") which could be formulated as **4**: again, a reaction with ample precedent.[6] However, dehydration of either of the hydroxysantonin oximes was reported to give, not the expected santonin oxime, but a product isomeric with it. This pointed to the possibility of skeletal rearrangement, and so we undertook the reexamination of Francesconi and Cusmano's compounds by the physical techniques (UV, IR, NMR) not available in their day. This work showed that the structures of Scheme I must be revised to those of Scheme II.

Our preliminary attempts to obtain other bridged epoxyimino compounds from cyclic dienones such as 4-trichloromethylcyclohexa-2,5-dienone and cholesta-1,4-dien-3-one were unsuccessful;[1] however, more recently Rice and Weiss[7] have observed a double Michael-type addition of the OH and NH of hydroxylamine across the double bonds of phorone to give an oxazepine, and the generality of this reaction remains yet to be explored.

Scheme I



Scheme II



Results and Discussion

We now review the spectroscopic properties of these compounds which necessitated the reformulations of Scheme II.

Epoxyaminosantonin Oximes 5 and 6. The isomeric α- and β-hydroxylaminosantonin oximes of Francesconi and Cusmano were obtained by reaction of santonin with an excess of hydroxylamine, the α compound under strongly basic conditions and the β compound under the approximately neutral conditions provided by 4 molar equiv of hydroxylamine and 0.4 molar equiv of hydroxylamine hydrochloride. These compounds had the correct analyses and had physical properties (mp, $[\alpha]_D$) in good agreement with those reported.[2] However, while the α compound gave single spot on TLC, the β compound gave two spots and is probably a mixture of (*E*)- and (*Z*)-oximes (see below).

The UV, IR (see Experimental Section for details), and ^1H NMR spectra (discussed below) excluded α,β-unsaturated oxime structures such as **2** and pointed to the saturation of the 4,5-double bond as in **5**/**6** (Scheme II). Such a bridged structure also accounted for the presence of only two exchangeable hydrogen atoms and not three as required by **2**. This was shown by treatment of both α and β isomers with excess D_2O, which caused the disappearance of a sharp NMR singlet at δ 10.42 (oxime OH) and a broad peak (NH; δ 7.07 for α and 7.10 for β compound). The two *O*,*N*-dibenzoyl derivatives had no exchangeable hydrogens.

Accepting a bridged structure, four isomers appear plausible on mechanistic grounds, according to whether the bridge is below (α) or above (β) the molecule and whether nitrogen is attached to C_1 or C_5. The evidence for the particular structures **5** and **6** comes from the decomposition products of the nitroso derivatives discussed below.

Stereochemical Difference between Hydroxylaminosantonin Oximes α and β. Santonin forms two isomeric oximes (α, mp 230 °C; β, mp 218 °C),[4] presumably geometrical isomers, and the difference between the hydroxylaminosantonin oximes α and β could be due to a similar difference of oxime configuration. Consequently, the oxime grouping was removed under conditions mild enough not to affect the rest of the molecule.[8] Reaction of the α isomer with sodium bi-

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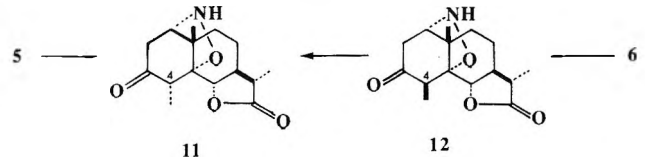
Scheme III



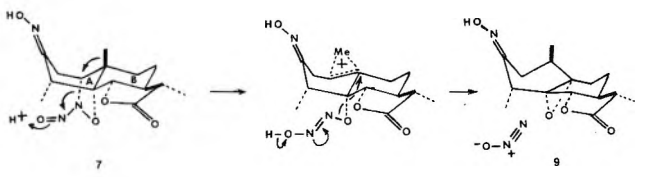
sulfinte in aqueous ethanol, followed by decomposition of the intermediate bisulfite complex with dilute hydrochloric acid,[10] gave a little santonin and a good yield of an epoxyimino ketone, $C_{15}H_{21}NO_3$, which we can formulate as **11** (Scheme III), because of the disappearance from the IR spectrum of the oxime O–H band and the appearance of a ketone band (IR, 1710 cm^{-1}; UV, λ_{max} 294 nm, ϵ_{max} 17).

The reaction of the β isomer gave initially a more complex mixture, as shown by TLC. However, on workup the major product turned out to be the same epoxyimino ketone (formulated above as **11**) accompanied by some santonin. Thin-layer chromatography of the mother liquors showed the presence of another compound in addition to **11**; when a small amount of sodium methoxide was added to the mother liquors, this compound disappeared and the amount of **11** increased. This is most easily interpreted as the epimerization of an axial C_4 methyl in **12** to an equatorial C_4 methyl in **11** (Scheme III); such alkali-catlayzed epimerization cannot take place until the oximino has been converted into a carbonyl group.

This evidence would require α and β isomers to have the epoxyimino bridge attached in the same way to the santonin skeleton so that the difference between them resides in the configuration at C_4 (and possibly also in the oxime configuration). It also indicates the probable genesis of α and β compounds. The latter is formed under approximately neutral conditions and requires the formation first of **12** by attack of hydroxylamine on the underside of the molecule, followed by rapid reaction of **12** with the large excess of hydroxylamine to give the stable β-compound **6** before epimerization at C_4 can take place. On the other hand, when the reaction is carried out in strongly alkaline solution, the intermediate **12** first formed epimerizes to **11**, which then reacts with excess hydroxylamine to give the α-compound **5.** This route is supported by the observation that **5** was obtained by the reaction of hydroxylamine with **11** but not with santonin oxime.

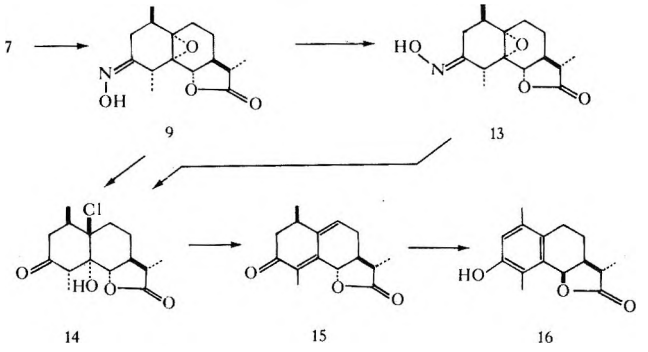
Reactions of the α-Nitroso Derivative 7. (Scheme IV). Hydroxylaminosantonin oxime α reacted with nitrous acid to give a nitroso compound having properties in general agreement with those described by Francesconi and Cusmano. The UV spectral data indicated a nitrosamine[11] (e.g., **7**) and not a nitrimine.[12]

When heated in 50% aqueous acetic acid, the nitroso compound formed nitrous oxide and the compound $C_{15}H_{21}NO_4$, for which the hydroxy structure **4** had been advanced[4] (Scheme I). This structure can be eliminated, because of the absence of a UV peak above 200 nm and because the NMR spectrum shows only one exchangeable proton (oxime, δ 8.75). The rearranged structure **9** is indicated by the fact that all methyl peaks in the NMR spectrum are now doublets and is further confirmed by the reactions of Scheme IV, discussed below. First, however, we should note that the formation of **9** supports, in turn, the structure **7** for the nitroso compound,



with the nitrosamine group axial and trans to the 10-methyl group, so that a facile rearrangement can be envisaged. Accepting such a mechanism requires the epoxyimino bridge to be attached to the underside (α) of the molecule, with the nitrogen linked to C_1 rather than C_5.

Scheme IV



Treatment of the epoxy oxime **9** with levulinic acid–hydrochloric acid at room temperature to remove the oxime grouping[8] gave crystalline material, shown by TLC to be a mixture of two compounds. These were separated by preparative TLC. One proved to be a compound isomeric with **9** to which we assign the structure **13.** The epoxide ring forces rings A and B in both compounds to adopt half-chair conformations (if we choose to ignore boat conformations). That of ring B is fixed by the trans-fused lactone ring. However, ring A can adopt two half-chair conformations. In one (shown in **9**), the C_1 methyl group is in a quasiaxial position, involving an interaction energy of ca. 0.7 kcal/mol; in the other, the C_4 methyl group and the oxime hydroxyl are involved in an $A^{(1,3)}$ interaction (ca. 3.7 kcal/mol).[13] In acid solution, isomerization of the oxime group[14] to the configuration shown in **13** permits a half-chair conformation in which both C_1 and C_4 methyl groups avoid these interactions.

The second compound was rather unstable, but its analysis and spectral properties pointed to the chlorohydrin structure **14.**

Treatment of **9** with levulinic acid–hydrochloric acid at a higher temperature (100 °C) gave a crystalline compound $C_{15}H_{18}O_3$ whose ultraviolet[15] and NMR spectrum indicated a diunsaturated ketone structure as in **15.** More prolonged treatment of **9** at 100 °C gave (−)-α-desmotroposantonin (**16**).[4] This compound is known to have the β conformation at C_6.[3] The work of Cocker and McMurry[16] makes it likely that isomerization of **15** first affords the C_6 epimer of **15,** which then epimerizes to the more stable **16,** and this accords with NMR data discussed below.

Reactions of the β-Nitroso Compound 8 (Scheme V). When the β-nitroso compound **8** was heated in 50% acetic acid, nitrous oxide was again evolved and three compounds were obtained. One proved to be the oxime **19,** converted by treatment with sodium bisulfite into **15** in quantitative yield.

The other two compounds were separated by column and

Scheme V

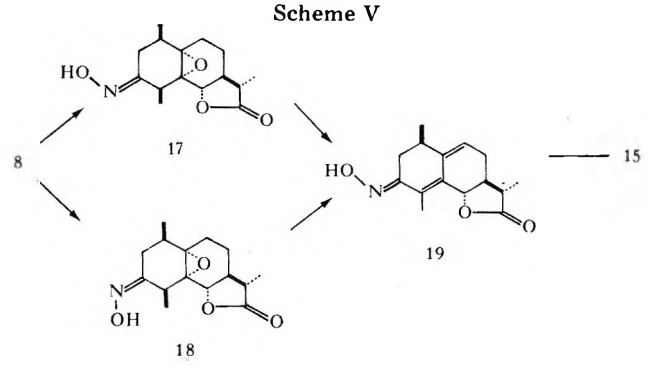


Table I. Chemical Shifts (δ) of Compounds[a] Having a 10-Methyl Group

Compound	Registry no.	4-CH_3[c]	6-H[d]	10-CH_3[e]	11-CH_3[f]
1	481-06-1	2.13[g]	4.88	1.34	1.27
Santonin oxime	1618-82-2	2.16[g]	4.80	1.27	1.25
5[b]	64201-45-2	1.24[h]	4.10	1.07	1.07
O,N-Dibz-5	64201-46-3	1.62[i]	4.07	1.31	1.15
6		1.23[h]	4.22	1.12	1.06
O,N-Dibz-6		1.60[j]	4.14	1.28	1.13
11	64201-47-4	1.33[h]	3.98	1.27	1.21
23-α		1.42[h]	4.12	1.23	1.24
23-β		1.35[k]	4.22	1.32	1.18

[a] Dissolved in $CDCl_3$ except 5. [b] Dissolved in Me_2SO-d_6. [c] d, 3 H. [d] d, J = 10 Hz, 1 H. [e] s, 3 H. [f] d, J = 7 Hz, 3 H. [g] J, 1 Hz. [h] J = 7 Hz. [i] J = 6 Hz. [j] J = 8 Hz. [k] J = 10 Hz.

Table II. Chemical Shifts (δ) of Compounds[a] Having the 10-Methyl Group Shifted to the 1 Position

Compound	Registry no.	4-CH_3	6-H[b]	1-CH_3	11-CH_3[c]
9	64201-48-5	1.36[d]	4.19	1.24[e]	1.08
O-Bz-9	64201-49-6	1.45[d]	4.12	1.17[e]	1.07
13	64234-76-0	1.35[d]	4.16	1.24[e]	1.05
14	64201-50-9	1.12[d]	4.50	1.12[e]	0.99
17	64234-77-1	1.38[d]	4.34	1.10[e]	1.05
18	64234-78-2	1.45[d]	4.30	1.20[e]	1.12
15	64201-51-0	1.93[f]	4.58	1.15[e]	1.02
19	64201-52-1	2.15[f]	4.69	1.23[e]	1.00
16	13743-88-9	2.20[f]	5.72	2.20[f]	1.28

[a] Dissolved in $CDCl_3$. [b] d, J = 8.5–10 Hz, 1 H, except for 16 (see text). [c] d, J = 6–8 Hz, 3 H. [d] d, J = 7 Hz, 3 H. [e] d, J = 6 Hz, 3 H. [f] s, 3 H.

Scheme VI

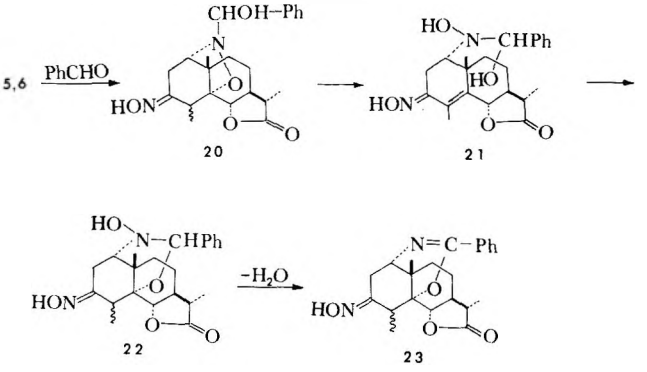


plate chromatography and proved to be isomeric with the epoxy oximes **9** and **13** already described (Scheme IV). They were assigned the structures **17** and **18** from arguments similar to those outlined above for **9** and **13** and based on NMR spectra. A mixture of **17** and **18** in refluxing 50% acetic acid after 1 h was converted into **19**.

Since the epoxy oxime **9** is the sole product from the decomposition of the nitroso compound **7** in 50% acetic acid, we may conclude that **7** and its precursor **5** (Scheme II) have the oxime hydroxyl syn to C_4. On the other hand, the simultaneous formation of the syn (**18**) and anti (**17**) compounds from decomposition of the nitroso compound **8** in 50% acetic acid indicates that **6** and **8** are probably each a mixture of geometrical isomers, as concluded earlier from TLC studies. However, the mixture is probably made up mostly of the anti isomer, because alkaline treatment of **8** (which we have not studied) was reported by Francesconi and Cusmano[2] to eliminate the bridge and give santonin oxime β, mp 218 °C, while similar treatment of **7** gave santonin oxime α, mp 230 °C (dec). These compounds can differ only in the configuration of the oximino group; on the basis of the arguments advanced above, the first oxime would be *E* containing some *Z* and the second *Z*.

Reaction of Hydroxylaminosantonin Oximes α and β with Benzaldehyde. Francesconi and Cusmano[2] found that both hydroxylaminosantonin oxime α and β reacted with benzaldehyde in refluxing ethanol to give "benzal" derivatives $C_{22}H_{26}N_2O_4$. Following their procedure, we obtained a product from **5** having properties agreeing well with those reported. From **6** we obtained a compound having almost the same melting point as the compound from **5**; however, a mixture melting point showed the two compounds to be different.[17] The IR and NMR spectra of these compounds again indicated the absence of both olefinic double bonds and hence the presence of bridged structures; the NMR spectra also showed the disappearances of the bridge NH groups of **5** and **6**. The only reasonable structure permitted by the empirical formulas is **23**, which accords with the UV spectra of the compounds in neutral and acid solution and with their p*K*s (α, 4.65; β, 4.70) all close to the values expected from that of methyl benzimidate.[18,19]

A possible route to the phenylimino ether structure **23** is advanced very tentatively in Scheme VI.[20] We have already noted above the elimination of the epoxyimino bridge from **5** and **6** under strongly basic or acidic conditions and the regeneration of the two olefinic double bonds; the elimination step **20** → **21** under near-neutral conditions represents the first stage of a similar elimination and the ring-closure **21** → **22** a reversal in which a less-strained ring system is formed. Dehydration of **22** to yield **23** would be favored by the resonance stabilization of the phenylimino ether product. The reaction sequence of Scheme VI would require the elimination of the stereochemical distinction between α and β compounds at C_4, so that the two products **23** would differ only in the configuration of the oxime function, that form **5** being *Z* and that from **6** being *E* with some *Z*. Unfortunately, we were unable to study further this remarkable reaction, which clearly merits further work.

In deriving the structures **5–23**, the information obtained from ^1H NMR was vital. The peaks at high field due to the three methyl groups and the doublet at low field due to the hydrogen at the 6-position were most easily recognized; their chemical-shift values are given in Tables I and II. The coupling constant of the 6-hydrogen doublet remained constant for all compounds until (−)-α-desmotroposantonin (**16**) was reached, when it decreased from 10 to 5 Hz as expected from the change at this stage from a trans to a cis-fused lactone. The peak of the 11-methyl group remained as a doublet ($J \approx 7$ Hz) in all compounds. On the other hand, the 4-methyl peak in santonin was barely split ($J \approx 1$ Hz) because of long-range coupling, but became a well defined doublet (J = 6–8 Hz) when the Δ^4 double bond was saturated on bridge formation to give **5** and **6** and only became a singlet when the double bond reappeared in **15**, **16**, and **19**. Similarly, the angular methyl at the 10-position gave rise to a singlet in all the

compounds of unrearranged carbon skeleton in Table I, but to a doublet (J = 6 Hz) when it had migrated to the 1-position to afford the compounds of Table II (with the exception only of **16**, where aromatization of the ring had removed the vicinal hydrogen responsible for the splitting).

Other NMR peaks important in establishing structures are given earlier or in the Experimental Section.

Experimental Section

General Methods. Melting points are corrected. IR spectra were obtained with Perkin-Elmer Model 337 and 521 spectrophotometers. UV spectra were obtained using a Unicam Model S.P.-800 recording spectrophotometer and are for ethanol solutions, unless otherwise noted. NMR spectra were obtained with a Varian Associates A-60 instrument. Optical rotations were determined with a Carl Zeiss automatic polarimeter at 25 °C, using a 1.0-dm cell and solute concentrations of about 8% in EtOH. Silica gel G and calcium sulfate were used for preparative thick-layer chromatography and for TLC, and silical gel (Grace Davison Chemical, grade 923) was used for column chromatography. Unless otherwise noted, three solvent mixtures were used to elute TLC plates: (a) 50% benzene, 50% ether; (b) 45% benzene, 45% ether–10% ethanol; (c) a mixture of chloroform (15 mL), ether (10 mL), methylene chloride (15 mL), methanol (2 mL). R_f values quoted below indicate the solvent mixture used.

(1*S*,4*R*,5*R*)-5,1-(Epoxyimino)tetrahydrosantonin (*Z*)-Oxime (5). (a) From Reaction of Santonin with Hydroxylamine. The following method achieved somewhat better yields than that of Francesconi and Cusmano.[2] A solution of sodium methoxide, prepared from 46.6 g (2 mol) of sodium and 1 L of methanol, was mixed with a solution of 140 g (2 mol) of hydroxylamine hydrochloride in methanol. After removing sodium chloride by filtration, more sodium methoxide [from 7 g (0.3 mol) of sodium] was added, and the solution was concentrated to 1 L. Santonin (120 g) was added, and the solution was refluxed under nitrogen until no santonin was shown by TLC (about 24 h). The solution was concentrated to a volume of 150 mL under reduced pressure, and 100 mL of water was added. The clear solution at room temperature deposited a first crop of 30 g of fine white needles, shown by TLC to be a mixture of santonin oxime and of **5**. The solid was extracted with 50 mL of hot methanol. The residue (15 g) was almost pure **5**.

Evaporation of the mother liquor from the first crop gave a second crop of **5** (15 g, total 20%); further concentration of the filtrate gave only santonin oxime. The compound **5** crystallized from methanol in fine white prisms, giving a single spot on TLC, turning brown at ca. 200 °C: mp with evolution of gas 230 °C; $[\alpha]^{25}_D$ +46.5° (lit.[2] mp 229–230 °C; $[\alpha]^{12}_D$ +47.44°); IR (KBr) ν_{max} 3550 (s) (oxime OH), 3250 (s) (N–H), 1750 (s) (lactone C=O), 1650 (w) (oxime C=N) cm^{-1}; UV, end absorption only.

Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.20; H, 7.53; N, 9.52; mol wt 294.34. Found: C, 60.66; H, 7.28; N, 9.40; mol wt 297 (osmometry), 294 (mass spectrum).

The *N,O*-dibenzoyl derivative, prepared by reaction with benzoyl chloride in pyridine, had mp 175–178 °C; IR (KBr) ν_{max} 1785, 1750, 1640, 1600, and 1505 cm^{-1}.

Anal. Calcd for $C_{29}H_{30}N_2O_6$: C, 69.30; H, 6.02; N, 5.57. Found: C, 68.10; H, 6.05; N, 6.01.

(b) From Reaction of (1*S*,4*R*,5*R*)-5,1-(Epoxyimino)tetrahydrosantonin (11) with Hydroxylamine. The ketone **11** (0.192 g) (see below) was heated with hydroxylamine in 5 mL of methanol. TLC showed the reaction to be complete in 3 h; the solution when cooled deposited colorless prisms identical with **5** obtained above (mp, mmp, TLC, IR, $[\alpha]^{25}_D$ +46.5°).

(1*S*,4*S*,5*R*)-5,1-(Epoxyimino)tetrahydrosantonin (*E*)- and (*Z*)-Oximes (6). The following procedure is an improvement over that of Francesconi and Cusmano.[2] Santonin, hydroxylamine hydrochloride, and sodium methoxide were allowed to react under the conditions used in the preparation of the α isomer, the mole ratio of hydroxylamine hydrochloride to sodium methoxide now being 1.15:1.00. After 24 h of refluxing, the solution was concentrated to about 200 mL. On cooling, 30 g of santonin oxime crystallized out. On addition of 300 mL of water, a further 35 g of santonin oxime precipitated. After being extracted several times with chloroform to remove more santonin oxime, the aqueous solution was boiled for 15 min. On cooling, 25 g (16.5%) of **6** separated as colorless needles. After crystallization from aqueous dimethyl sulfoxide, this still showed two overlapping spots [R_f (b) 0.50] on TLC: turning brown at ca. 200 °C; mp (evolution of gas) 232–233 °C; mmp with α isomer (**5**) 210 °C; $[\alpha]^{25}_D$ 0.0° (lit.[2] mp 232–233 °C; $[\alpha]^{12}_D$ −3.0°). The IR and UV spectra were similar to those of the α isomer.

Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.20; H, 7.53; N, 9.52. Found: C, 60.54; H, 7.14; N, 10.07.

The *N,O*-dibenzoyl derivative, prepared as above, crystallized from methanol as needles: mp 185–186 °C (lit.[2] mp 184 °C); UV λ_{max} 233.5 nm, ϵ_{max} 25 000, λ_{max} 273 nm, ϵ_{max} 4780 (MeOH); IR ν_{max} (KBr) 1785, 1750, 1640, 1615, 1582, and 1505 cm^{-1}.

Anal. Calcd for $C_{29}H_{30}N_2O_6$: C, 69.30; H, 6.02; N, 5.57. Found: C, 69.42; H, 6.13; N, 5.96.

Levulinic Acid Treatment of (1*S*,4*R*,5*R*)-5,1-(Epoxyimino)-tetrahydrosantonin (*Z*)-Oxime (5). One gram of **5** was heated at 100 °C with 15 mL of levulinic acid reagent[10] for 4 h. Neutralization ($NaHCO_3$) and extraction with chloroform removed 0.78 g of white crystalline product found by mp, IR, and NMR to be identical with santonin oxime.[2,4] The same result was obtained with the β isomer **6**.

(1*S*,4*R*,5*R*)-5,1-(Epoxyimino)tetrahydrosantonin (11). (a) From (1*S*,4*R*,5*R*)-5,1-(Epoxyimino)tetrahydrosantonin Oximes (6). The β compound **6** (1.5 g) in 20 mL of ethanol was treated with a solution of 2.8 g of sodium bisulfite in 10 mL of water. Partial precipitation of both reagents occurred. The mixture was heated under reflux on a steam bath while nitrogen was bubbled through to keep the solids in suspension. After 30 min the solids had dissolved, and TLC showed starting material [R_f (a) 0.35] and three other spots: one (feeble) with the same R_f (a) as santonin (0.70); a second (ca. 40% of reaction mixture) R_f (a) 0.24; and a third R_f (a) 0.00 (50% of reaction mixture). After 4 h, starting material was gone and TLC showed a new spot [R_f (a) 0.55]. The solution was concentrated to 10 mL, acidified with 50 mL of cold dilute hydrochloric acid, and extracted with chloroform (2 × 50 mL). Evaporation of the chloroform gave 0.25 g of a yellow oil, which crystallized after addition of ether and cooling as white platelets, mp 171 °C, identified by IR and UV as santonin.

The aqueous layer from the extraction was neutralized ($NaHCO_3$) and extracted with 2 × 50 mL of chloroform. Evaporation of the chloroform gave 0.5 g of a yellow crystalline product. Two crystallizations from 96% ethanol gave 0.2 g of colorless needles of **11**: R_f (a) 0.24; mp 190.5 °C; $[\alpha]^{25}_D$ +13.9°; UV λ_{max} 294 nm, ϵ_{max} 17; IR (KBr) ν_{max} 3260 (s) (NH), 1775 (s) (lactone C=O), 1710 cm^{-1} (s) (ketone C=O).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.39; H, 7.55; N, 5.10.

The mother liquor showed a spot [R_f (a) 0.55] (attributed to **12**) as well as santonin [R_f (a) 0.70] and **11** [R_f (a) 0.24]. When the mother liquor was made alkaline with sodium methoxide and allowed to stand at room temperature for 3 min, the spot [R_f (a) 0.55] was shown by TLC to have disappeared and the spot R_f (a) 0.24 to have been strengthened.

(b) From (1*S*,4*R*,5*R*)-5,1-(Epoxyimino)tetrahydrosantonin (*Z*)-Oxime (5). The α isomer **5** (0.5 g) was allowed to react under the conditions described above for the β isomer. Santonin (0.125 g) was recovered by chloroform extraction of the acidified reaction mixture. After neutralization of this ($NaHCO_3$), chloroform extraction gave 0.225 g of a crystalline product, mp 190 °C, identical by mmp, IR, UV, and NMR with the product **11** from **6**. The mother liquors from which this compound separated showed only santonin and **11** [R_f (a) 0.24], but no spot with R_f (a) 0.55.

(1*S*,5*R*)-5,1-[Epoxy(phenylmetheno)nitrilo]tetrahydrosantonin (*E*)- and (*Z*)-Oximes (23). A solution of 1 g of **5** and 1 mL of benzaldehyde in 10 mL ethanol was refluxed for 26 h, concentrated, and cooled. The precipitate was washed with cold ether and crystallized from aqueous methanol, giving 0.75 g of colorless needles: mp 215–217 °C (lit.[2] mp 217 °C); UV λ_{max} 235 nm, ϵ_{max} 11 200; IR (KBr) ν_{max} 3550 (w) (oxime OH), 3200 (s), 3080 (s), 1790 (s) (lactone C=O), 1662 (s) (oxime C=N), 1615 (w), 1600 (w), 1510 (m), and 1490 (m) cm^{-1}.

Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.08; H, 6.85; N, 7.33. Found: C, 69.36; H, 6.89; N, 7.54.

The same procedure, applied to the β isomer **6**, gave 0.75 g of colorless needles: mp 219–220 °C: mmp with product from **5** 190–200 °C; UV λ_{max} 235 nm, ϵ_{max} 10 600; IR ν_{max} (KBr) 3450 (w), 3250 (s), 1787 (s), 1655 (s), 1613 (w), 1592 (m), and 1505 (m) cm^{-1}.

Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.08; H, 6.85; N, 7.33. Found: C, 68.86; H, 7.05; N, 7.12.

In acid solution both compounds had λ_{max} 252 nm. A series of spectra in solutions of pH 8.9, 6.6, 4.5, 3.7, 1.0, and −1.0 (H_0) passed through an isobestic point at 239 nm, and analyzed by the usual method[21] gave pK values of 4.65 and 4.70 for α and β compounds, respectively.

(1*S*,4*R*,5*R*)-5,1-(Epoxynitrosoimino)tetrahydrosantonin (*Z*)-Oxime (7). (1*S*,4*R*,5*R*)-5,1-(Epoxyimino)tetrahydrosantonin (*Z*)-Oxime (**5**) (5.0 g) in 50 mL of water containing 0.65 g of hydrochloric acid was treated with 1.15 g of sodium nitrite in 5 mL of water. A pale yellow precipitate formed, which was digested in 25 mL of hot ethanol, and then **7** was filtered off. A portion was recrystallized from methanol and obtained as minute needles, very faintly yellow, giving a single spot on TLC analysis. The needles turned brown at 160 °C and melted at 164–165 °C with evolution of gas: $[\alpha]^{25}_D$ −112.9° (lit.[2] mp 164 °C; $[\alpha]^{12}_D$ −112.8°); UV λ_{max} 246 nm, ϵ_{max} 7650; IR (KBr) ν_{max} 3425 (s), (oxime OH), 1775 (s) (lactone C=O), 1630 (w), (oxime C=N), 1570 (w), and 1350 (s) cm^{-1} (N=O).

Anal. Calcd for $C_{15}H_{21}N_3O_5$: C, 55.72; H, 6.55; N, 13.00. Found: C, 55.89; H, 6.29; N, 12.86.

No NMR spectrum could be obtained because of the compound's low solubility at ordinary temperatures and facile decomposition in solution when warmed.

(1*S*,4*S*,5*R*)-5,1-(Epoxynitrosoimino)tetrahydrosantonin (*E*)- and (*Z*)-Oximes (8). This product was prepared in the same way from the β isomer **6** except that glacial acetic acid was used as solvent. It crystallized from methanol in large yellow needles: R_f (b) 0.30 and 0.45; turning brown at 160 °C; evolved gas at 168 °C; mp 172 °C (lit.[2] mp 172 °C); mmp with α isomer 152–154 °C; UV λ_{max} 245 nm, ϵ_{max} 7300; IR (KBr) ν_{max} 3425 (s), 1775 (s), 1630 (w), 1570 (w), and 1360 (m) cm^{-1}.

Anal. Calcd for $C_{15}H_{21}N_3O_5$: C, 55.72; H, 6.55; N, 13.00. Found: C, 56.85; H, 6.71; N, 12.37.

On standing the material decomposed slowly, and after a few days TLC showed the presence of another, less polar compound, R_f (b) 0.70, the same R_f (b) as shown by **17** and **18**. The poor analysis was probably due to partial decomposition to the compounds **17** and **18**; a 12% decomposition would lead to the analytical figures shown above.

(1*R*,4*R*,5*S*,10*S*)-3-(*Z*)-Oximino-5,10-epoxyhexahydrohyposantonin (9). The 4α-nitroso compound **7** (1.025 g) was suspended in 10 mL of 50% aqueous acetic acid in a round-bottom flask connected via a reflux condenser to a trap cooled in liquid air. The apparatus was flushed with nitrogen and the flask was heated on a water bath. The evolved gas condensed in the trap as a white solid. The trap was warmed to room temperature and the gas taken into a previously evacuated IR cell: ν_{max} 3840 (w), 3487 (s), 3460 (s), 3370 (w), 3340 (w), 2790 (m), 2470 (s), 2450 (m), 2210 (s), 1300 (s), 1270 (s), and 1265 (m) cm^{-1}, identical to spectrum reported for nitrous oxide.[22]

The yellow solution from the flask, on addition of water, gave 0.683 g of white precipitate, which crystallized from methanol as prisms, giving a single spot on TLC: R_f (a) 0.50; mp 199–200 °C; $[\alpha]^{25}_D$ +220° (lit.[2] mp 199–200 °C; $[\alpha]^{25}_D$ +219°); IR (KBr) ν_{max} 3440 (s) (oxime OH), 1760 (s) (lactone C=O), and 1653 (w) cm^{-1} (oxime C=N).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.78; H, 7.32; N, 5.05.

The benzoyl derivative, prepared in the usual way, crystallized from methanol/ether in plates: R_f (a) 0.75; mp 134–138 °C (dec); IR (KBr) ν_{max} 1775 (s), 1738 (s), 1620 (m), 1595 (m), and 1250 (s) cm^{-1}.

Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.71; H, 6.10; N, 3.81.

Levulinic Acid Treatment of (9). (a) At Room Temperature. The oxime **9** (0.5 g) was stirred for 15 h at room temperature in a mixture of 18 mL of levulinic acid and 2 mL of 1.0 N hydrochloric acid. TLC showed one spot having the same R_f (a) 0.50 as the starting material and a second of R_f (a) 0.60. The mixture was poured into 50 mL of water, filtered from resinous material, and neutralized ($NaHCO_3$). The precipitate was taken up in ether, washed with sodium bicarbonate solution, and evaporated to yield 0.33 g of a white crystalline product. This was chromatographed on five silica gel plates using solvent a. (1*R*,4*R*,5*S*,10*S*)-3-(*E*)-Oximino-5,10-epoxyhexahydrohyposantonin (**13**), R_f (a) 0.50, was recovered as a white crystalline solid (0.119 g). Recrystallization from aqueous methanol gave colorless prisms: mp 187–190 °C; mmp with **9**, 173 °C; IR (KBr) 3450 (s), 1750 (s), and 1636 (m) cm^{-1}.

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.66; H, 7.42; N, 5.04.

The second compound of R_f (a) 0.60 was obtained as 0.084 g of white crystals from cold ether. It showed a single spot on TLC, but decomposed to a brown solid at ca. 130 °C (depending on rate of heating). The compound (14?) on sodium fusion gave a positive test for halogen and negative test for nitrogen; IR ν_{max} (KBr) 3425 (s) (OH), 1763 (s) (lactone C=O), 1705 (s), (ketone C=O), and 682 (s) cm^{-1} (CCl).

Anal. Calcd for $C_{15}H_{21}O_4Cl$: C, 59.99; H, 7.03. Found: C, 59.55; H, 6.83.

(b) At 100 °C for 4 h. The oxime **9** (1.17 g) was heated with 30 mL of the levulinic acid reagent on the steam bath for 4 h. The product, worked up as above, gave white crystals of (1*R*)-3-oxo-$\Delta^{4,9}$-dihydrohyposantonin (**15**), R_f (a) 0.75. On recrystallization from aqueous methanol, mp 108–109 °C, UV λ_{max} 288 nm, ϵ_{max} 11 100, and λ_{max} 232.5 nm, ϵ_{max} 3800; IR (KBr) ν_{max} 1780 (s) (lactone C=O), 1660 (s) (conjugated C=O), and 1620 (m) cm^{-1} (C=C); NMR δ 5.32 (olefinic H).

Anal. Calcd for $C_{15}H_{21}O_3$: C, 73.14; H, 7.37. Found: C, 73.60; H, 7.12.

(c) At 100 °C for 15 h. More prolonged treatment of 1.0 g of the oxime **9** with 30 mL of levulinic acid reagent gave 0.44 g of a different white crystalline compound: R_f (a) 0.65; mp 194 °C. Its UV (λ_{max} 289 nm, ϵ_{max} 3800), IR, and NMR spectra were identical with those of an authentic sample of (−)-α-desmotroposantonin (**16**).[16]

Acid Treatment of 8. The 4β-nitroso compound **8** (0.95 g) was treated with 50% aqueous acetic acid and then worked up as described above for the α isomer **7**. Evolution of nitrous oxide was again observed, and a crystalline product was isolated in two crops. The first crop was shown by TLC to consist of three compounds [R_f (a) 0.50, 0.58, 0.80] and the second of only one [R_f (a) 0.80]. This compound was readily separated from the other two in the first crop by crystallization from methanol, in which it was much more soluble. After two crystallizations from methanol, white crystals of (1*R*)-$\Delta^{4,9}$-dihydrohyposantonin (*E*)-oxime (**19**) were obtained, mp 255 °C (dec); UV λ_{max} 276 nm, ϵ_{max} 24 870; IR (KBr) 3400 (s) (oxime OH), 3035 (w) (olefinic CH), 1750 (s) (lactone C=O), 1602 (w) (C=C), and 1590 (w) cm^{-1} (oxime C=N); NMR δ 5.65 (olefinic H).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.06; H, 7.59; N, 5.34.

The other two compounds [R_f (a) 0.50, 0.58] were partially separated on a silica gel column and finally purified by TLC plates. One [R_f (a) 0.50] crystallized from aqueous ethanol as fine white needles of (1*R*,4*S*,5*S*,10*S*)-3-oximino-5,10-epoxyhexahydrohyposantonin (**17** or **18**): mp 186.5 °C; IR (KBr) ν_{max} 3560 (s) (oxime OH), 3200 (s, br) (H-bonded OH), 1760 (s) lactone (C=O), and 1660 (m) cm^{-1} (oxime C=N); UV, end absorption only; NMR δ 9.87, exchangeable with D_2O (oxime OH).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.73; H, 7.65; N, 5.21.

The second compound [R_f (a) 0.58] crystallized from aqueous ethanol as white platelets of isomeric (1*R*,4*S*,5*S*,10*S*)-3-oximino-5,10-epoxyhexahydrohyposantonin (**17** or **18**): mp 196.5 °C; IR (KBr) 3500–3450 (s), 1760 (s), and 1630 (w) cm^{-1}; UV, end absorption only.

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.63; H, 7.83; N, 4.90.

Registry No.—(*E*)-**6**, 64234-79-3; (*E*)-**6** *O*,*N*-dibenzoyl derivative, 64234-81-7; (*Z*)-**6**, 64234-80-6; (*Z*)-**6** *O*,*N*-dibenzoyl derivative, 64234-82-8; **7**, 64201-53-2; (*E*)-**8**, 64234-83-9; (*Z*)-**8**, 64234-84-0; **12**, 64234-85-1; (*E*)-**23a**, 64201-54-3; (*Z*)-**23a**, 64234-86-2; (*E*)-**23b**, 64234-87-3; (*Z*)-**23b**, 64234-88-4; hydroxylamine hydrochloride, 5470-11-1; hydroxylamine, 7803-49-8; benzaldehyde, 100-52-7.

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Isonucleosides. 2. Purine and Pyrimidine Derivatives of 1,4-Anhydro-2-deoxy-D-arabinitol

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1,4-Anhydro-D-xylitol (1), prepared from sorbose by three steps, was converted into 1,2:3,4-dianhydro-D-ribitol (7) by a sequence of six high-yield reactions. Reaction of 7 with concentrated ammonium hydroxide resulted in exclusive attack at C-2 to give 2-amino-1,4-anhydro-D-arabinitol (8), which was converted in three steps to the adenosine analogue 2-(6-amino-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol (11). It was also converted to the uridine analogue **15**.

The naturally occurring nucleosides and nucleotides are those in which the purine or pyrimidine base is attached to C-1 of ribose or 2-deoxyribose. This linkage is part of an aminal structure that is quite susceptive to both hydrolytic and enzymatic cleavage. For many years, the design of congeners of these compounds was based on the assumption that only analogues with bases attached in the β configuration to C-1 of D-furanoses were likely to fit the active sites of the anabolic enzymes necessary for activation of the enzymes whose inhibition by the resultant nucleotides results in cell death. The same requirements were assumed to apply also to the incorporation of analogues into cofactors or macromolecules. However, the discovery of the biologic activity of α-2′-deoxythioguanosine,[1] of the *α-arabino* nucleosides,[2] and of the carbocyclic analogues of nucleosides[3] has made it necessary to revise these concepts about structural requirements. Thus, it seemed worthwhile to investigate the biologic potential of isonucleosides—compounds in which the base is attached to the sugar at positions other than the normal C-1 position.

Previous work in this laboratory resulted in the preparation of purine isonucleosides by the reaction of methyl 2,3-anhydro-α-D-arabinofuranoside with ammonium hydroxide to give a mixture of methyl 2-amino-2-deoxy-α-D-arabinofuranoside and methyl 3-amino-3-deoxy-α-D-xylofuranoside.[4] The reaction of each of these compounds with 2,6-dichloro-5-aminopyrimidine followed by ring closure gave the isonucleosides, methyl 2-(6-chloro-9-purinyl)-2-deoxy-α-D-arabinofuranoside and methyl 3-(6-chloro-9-purinyl)-3-deoxy-α-D-xylofuranoside. In this manner, a number of purine isonucleosides were prepared by nucleophilic displacement of the 6-chloro group.[5,6]

We have now extended this work by the synthesis of compounds lacking the 1-*O*-methyl group of the sugar moiety in the hope that such compounds might be substrates for the anabolic enzymes such as adenosine kinase, and that they might therefore be activated to forms capable of interfering with vital cellular metabolism, such as the biosynthesis or function of nucleic acids.

The success of the reaction of methyl 2,3-anhydro-α-D-arabinofuranoside with ammonium hydroxide[4] led us to undertake the preparation of 1,2:3,4-dianhydro-D-ribitol (**7**). Preparation of **7** was initially attempted by reaction of 1,2-di-*O*-acetyl-3-*O*-mesyl-5-*O*-methoxycarbonyl-D-xylofuranose[7] with ethereal HCl (saturated at 0 °C) to give 2-*O*-acetyl-3-*O*-mesyl-5-*O*-methoxycarbonyl-β-D-xylofuranosyl chloride.[8] Reduction of this chloride followed by ring closure should give the corresponding epoxide; however, all attempts to reduce the glycosyl chloride, either catalytically or chemically, were unsuccessful, giving in most cases unchanged starting material. Attempts were made to displace the 1-chloro group with sodium ethylmercaptide[9] and at the same time effect ring closure to the epoxide to give ethyl 2,3-anhydro-1-deoxy-1-thio-β-D-ribofuranose, which could then be reduced to give **7**. The reaction to prepare the thio sugar was unsuccessful, giving an intractable mixture.

An alternative approach to **7** involved the anhydridizing of sorbitol with sulfuric acid catalyst to give arlitan (1,4-sorbitan).[10] When the reaction was carried out as described in the literature (i.e., 135–145 °C for 30 min), we obtained, in addition to the product, a large amount of a by-product tentatively identified as isosorbide, since it is known that further treatment of arlitan with sulfuric acid results in the formation of isosorbide in high yield.[11] When the reaction was carried out at a lower temperature, 130 °C for 45 min, a cleaner product was obtained free of isosorbide. The method of Kjølberg for shortening the chain length of glycosides was used for the synthesis of 1,4-anhydro-D-xylitol (**1**).[12] Cleavage of the C^5–C^6 bond of arlitan with periodate gave the aldehyde, which was reduced with sodium borohydride to **1**.[13] (For the syntheses of compounds **2–16**, see Scheme I.) The 1,4-anhydro-3,5-*O*-isopropylidene-D-xylitol (**2**), a white crystalline solid, was prepared by the reaction of **1** with acetone containing 2,2-dimethoxypropane and 60% perchloric acid. Acetylation of **2** with pyridine–acetic anhydride furnished 2-*O*-acetyl-1,4-anhydro-3,5-*O*-isopropylidene-D-xylitol (**3**), a crystalline solid. By deacetonation of **3** in 1 N ethanolic HCl, 2-*O*-acetyl-1,4-

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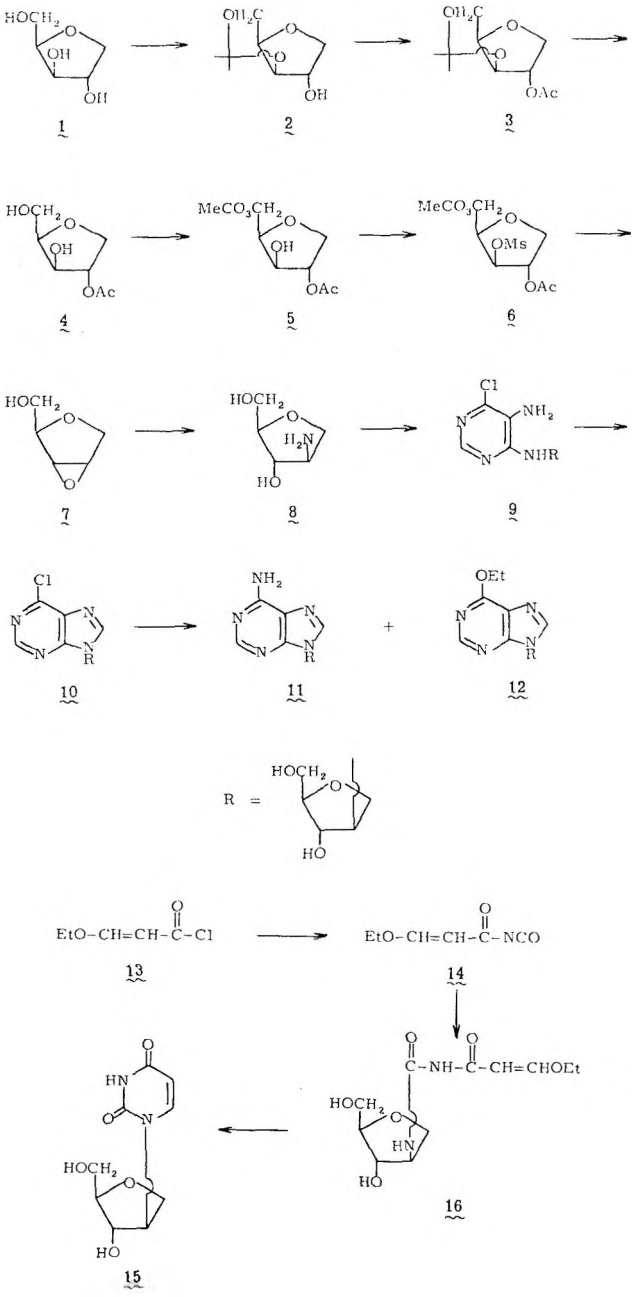
Scheme I



anhydro-D-xylitol (4) was obtained and subsequently acylated with an excess of methyl chloroformate in pyridine to 2-*O*-acetyl-1,4-anhydro-5-*O*-methoxycarbonyl-D-xylitol (5). Because of the large difference in the rate of acylation of the two hydroxyl groups, only a very small amount of the 3,5-di-*O*-methoxycarbonyl derivative was observed (TLC). The reaction of 5 with methanesulfonyl chloride in pyridine gave 1-*O*-acetyl-1,4-anhydro-3-*O*-mesyl-5-*O*-methoxycarbonyl-D-xylitol (6), which was cyclized with cold 1 N sodium methoxide in methanol to the epoxide 7. The reaction of 7 with concentrated ammonium hydroxide at 100 °C took place exclusively at C-2 to give 2-amino-1,4-anhydro-2-deoxy-D-arabinitol (8) (the overall yield of 8 from 1, a seven-step sequence, was 33%). This is in contrast to the similar reaction with the methyl 2,3-anhydro-α-D-ribofuranose in which attack occurs at both C-2 and C-3 to give an almost equal mixture of arabino and xylo compounds,[4] indicating the electron-releasing properties of the glycosidic methoxy group; methyl 2,3-anhydro-β-D-ribofuranose is attacked exclusively at C-3,[14,15] a result of both steric and electronic effects. The structures of compounds 1–7 were confirmed by NMR spectral data. The structure of 8 as the arabino rather than the xylo isomer (resulting from attack at C-2 rather than C-3) could not be established from its NMR spectra alone, because the ^1H NMR peaks were largely unresolved, even in trifluoroacetic acid, and the ^{13}C spectrum was not stereochemically definitive, although it did establish that 8 was a single entity. The spectrum of the purine (11) prepared from 8 (see below), however, was well resolved and its arabino structure could be established unequivocally by spin-decoupling experiments.

The reaction of 8 with 5-amino-4,6-dichloropyrimidine in refluxing 1-butanol gave 2-(5-amino-6-chloro-4-pyrimidinylamino)-1,4-anhydro-2-deoxy-D-arabinitol (9), which was obtained pure in 45% yield by silica gel column chromatography. Ring closure in triethylorthoformate–concentrated HCl furnished 2-(6-chloro-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol (10), which reacted with ethanolic ammonia to give a mixture that was resolved by silica gel chromatography providing a 67% yield of 2-(6-amino-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol (11) and an 11% yield of 2-(6-ethoxy-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol (12). The structures of 9–11 were confirmed by elemental analyses and UV and NMR spectral data. The structure of 12 was confirmed by elemental analysis and UV spectral data.

β-Ethoxyacryloyl chloride (13), prepared from the sodium salt of β-ethoxyacrylic acid by the method of Shaw and Warrener,[16] was allowed to react with silver cyanate in benzene under anhydrous conditions to give β-ethoxyacryloyl isocyanate (14). Reaction of 14 with the arabinitol 8, carried out in cold *N,N*-dimethylformamide solution,[17] provided the urea 16, which cyclized in concentrated ammonium hydroxide to give 1,4-anhydro-2-deoxy-2-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-D-arabinitol (15), purified via its lead salt, in an overall yield of 18% from 8. The structure of 15 was verified by UV and NMR spectroscopy as well as elemental analysis.

None of these isonucleosides have been found to be cytotoxic, and the ones so far evaluated have shown no activity against leukemia L1210.

Experimental Section

All evaporations were carried out in vacuo with a rotary evaporator. Analytical samples were normally dried in vacuo over P_2O_5 at room temperature for 16 h. Analtech precoated (250 μm) silica gel G(F) plates were used for TLC analyses; the spots were detected by irradiation with a Mineralight and by charring after spraying with saturated $(NH_4)_2SO_4$. Compounds containing amino groups were also detected with ninhydrin spray. All analytical samples were essentially TLC homogeneous. Melting points were determined with a Mel-Temp apparatus and are not corrected. The UV absorption spectra were determined in 0.1 N HCl, pH 7 buffer, and 0.1 N NaOH with a Cary 17 spectrophotometer: the maxima are reported in nm ($\epsilon \times 10^{-3}$). The NMR spectra were determined with a Varian XL-100-15 spectrometer in the solvent indicated with tetramethylsilane as an internal reference: chemical shifts (δ in ppm) quoted in the case of multiplets are measured from the approximate center. The ^{13}C spectra were measured at 25.2 MHz in the pulsed, Fourier transform mode with a Digilab Model 400-2 pulser and NMR-3 data system.

1,4-Anhydro-3,5-*O*-isopropylidene-D-xylitol (2). A solution of anhydrous acetone (1.22 L) and 2,2-dimethoxypropane (32.9 mL) was stirred for 2 min before 60% perchloric acid (44 mL) was added. The resulting solution was stirred for 5 min and then poured into a flask containing 1,4-anhydro-D-xylitol[13] (12.8 g, 9.5 mmol). Vigorous stirring produced a complete solution within 5 min. After 50 min of additional stirring, the solution was chilled in an ice bath, neutralized with solid $NaHCO_3$, and evaporated to dryness in vacuo at ambient temperature. The residue was partitioned between H_2O and $CHCl_3$ (100 mL each). Further extraction of the aqueous layer was carried out seven times with $CHCl_3$ (100 mL each time). The $CHCl_3$ extracts were combined, dried over $MgSO_4$, and evaporated to dryness in vacuo to yield a white crystalline solid: yield 12 g (80%). Recrystallization from ether–petroleum ether gave the analytical sample (TLC, 9:1 $CHCl_3$–MeOH); ^1H NMR ($CDCl_3$) δ 1.35 (s, CH_3), 1.43 (s, CH_3), 2.88 (d, O_2H), 3.8, 4.0, and 4.2 (br m's, 2-H_1, H_2, H_3, H_4, 2-H_5); ^{13}C NMR

($CDCl_3$) δ 19.55 and 28.53 (CH_3 of IP), 60.70 (C-5), 72.20 (C-1), 74.43 (C-3), 75.59 and 76.61 (C-2 and C-4), 97.52 (C of IP).

Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.99; H, 7.84.

2-*O*-Acetyl-1,4-anhydro-3,5-*O*-isopropylidene-D-xylitol (3). To a cold (0 °C) solution of 1,4-anhydro-2,3-*O*-isopropylidene-D-xylitol (2.68 g, 15.3 mmol) in pyridine (10 mL) was added acetic anhydride (2.9 mL, 30.6 mmol). The resulting solution was allowed to warm up to ambient temperature and kept there for 20 h before it was poured into ice-saturated $NaHCO_3$ (100 mL). The resulting mixture was extracted with $CHCl_3$ (100 mL), which was washed with saturated $NaHCO_3$ (100 mL) and then H_2O (5 × 100 mL), dried over $MgSO_4$, and evaporated to dryness in vacuo at 70 °C (until there was no longer an odor of pyridine in the residue). A white crystalline solid was obtained: yield 2.91 g (88%) (TLC, 99:1 $CHCl_3$–MeOH); ^1H NMR ($CDCl_3$) δ 1.36 (s, CH_3), 1.43 (s, CH_3), 2.05 (s, CH_3 of Ac), 3.94 (br m, 2-H_1, 2-H_5), 4.34 (br m, H_2, H_4), 5.12 (d, H_3); ^{13}C NMR ($CDCl_3$) δ 19.48 and 28.46 (2 CH_3 of IP), 20.91 (CH_3 of Ac), 60.48 (C-5), 72.17 (C-1), 72.61 and 73.51 (C_3 and C_4), 78.92 (C_2), 97.74 (C of IP), 169.89 (C of C=O).

2-*O*-Acetyl-1,4-anhydro-D-xylitol (4). To a cold solution of 2-*O*-acetyl-1,4-anhydro-3,5-*O*-isopropylidene-D-xylitol (7.5 g, 34.7 mmol) in ethanol (175 mL) was added 1 N HCl (34.7 mL). The resulting solution was allowed to warm up to ambient temperature and kept there until the hydrolysis was complete as determined by hourly examinations by TLC (95:5 $CHCl_3$–MeOH). After 3 h, the solution was evaporated to dryness in vacuo. A solution of the residue in $CHCl_3$ (100 mL) was neutralized with solid Na_2CO_3, filtered, dried over $MgSO_4$, and evaporated to dryness in vacuo. A yellow syrup was obtained: yield 5.2 g (86%); ^1H NMR (Me_2SO-d_6) δ 2.0 (s, CH_3), 3.5 (m, H_4 and 2 H_5), 3.8 and 4.0 (m's, 2 H_1 and H_3), 4.5 (t, C_5OH), 4.9 (m, H_2), 5.3 (d, C_4OH); ^{13}C NMR (Me_2SO-d_6) δ 20.67 (CH_3 of Ac), 59.07 (C-5), 70.11 (C-1), 73.26, 79.52, and 81.49 (C-3, C-2, and C-4).

2-*O*-Acetyl-1,4-anhydro-5-*O*-methoxycarbonyl-D-xylitol (5). A solution of 2-*O*-acetyl-1,4-anhydro-D-xylitol (546 mg, 3.1 mmol) in pyridine (20 mL) and $CHCl_3$ (10 mL) was stirred and chilled in an ice bath while methyl chloroformate (0.48 mL, 6.2 mmol) was slowly added. After complete solution was attained, the reaction was kept at 3–5 °C. After 48 h another 6.2 mmol of methyl chloroformate was added and the resulting solution was kept at 3–5 °C for another 48 h. The solution was then poured into ice water (200 mL) and $CHCl_3$ (200 mL) was added. The $CHCl_3$ layer was washed with cold dilute H_2SO_4 until the aqueous layer remained acidic and then cold H_2O, dried over $MgSO_4$, and evaporated to dryness in vacuo. A yellow syrup was obtained: yield 570 mg (79%) (TLC, 95:5 $CHCl_3$–MeOH). This material, on TLC examination, contained a small amount of a faster moving material, possibly the disubstituted compound. It was, however, used in the next step without further purification.

2-*O*-Acetyl-1,4-anhydro-3-*O*-mesyl-5-*O*-methoxycarbonyl-D-xylitol (6). To a cold (0–3 °C) solution of 2-*O*-acetyl-1,4-anhydro-5-*O*-methoxycarbonyl-D-xylitol (570 mg, 2.34 mmol) in pyridine (10 mL) was added mesyl chloride (0.46 mL, 4.68 mmol). After 4 h at ambient temperature, the solution was poured over ice and extracted with $CHCl_3$ (100 mL). The $CHCl_3$ solution was washed with saturated $NaHCO_3$ (100 mL), then H_2O (100 mL), ice-cold dilute H_2SO_4 until the aqueous layer remained acidic, and then H_2O, dried over $MgSO_4$, and evaporated to dryness in vacuo. A nearly colorless syrup was obtained: yield 671 mg (91%) (TLC, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.10 (s, CH_3 of Ac), 3.14 (s, CH_3 of mesyl), 3.78 (s, OCH_3), 3.82 (br m, sugar CH), 4.30 (br m, sugar CH), 5.22 (br m, sugar CH); ^{13}C NMR ($CDCl_3$) δ 20.72 (CH_3 of Ac), 38.45 (CH_3 of mesyl), 55.09 (CH_3 of MeOCO), 64.72 (C-5), 71.37 (C-1), 77.24 and 77.39 (C-3 and C-4), 81.49 (C-2), and 169.89 (C of C=O).

1,2:3,4-Dianhydro-D-ribitol (7). A solution of 2-*O*-acetyl-1,4-anhydro-3-*O*-mesyl-5-*O*-methoxycarbonyl-D-xylitol (6.6 g, 21.1 mmol) in 1 N NaOMe in MeOH (73 mL) with glacial acetic acid, and evaporated to dryness in vacuo. A $CHCl_3$ extract (100 mL) of the residue was dried over $MgSO_4$ and evaporated to dryness in vacuo. A thin syrup was obtained: yield 2.1 g (86%) (TLC, 95:5 $CHCl_3$–MeOH). This material was used in the next step without further purification.

2-Amino-1,4-anhydro-2-deoxy-D-arabinitol (8). A solution of 1,2:3,4-dianhydro-D-ribitol (1.32 g, 11.3 mmol) in concentrated NH_4OH (50 mL) was heated in a stainless-steel bomb at 100 °C for 8 h and evaporated to dryness in vacuo. A solution of the residue in EtOH (50 mL) was filtered to remove an insoluble solid and evaporated to dryness, giving an orange syrup: yield 1.32 g (87%) (TLC, MeOH); ^{13}C NMR (Me_2SO-d_6) δ 58.71 (C-2), 61.67 (C-5), 72.27 (C-1), 78.24 and 86.41 (C-3 and C-4).

2-(5-Amino-6-chloro-4-pyrimidinylamino)-1,4-anhydro-2-deoxy-D-arabinitol (9). A solution of 2-amino-1,4-anhydro-2-deoxy-D-arabinitol (2.26 g, 17 mmol), 5-amino-4,6-dichloropyrimidine (2.79 g, 17 mmol), and triethylamine (2.38 mL, 17 mmol) in 1-butanol (300 mL) was refluxed for 6 days and evaporated to dryness in vacuo. A solid weighing 5.44 g was obtained. A solution of the solid in MeOH (15 mL) was applied to a column of Biosil A (250 g). Elution of the column with 9:1 $CHCl_3$–MeOH gave the product as a white crystalline solid, yield 2.76 g (61%).

The analytical sample was obtained by recrystallization from MeOH–$CHCl_3$: yield 2.06 g (45%); mp 199–201 °C; UV; λ_{max} (pH 1) 305 (13.1), (pH 7, 13) 262, 292, (8.52, 9.70) nm; TLC, 9:1 $CHCl_3$–MeOH; ^1H NMR (Me_2SO-d_6) δ 3.6 (m, H_1', H_4', and H_5'), 4.1 (m, H_1' and H_3'), 4.3 (m, H_2'), 4.8 (t, $C_5'OH$), 5.1 (s, NH_2), 5.35 (d, $C_3'OH$), 6.9 (d, NH), 7.8 (s, H_2); ^{13}C NMR (Me_2SO-d_6) δ 59.63 (C_2'), 61.42 (C_5'), 70.74 (C_1'), 75.88 (C_3'), 85.68 (C_4'), 123.60 (C_5), 137.16 (C_6), 145.65 (C_2), 151.64 (C_4).

Anal. Calcd for $C_9H_{13}ClN_4O_3$: C, 41.47; H, 5.03; N, 21.49. Found: C, 41.24; H, 4.81; N, 21.68.

2-(6-Chloro-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol (10). A suspension of 2-(5-amino-6-chloro-4-pyrimidinylamino)-1,4-anhydro-2-deoxy-D-arabinitol (920 mg, 3.52 mmol) in triethylorthoformate (17 mL) containing concentrated HCl (0.4 mL) was stirred for 16 h at ambient temperature. Another 0.6 mL of concentrated HCl was added, and stirring was continued for 1 h before the solid was collected by filtration to give 836 mg of white solid. Evaporation of the filtrate and trituration of the residue with ether gave a second crop of 156 mg: total yield 992 mg (84%). The analytical sample was obtained by recrystallization from EtOH: mp 192–194 °C, UV, λ_{max} (pH 1, 7) 265 (935), (pH 13) 257 (8.55) nm; TLC 9:1 $CHCl_3$–MeOH; ^1H NMR (Me_2SO-d_6) δ 3.7 (m, H_4' and H_5'), 4.2 (d, 2 H_1'), 4.5 (m, H_3'), 5.1 (q, H_2'), 5.8 (m, C_3'-OH), 8.75 and 8.8 (H_2 and H_8).

Anal. Calcd for $C_{10}H_{11}ClN_4O_3$: C, 44.37; H, 4.10; N, 20.70. Found: C, 44.69; H, 4.47; N, 20.74.

2-(6-Amino-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol (11) and 2-(6-Ethoxy-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol (12). A solution of 2-(6-chloro-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol (651 mg, 2.4 mmol) in 125 mL of EtOH–NH_3 (saturated at 0 °C) was heated in a stainless-steel bomb at 80 °C for 20 h and then evaporated to dryness in vacuo, giving 784 mg of a white solid. The solid was purified by chromatography on silica gel plates using 9:1 $CHCl_3$–MeOH as the developing solvent. Elution of the slower moving band with MeOH gave 2-(6-amino-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol as a white crystalline solid: yield 406 mg (67%); mp 220–221 °C. The analytical sample was obtained by recrystallization from MeOH; mp 221–222 °C; UV, λ_{max} (pH 1) 258 (14.2), (pH 7, 13) 260 (14.4) nm; ^1H NMR (Me_2SO-d_6) δ 3.7 (m, H_4' and 2 H_5'), 4.2 (m, 2 H_1'), 4.5 (m, H_3'), 5.0 (m, H_2' and $C_5'OH$), 5.9 (d, $C_3'OH$), 7.4 (s, NH_2), 8.24 and 8.28 (2 s, H_2 and H_8).

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.81; H, 5.22; N, 27.87. Found: C, 47.67; H, 5.52; N, 28.19.

Elution of the faster moving band with MeOH gave 2-(6-ethoxy-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol as a white crystalline solid, yield 72 mg (11%). Recrystallization from ethanol gave the analytical sample: mp 183–184 °C; UV, λ_{max} (pH 1, 7, 13) 252 (11.7) nm.

Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.05; H, 5.82; N, 20.10.

1,4-Anhydro-2-deoxy-2-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-D-arabinitol (15). A solution of the urea **16** (427 mg, 1.56 mmol) in concentrated NH_4OH (40 mL) was heated at 100 °C for 30 min and evaporated to dryness in vacuo. An aqueous solution of the residue was neutralized with 0.3 N HCl before an aqueous solution of $Pb(OAc)_3$·$3H_2O$ (4.68 mmol) was added. The resulting cloudy solution was filtered and the filtrate treated with an excess of concentrated NH_4OH. The precipitate that formed was collected by filtration, washed with H_2O, and dissolved in 20% aqueous acetic acid (25 mL). The solution was treated with H_2S, and the black precipitate of PbS was removed by filtration. Evaporation of the filtrate gave 145 mg of a white glass that was chromatographed on silica gel plates (9:1 $CHCl_3$–MeOH). The major band was eluted with MeOH and the solution deionized with Amberlite IR-120 (H^+) ion-exchange resin before evaporation to yield a white glass: yield 124 mg (40%); UV, λ_{max} (pH 1, 7) 267 (9.82), (pH 13) 266 (7.34) nm; ^1H NMR (Me_2SO-d_6) δ 3.5 (m, H_4' and 2 H_5'), 3.9 (m, 2 H_1'), 4.1 (m, H_3'), 4.8 (m, H_2' and $C_5'OH$), 5.6 (m, $C_3'OH$ and H_5), 7.6 (d, $J_{5,6}$ = 8 Hz, H_6). After addition of D_2O, the multiplet at 5.6 became a doublet ($J_{5,6}$ = 8 Hz).

Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.36; H, 5.30; N, 12.28. Found: C, 47.68; H, 5.56; N, 11.98.

1,4-Anhydro-2-deoxy-2-[3-(3-ethoxyacryloyl)ureido]-D-arabinitol (16). To a cold (−14 °C) solution of 2-amino-1,4-anhy-

dro-2-deoxy-D-arabinitol (666 mg, 5 mmol) in DMF (50 mL) was slowly added 24 mL of a benzene solution containing 5 mmol of β-ethoxyacryloyl isocyanate[16] at such a rate as to keep the temperature of the reaction solution below −10 °C. The resulting solution was kept for 1 h at −10 °C and then 18 h at ambient temperature before it was evaporated to dryness. The residue was purified by silica gel plates using 9:1 $CHCl_3$–MeOH as the developer. The product was obtained as a glass by elution with MeOH: yield 692 mg (44%).

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Purine *N*-Oxides. 65. On the Mechanisms of the Reactions of 3-Acetoxyxanthine[1]

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The redox chemistry of 3-acetoxyxanthine, a model "activated ester" for the proximate form of the oncogen 3-hydroxyxanthine, has been explored. The results indicate that the oxidizing reactivity of the ester, previously attributed to the participation of a radical intermediate, is instead due to reactions at the electron-deficient nitrogen of an intermediate of the S_N1' 8-substitution reaction. A two-step reaction sequence is proposed for the reduction of the nitrenium ion in the presence of iodide and thiourea. 8-Iodoxanthine is shown not to be an intermediate in the reduction by iodide ion. Studies with formate, acetate, and phosphate buffers at pH's 4.0, 5.0, and 7.0, respectively, show that changes in the concentration of each buffer system elicit different responses in the reactions of 3-acetoxyxanthine. The combined studies provide support for a unifying mechanism for competitive redox and C-substitution reactions from a single ambident electrophile. It is proposed that redox reactions are frontier orbital controlled and result from soft–soft interactions at the nitrenium ion, while C-substitution reactions are charge controlled and occur via hard–hard interactions at the carbonium ion. The proposal accommodates the observations that in the presence of 3-acetoxyxanthine certain nucleophiles undergo oxidation only, other nucleophiles lead only to C-8 substitution, while some may participate in both types of reaction.

3-Hydroxyxanthine (**5**) (Scheme I) and certain related purine *N*-oxides are potent oncogens.[2-6] Studies to elucidate the mechanism of cancer induction by **5** have shown that while 3-hydroxyxanthine itself is relatively inert chemically its esters are extremely reactive.[7-11] Esterification in vivo is apparently a prerequisite for the initiation of oncogenesis.[6,12,13] 3-Acetoxyxanthine (**1**) was selected as a model ester for in vitro studies of the presumed "activated" or "proximate" form of 3-hydroxyxanthine.[10,11] Those studies demonstrated the diversity of spontaneous reactions that **1** can undergo, the high reactivity of **1** with nucleophiles,[10] and the strong influence that pH, temperature, and dielectric constant of the medium can exert on the course of these reactions.[11] The reaction with nucleophiles, designated the "3-acyloxypurine 8-substitution reaction",[11] can proceed by either of two routes, paths a and b (Scheme I), depending upon the pH of the medium. A second reaction of **1**, reduction to xanthine (**4**), was observed to be a characteristic only of path b. A radical anion (**3**) was proposed as an intermediate in this reduction, based in part on the quantitative oxidation of iodide ion but not of other halide ions. We now present evidence on the mechanisms of the reactions of 3-acetoxyxanthine that indicates the nitrenium ion (**6a**) rather than the radical anion (**3**) is the agent responsible for the oxidation of iodide ion, and possibly other species as well, and propose an integrated mechanism that accounts for the predominance of redox reactions with certain nucleophiles and of 8-substitution with others.

Results

Syntheses. 3-Acetoxyxanthine (1). The reported preparation of **1**,[14] utilizing equal volumes of acetic acid and acetic anhydride, was found to give incomplete acetylation. Extended reaction times and mild heating did not improve the conversion of **5** to **1**. The addition of acetyl chloride to the reaction medium, however, induced the conversion of almost all of **5** to **1**, which was isolated in 78% yield as the hydrochloride.

8-Iodoxanthine. Attempts to prepare 8-iodoxanthine by

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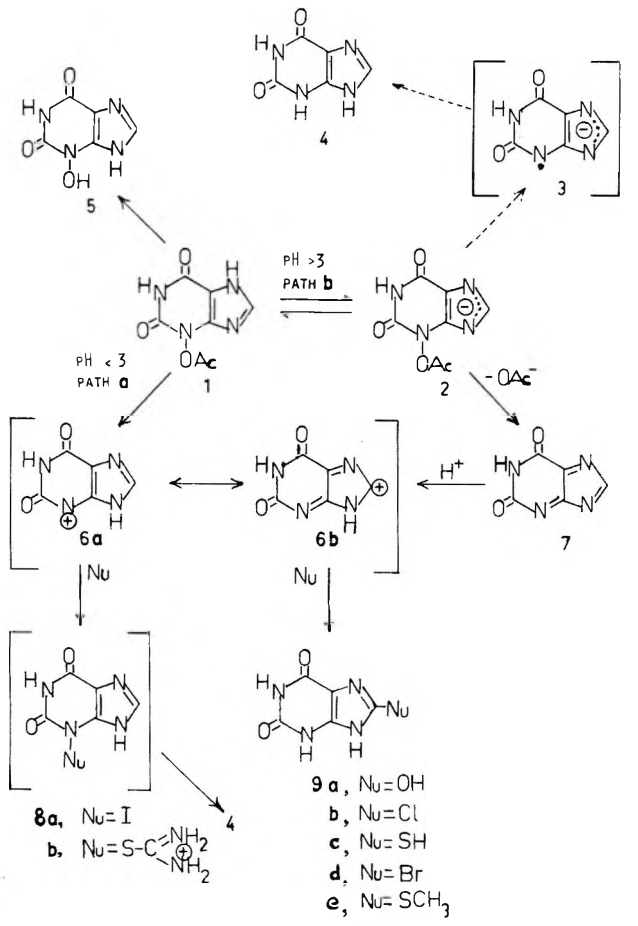
Scheme I



the reported[15] procedure of hydrolysis of 8-iodoxanthosine[15,16] met with limited success. Iodination of xanthosine yielded a gummy solid that rapidly turned to an oil when exposed to air. Hydrolysis of the crude oil in 50% aqueous CF_3COOH at room temperature afforded a low (15%) yield of very impure 8-iodoxanthine. Diazotization of 8-iodoguanine in aqueous CF_3COOH proved to be a superior route to the desired product, although also in low (15%) yield. The structure of 8-iodoxanthine was confirmed by elemental, NMR, and mass spectral analyses and by the similarity to the values reported for UV absorption maxima of it at two pH's.[15]

Reactions of 3-Acetoxyxanthine with Nucleophiles. Studying the mechanisms of reactions from 3-acetoxyxanthine (**1**) is complicated by the diversity of spontaneous reactions it can undergo and by the high reactivity of **1** with nucleophiles. Consequently the effect of changing conditions on the multiple reactions of **1** was studied by determining the products after all reactions were completed. The effect of varying concentrations of iodide ion on the reduction of **1** to xanthine (**4**) was studied at pH 1. At that pH the 8-substitution reaction was deduced[11] to proceed solely by path a (Scheme I). The products from **1** at pH 1 (0.1 N HCl) in the absence of KI are 3-hydroxyxanthine, **5** (85%), and 8-chloroxanthine, **9b** (5%) (Figure 1). In the presence of 0.5 equiv of iodide ion (0.001 M) at pH 1, some **9b** was still isolated (~1%), but xanthine was obtained in 5% yield. With ≥2 equiv of iodide ion, no 8-substitution product, **9**, was detectable, the yield of **5** remained unchanged, and ~5% of xanthine was isolated. The effect of varying pH on the products from **1** in the presence of 2 equiv of iodide (4×10^{-3} M) is illustrated in Figure 2. No uric acid (**9a**) or 8-chloroxanthine (**9b**) was obtained at any pH in the presence of 2 equiv of iodide. The yield of xanthine increased slightly from pH 0 to 3 and then rose dramatically from 10 to

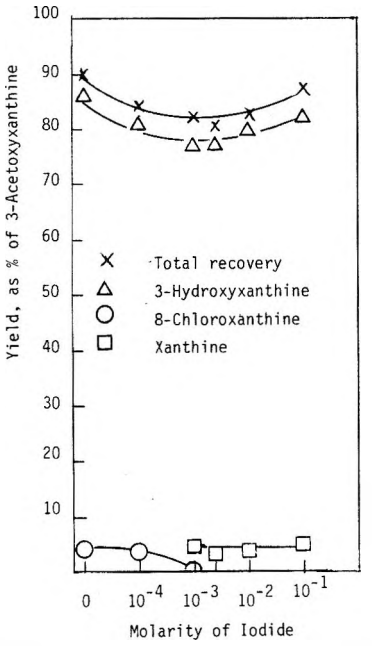


Figure 1. Effect of changes in iodide ion concentration on the composition of products from 3-acetoxyxanthine at pH 1.

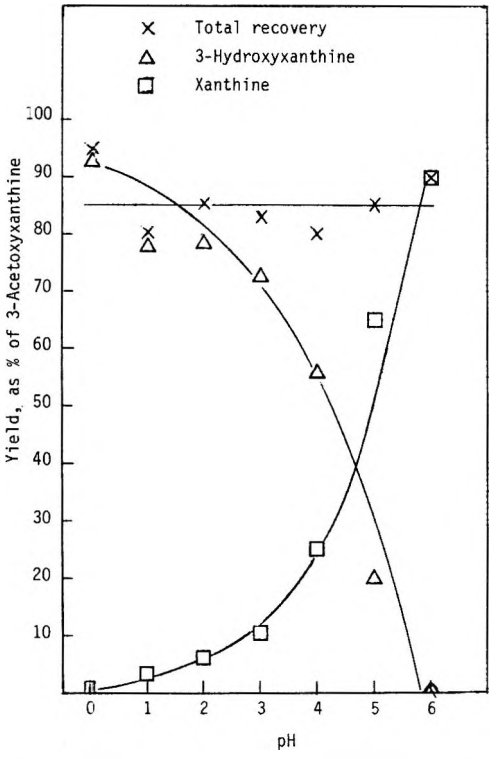


Figure 2. Effect of changes in pH on the composition of products from 3-acetoxyxanthine in the presence of 2 equiv of iodide ion (4×10^{-3} M).

90% over the pH range 3 to 6. The yield of **5** decreased in inverse proportion to that of **4** while the overall recovery remained essentially unchanged.

The effect of varying concentrations of thiourea on the reaction products from **1** was studied at pH 3 (Figure 3). At this pH path a predominates and without added nucleophile only uric acid (**9a**) (~5%) and **5** (85 to 90%) were obtained.[11] With added thiourea over the range of 0.001 to 1 M, no uric acid was detectable, but 8-thiouric acid[17] (**9c**) (4 to 8%), **4** (7 to 19%), and **5** (60 to 70%) were formed (Figure 3). The yields of the

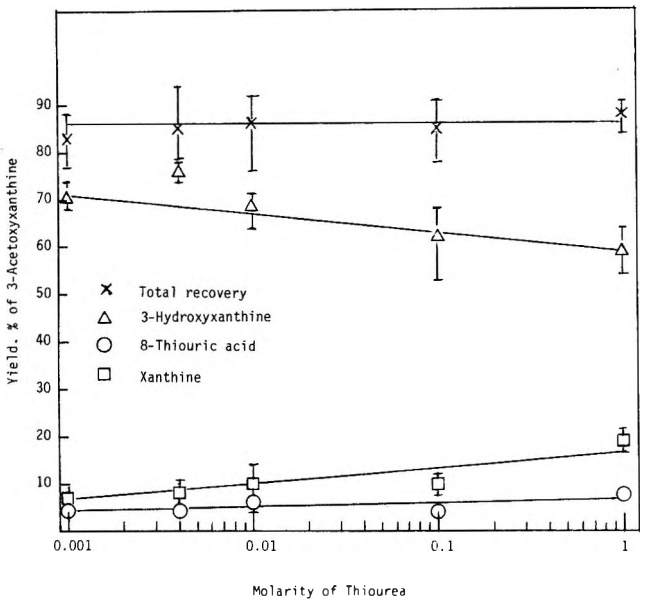


Figure 3. Effect of changes in the concentration of thiourea on the composition of products from 1 at pH 3.

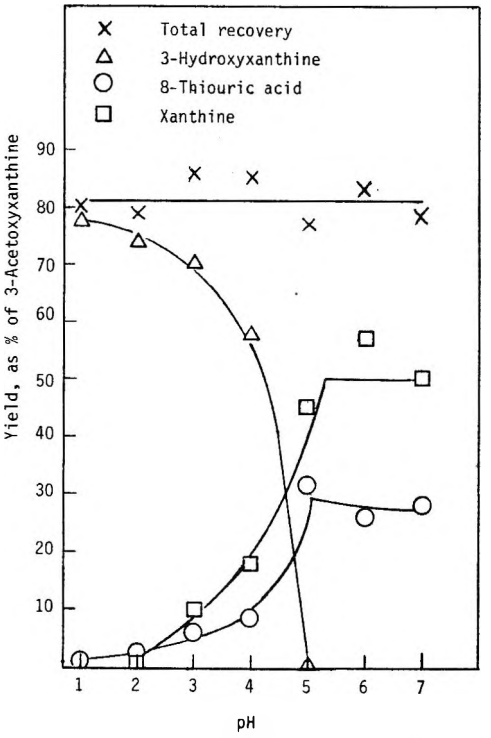


Figure 4. Effect of changes in pH on the composition of products from 1 in the presence of 5 equiv of thiourea.

products were only slightly affected by changes in the concentration of thiourea.

When the pH was varied over the range 1 to 7 in the presence of 5 equiv of thiourea per mol of **1**, the yields of **9c** and **4** showed parallel increases up to pH 5, while that of **5** decreased (Figure 4). Above pH 5 no **5** was detectable and the yields of **9c** and **4** remained unchanged. The overall recovery remained constant over the entire pH range. No uric acid (**9a**) was detected at any pH.

Effect of Varying Buffer Concentrations. Three buffer systems were examined to determine the effect of varying buffer concentration on the reactions of **1**. With an increase in the concentration of formate buffer from 0.01 to 0.1 M, there was little change in the composition of the products from

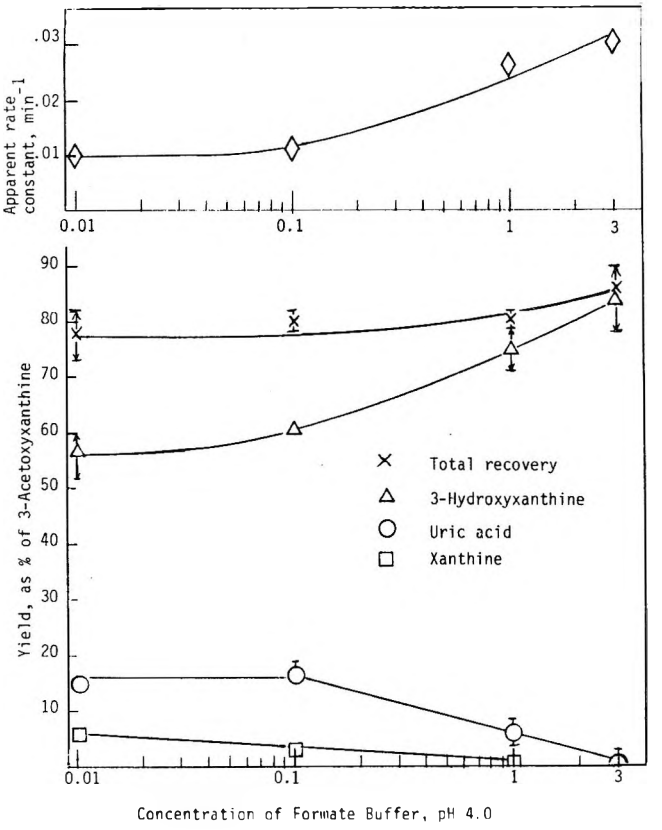


Figure 5. Effect of changes in the concentration of formate buffer at pH 4.0 on the product composition and pseudo-first-order rate constant for the reaction of 3-acetoxyxanthine.

1 (Figure 5). Further increases from 0.1 to 3 M caused an increase in the yield of **5** and a corresponding decrease in the yield of **9a**. The small yield of **4** was reduced to zero. This effect is similar to that obtained by decreasing the pH.[11] Associated with the higher yields of **5** there was an increase in the rate of reaction (Figure 5). These observations suggest that an increased ratio of formic acid to **1** at this low pH effectively acts as though the pH were lowered and hydrolysis of **1** to **5** is favored over other reactions from **1**.

Increases in the concentration of acetate buffer from 0.01 to 3 M produced a large increase in the yield of **9a** from 25% at 0.01 M to 70% at 3 M buffer (Figure 6). The increase in the yield of **9a** was accompanied by a corresponding, but not proportionate, decrease in the yield of **4**. There was little difference in the overall recovery between 0.01 and 0.1 M buffer, but from 0.1 to 3 M there was a significant increase from 60 to 90%. These changes were also accompanied by changes in the reaction rate (Figure 6). Between 0.01 and 2 M acetate buffer there was a gradual increase in the pseudo-first-order rate constant from 0.027 to 0.038 min^{-1}. At higher concentrations of buffer there was a sharp increase in the rate constant to 0.079 min^{-1} in 3 M buffer, which was accompanied by a rise in the yield of **5**. The sudden increase in reaction rate and concomitant rise in formation of **5** suggest that in high concentrations of acetate buffer transacetylation from **5** to acetate ion becomes significant. This conclusion accords with an earlier demonstration that transacetylation can occur between 3-acetoxy- and 3-hydroxyxanthines.[18]

Variation of the phosphate buffer concentration at pH 7.0 from 0.01 to 1 M caused essentially no change in the yield of the reaction products from **1** (Figure 7). A further increase to 1.5 M, i.e., using an almost saturated solution of the buffer, caused an increase in the yield of **9a** and a proportionate decrease in the yield of **4**. Thus only in this narrow concentration range was there an effect of the phosphate buffer and this

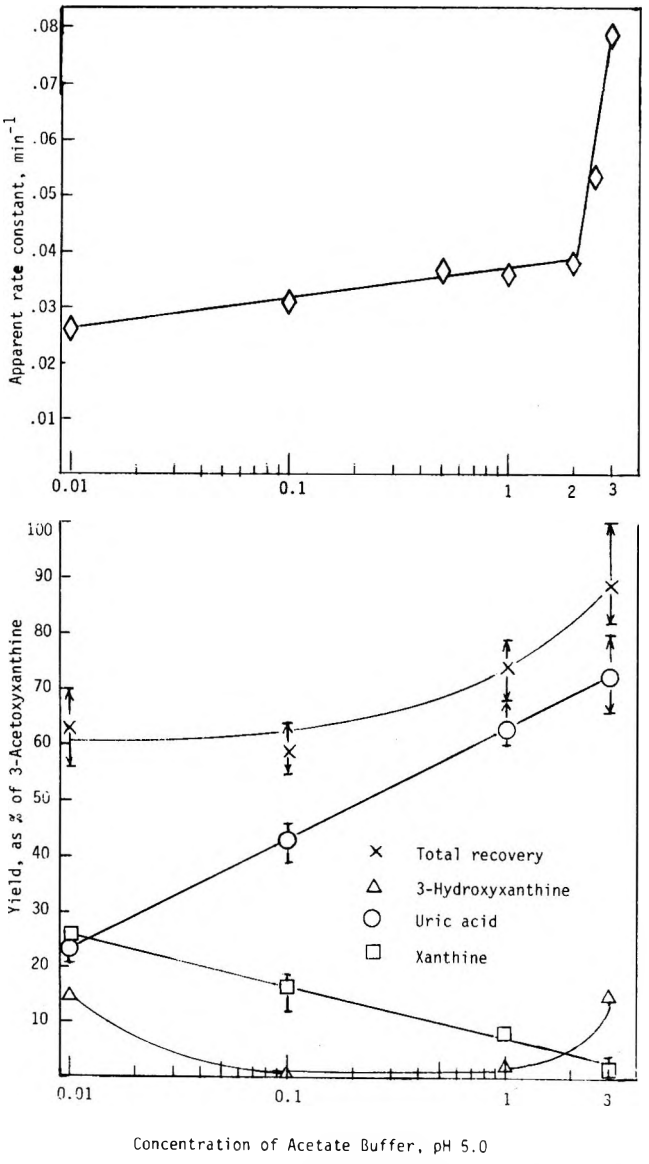


Figure 6. Effect of changes in the concentration of acetate buffer at pH 5.0 on the product composition and pseudo-first-order rate constant for **1**.

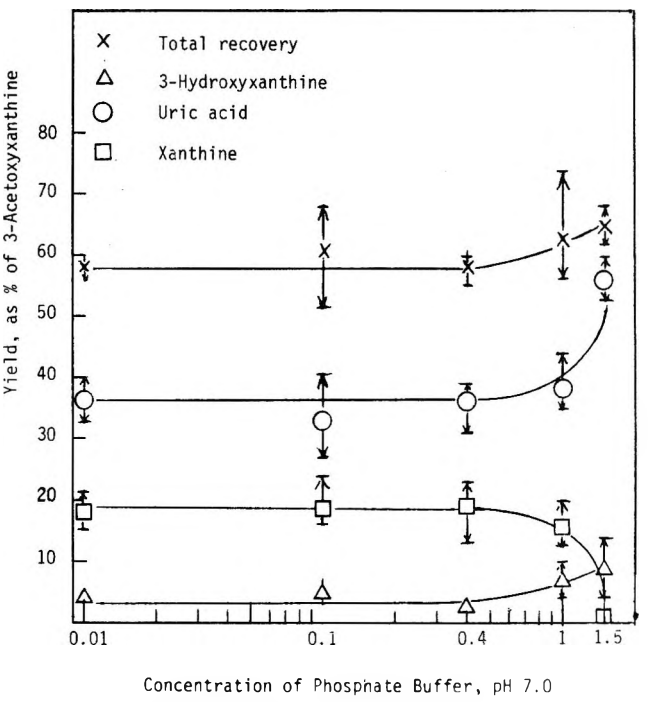


Figure 7. Effect of changes in the concentration of phosphate buffer at pH 7.0 on the product composition from **1**.

Table I. Effect of Variations of pH on the Reaction[a] of 8-Iodoxanthine[b] and Iodide Ion[c]

	Product yields, %, pH =			
	1	3	5	7
8-Iodoxanthine	82 (97)[d]	78	80	92 (98)[e]
Xanthine, **4**	14 (3)[d]	9	5	5 (2)[e]
Recovery	96 (100)[d]	87	85	97 (100)[e]

[a] Reactions were performed for 24 h, except as noted,[e] in the absence of light. Solutions were exposed to room illumination, except as noted,[d] during workup. [b] 2×10^{-3} M. [c] 4×10^{-3} M. [d] The reaction proceeded for 24 h; the reaction and all manipulations, including column chromatography, were performed in the complete absence of light. [e] The reaction was run for 30 min in the absence of light except for room illumination during workup.

effect was similar to the changes induced by increases in the acetate buffer concentration at pH 5.0.

The yields of products from **1** in 0.01 M formate buffer at pH 4 (Figure 5) and in 0.01 M acetate buffer (Figure 6) at pH 5 agree well with the values obtained earlier using 0.01 M buffers.[11] However, in the present experiments we did not observe the drop in yield of **9a** and the increase in yield of **4** at pH 7 that was noted at pH's near neutrality in the previous report.[11] Instead we observed at pH 7 a yield of **4** (20%) that is close to that obtained at pH 5 (0.01 M acetate buffer, Figure 6) and a yield of **9a** (35%) that is higher than that observed at pH 5 (0.01 M acetate buffer) (25%) and higher than the yield of **4** at pH 7 (18%) (Figure 7).

In contrast to earlier reports on the reactions of **1**,[11,18] we did not observe the precipitation of "blue compound" at pH's near neutrality. This may be because the present experiments were performed on a smaller scale (2 mg/5 mL) than that used previously (8 mg/20 mL).[11]

Stability of 8-Iodoxanthine in the Presence of Iodide Ion. Under the conditions used for the reactions of **1**, 8-iodoxanthine afforded a small (10–14%) yield of **4**, which was little affected by the presence of iodide ion, by changes in the concentration of it, or by changes in pH (Table I). The consistent formation of small amounts of **4** was explained when it was found that 8-iodoxanthine is readily reduced to **4** photochemically (Φ = 0.1). Reaction of 8-iodoxanthine with complete light exclusion for all manipulations, including chromatography, reduced the yield of **4** to 3%. Chromatography of a reaction of **1** performed under identical conditions did not reveal the presence of any 8-iodoxanthine. Since the half-life of **1** is only a few minutes at pH 7,[11] **1** and 8-iodoxanthine were each allowed to react for only 30 min with light exclusion in the presence of 2 equiv of iodide. Chromatography of the two solutions showed that under these conditions **1** was completely reduced to **4**, while 8-iodoxanthine was recovered in 98% yield with only a trace (2%) of **4**. No 8-iodoxanthine was detectable from the reaction of **1**. These experiments demonstrate that 8-iodoxanthine is not an intermediate in the reduction of **1** to **4** in the presence of iodide ion.

Discussion

Changes in the pH over the range 0 to 3 exert little effect on the rate of reaction of **1** or on the composition of the reaction products from it.[11] The mechanism proposed for the 8-substitution reaction in this pH range (path a, Scheme I) involves ionization of **1** to acetate ion and the delocalized cation

6 and reaction with a nucleophile at C-8 in the π-rich imidazole ring[19] to yield an 8-substitution product (9). At pH's above 3 the effects of changes of pH on the reaction of 1 were found to be complex.[11] As the pH was increased the reaction rate increased, the yield of 3-hydroxyxanthine dropped, the yield of uric acid rose, and a third product, xanthine, was obtained and its yield also increased. Ionization of the imidazole proton, $pK \sim 6.5$,[14] to the anion (2) appears to initiate this "fast" reaction. It was proposed that 2 can eliminate acetate ion to yield 7 and that this species upon protonation affords the cation (6) that then leads to 8-substitution products. The sequence 2 → 7 → 6 → 9 was designated path b. Since the reduction product, xanthine (4), was only formed under the conditions associated with path b, it was deduced that 4 arose from an intermediate formed only on path b. It was suggested that 2 might undergo not only elimination to 7 but also homolysis to 3 and that 4 arose from the radical anion (3). This deduction was supported by two observations: that a radical induced photochemically in solid 5, and deduced to have an amidyl structure comparable to 3, is rapidly reduced to 4 when dissolved in water,[23] and that in the presence of iodide ion 1 is completely reduced to 4 with the formation of 0.5 equiv of I_2. The inability to detect radicals in solutions either of 1[11] or of the radical from 5[23] by ESR suggested that both were too reactive to be detected by this technique. The absence of detectable radicals from 1 with the more sensitive spin-trapping technique,[24] however, suggested that the redox reaction of 1 with iodide merited closer examination for other possible mechanisms.

We now report that the amount of reduction of 1 in the presence of iodide ion is quite pH dependent and is complete only at pH's above 5. As the pH is decreased below 6 in the presence of 2 equiv of iodide ion, there is a steep decline in the yield of 4 (Figure 2), but no 8-substitution product, including 8-iodoxanthine (9, Nu = I), is detectable at any pH. At pH's below 3 8-substitution occurs via path a and only the cation 6 is involved. Neither the anion 2 nor a radical derived from it, e.g., 3, should be formed and in the absence of iodide ion 4 is not observed.[11] However, in the presence of 2 equiv of iodide ion, the amount of 1 normally reacting to form 9a or 9b in the pH range 1 to 3 (5%)[11] now yields 4 (Figure 2). The evidence that iodide reduced only the portion of 1 that normally reacts via 6 to afford an 8-substitution product in a pH region where the only intermediate from 1 appears to be 6 suggested that reduction by iodide ion proceeds via 6 or a product derived from it.

Several possible mechanisms have been considered to explain the redox reaction with iodide ion. Refluxing HI containing phosphonium iodide[25] or hypophosphorus acid[26] is reported to reduce 8-halopurines, including 8-chloroxanthine, 9b. However, under experimental conditions in which ~5% of 1 is reduced at pH 1 9b is recovered unchanged. Under the same conditions 8-iodoxanthine did afford a small (10–14%) amount of 4 at pH 1 (Table I), but this arises by photochemical reduction; in the absence of light, the formation of 4 from 8-iodoxanthine is negligible. Under conditions where 8-iodoxanthine could be recovered essentially quantitatively, 1 was reduced to 4 by iodide ion and 8-iodoxanthine could not be detected in the reaction mixture. Thus 8-iodoxanthine is not an intermediate in the reduction of 1 to 4 in the presence of iodide ion. 3-Acetoxyxanthine is a cyclic *N,O*-diacylaromatic hydroxylamine and *O*-acylhydroxylamines are known to liberate I_2 from acidic iodide solution.[27] However, increases in the concentration of iodide beyond 2 equiv did not result in a greater extent of reduction of 1 (Figure 1), indicating that iodide is not reacting directly with 1.[28] Iodide does not react with 5[11] and in confirmation of this the yield of 5 from 1 was unaffected by the presence of iodide or by changes in its concentration. It is conceivable that iodide might reduce 6 by promoting spin inversion of the nitrenium ion of the resonance contributor 6a to the triplet state, a process known to be catalyzed by heavy atoms,[29] and nitrenium triplets are reportedly rapidly reduced to the parent amine.[30] However, this process should be sensitive to changes in the concentration of the heavy atom and that was not observed in the reactions of 1 with iodide (Figure 1). In addition, that process should not induce oxidation of iodide. Thus catalyzed spin inverstion to the nitrenium triplet of 6a is also excluded.

The proposal most consistent with all of the available data is that the reduction of 1 to 4 in the presence of iodide occurs by nucleophilic addition of iodide at the electron-deficient nitrogen of 6, i.e., via the resonance contributor 6a, to form the intermediate 8a (Scheme I). This is then followed by nucleophilic displacement on 8a by a second iodide ion to yield the anion of 4 and I_2. This mechanism is analogous to that proposed for the oxidation of iodide by *O*-acyl esters of hydroxylamine[31,32] and the oxidation of iodide by the *N*-iodoamide, 8a, would correspond to a known reaction of *N*-haloamides.[33,34] The intermediacy of 6a in the redox reaction with iodide would also be quite consistent with the reduction only of the amount of 1 that normally leads to 9 via 6b at low pH's.

To test the hypothesis that the electron-deficient nitrogen of 6 is the intermediate in the oxidation of iodide the reaction of 1 with thiourea was examined, since thiourea shows a high reactivity with electron-deficient nitrogen centers.[35] If the nitrenium ion (6a) is the active redox intermediate, then thiourea should also produce an enhanced reduction of 6 to 4. The reaction of 1 with 5 equiv of thiourea at pH 3 did not result in the complete reduction of 1 but instead gave a mixture of 5, 4, and 8-thiouric acid, 9c (Figure 4). However, the formation of a significant amount of xanthine at pH 3, where this product is normally not formed, indicates that thiourea is reacting at least in part in a manner similar to that of iodide. Changes in the concentration of thiourea at pH 3 did not significantly alter the yields of the three products (Figure 3), which indicates that thiourea is not acting directly with 1. Increases in the pH from 1 to 5 caused parallel increases in the yields of 4 and 9c and a corresponding decrease in the yield of 5 (Figure 4). By pH 5 all of 1 reacted to yield either 4 or 9c and further increases to pH 7 did not affect the yields of the products. Significantly, and in contrast to the results in the absence of thiourea (Figures 5, 6, and 7, 0.1 M buffer), the yield of the reduction product, 4, is greater than that of the 8-substitution product, 9c, at pH's near neutrality. These data indicate that thiourea, like iodide, can react with an intermediate from 1 and lead to enhanced reduction of 1. Formation of an *S*-(3-xanthyl)isothiouronium intermediate, 8b, comparable to the *S*-nitrosoisothiouronium intermediate proposed for the oxidation of thiourea by nitrite[36] and subsequent reaction of 8b to 4 represent a plausible mechanism for the reduction of 6 to 4 by thiourea. These data thus agree with the conclusion that redox reactions occur via the nitrenium ion, 6a, rather than via a radical intermediate.

Additional support for that conclusion was provided by studies on the effect of changes in the concentration of buffers at pH's 5.0 and 7.0 on the reaction products from 1 (Figures 6 and 7). At those pH's path b predominates.[11] At a single pH the concentration of 2 should not be significantly affected by changes in the concentration of buffer. If the anion 2 were the common intermediate from which the spontaneous reduction and the 8-substitution reactions of 1 diverge, via 3 and 7 (Scheme I) as previously proposed, then changes in the buffer concentration should have little or no effect on the yields of the products from the two reactions. This was observed over most of the concentration range with the weakly nucleophilic phosphate buffer (Figure 7). However, increases in the concentration of acetate buffer at pH 5.0 caused a dramatic increase in the yield of 9a and a significant decrease in the yield

of 4 (Figure 6). These data indicate that acetate ion is acting as a nucleophile at C-8[41] and are incompatible with the interpretation that the anion 2 is the central intermediate from which the two reaction paths diverse.[42] It is apparent that acetate ion does not act as a common ion and suppress the 8-substitution reaction. Under those conditions the reaction rate should decrease as the concentration of acetate is increased. However, changes in acetate buffer concentration caused little change in the observed pseudo-first-order rate constant (Figure 6) except in extremely high concentrations of buffer, where it increased. These data are consistent with the conclusion[11] that on path b acetate ion is formed in the course of an elimination reaction, **2 → 7**, rather than through an ionization.

The reactions of **1** with iodide, thiourea, and acetate ion demonstrate that the relative proportion of 8-substitution and reduction products from **1** can vary considerably, depending upon the type of nucleophile added. These results appear explicable in terms of the "hard" and "soft" acid and base (HSAB) proposal of Pearson,[43,44] later extended by Klopman.[45] The present studies indicate that *both* electron-deficient sites of the delocalized cation **6** can react with nucleophiles. The evidence suggests that **6** is an ambident electrophile whose two reactive sites, represented by the nitrenium ion, **6a**, and the carbonium ion, **6b**, differ in their degree of polarizability and that the position and type of reaction with a nucleophile will be determined by the character of the approaching nucleophile. The high reactivity of **6** at N-3 with iodide, the "softest" base of the common anions, suggests that the electron-deficient nitrogen of **6a** must be a very "soft" acid. In agreement, thiourea, a slightly less "soft" base than iodide, reacts preferentially at the nitrenium ion of **6a**, as shown by the higher yield of **4** than of **9c** (Figures 3 and 4), but also reacts at the carbonium ion of **6b**. The preferential reaction of the "borderline" bases, azide, nitrite, and bromide, as well as the "hard" bases, water, amines, acetate, and chloride ions, with the "borderline" carbonium ion of **6b** to yield 8-substitution products[10] accords well with the HSAB interpretation. The available data on the reactions of **1** with nucleophiles indicate that reactions at the nitrenium ion of **6a** are frontier orbital controlled[45] "soft–soft" interactions that result in oxidation of the nucleophile with concomitant reduction of **6** to xanthine while charge controlled[45] interactions occur at the carbonium ion of **6b** and yield 8-substitution products. The single example to date of the reaction of a "soft" base at the C-8 position of **6b**, rather than at N-3 of **6a**, is the reaction of the "soft" thioether function of methionine with **6b** to afford 8-methylmercaptoxanthine, **9e**.[10] That evidence suggests that redox reactions at N-3 of **6a** may be better described in terms of frontier orbital control.[46]

Relationship to Oncogenesis. Although products have been isolated from nucleophilic substitution reactions at nitrenium ions derived from some *N,O*-diacylaromatic hydroxylamines, notably 8-(*N*-2-fluorenylacetamido)guanine from *N*-acetoxy-*N*-acetyl-2-aminofluorene,[48] no such products have been obtained from the cation, **6**, from **1**. The present studies are the first to indicate that reactions can occur at the nitrenium ion of cations from *N*-acetoxypurines. They also indicate that redox and nucleophilic substitution reactions are two manifestations of a single species derived from **1**, a conclusion that is further supported by studies on the reaction of 1,7-dimethylguanine 3-oxide with acetic anhydride.[49] These studies suggest that either mode of reactivity of esters of *N*-oxidized purines could be significant to the initiation of the oncogenic process.

The present work now makes it apparent why only certain[18] acetylated *N*-oxidized purines oxidize iodide ion. The data indicate that only those derivatives that can yield a nitrenium ion should oxidize iodide ion. Since neither the nonacetylated compounds[10] nor the corresponding *O*-acetyl derivatives themselves oxidize iodide, the oxidation of iodide ion represents a convenient method to detect the formation of a nitrenium ion. This technique should have applicability to studies on the mechanism of oncogenesis not only by purine *N*-oxides but also by other *N,O*-diacylaromatic hydroxylamines.

Experimental Section

General. UV spectra were determined with a Unicam SP800A recording spectrophotometer and NMR spectra with a Jeol 100 Hz spectrometer. The elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

The 3 M acetate and formate buffers were prepared by neutralizing solutions of glacial acetic acid (86.2 mL) and 98% formic acid (84.2 mL) with 1 N potassium hydroxide to the desired pH, 5.0 and 4.0, respectively, then diluting to yield 500 mL of the 3 M buffer. The 1.5 M phosphate buffer was prepared by neutralizing a solution of $NaH_2PO_4 \cdot H_2O$ (103.5 g) with 1 N KOH to pH 7.0 and diluting to 500 mL. Dilutions of the concentrated buffers afforded the lower concentrations of the buffers.

All reactions of 3-acetoxyxanthine were performed with $\sim 2 \times 10^{-3}$ M solutions. Weighed samples of 2.0 to 2.5 mg (8.5 to 10 μmol) were dissolved in 5.0 mL of the appropriate buffer in 50-mL round-bottom flasks. The reactions were allowed to proceed overnight with continuous stirring in the absence of light at room temperature, which remained near 20 °C with a maximum variation of ±2 °C. After the reactions were complete the solvent was removed under vacuum and the residue was redissolved in a minimum amount of water with a drop of NH_4OH. The mixtures were analyzed by ion-exchange chromatography with standardized Dowex 50 [H^+], X-8, 200–400 mesh, columns (9 × 120 mm) that had been cleaned by prior washing with 2 N HCl in 60% CH_3OH and water. Column eluates were monitored with an ISCO UA-2 UV analyzer with coordinated fraction collector.

Water eluted **9a–c**, 0.1 N HCl eluted **5**, while **4** required 1 N HCl. Molar quantities were calculated from the elution volumes and ε values: uric acid, **9a** (pH 2 to 4), λ_{max} 285 nm (ε 12 000);[7] 3-hydroxyxanthine, **5** (pH 2 to 4), λ_{max} 272 nm (ε 10 100);[7] 8-chloroxanthine, **9b** (pH 1), λ_{max} 273 nm (ε 11 900);[50] xanthine, **4** (pH 0), λ_{max} 260 nm (ε 9200); 8-thiouric acid, **9c** (pH 2), λ_{max} 303 nm (ε 18 200).[17] 8-Thiouric acid and 8-chloroxanthine were identified by comparison of their UV spectral values with those reported.[17,50] Thiourea was also eluted by water and in the presence of high concentrations of thiourea **9c** and thiourea were eluted together. To determine the yield of **9c**, the fractions containing the mixture were evaporated to dryness and were applied to a longer (9 × 250 mm) Dowex 50 [H^+] column on which **9c** was eluted by water just before thiourea.

All yields and recoveries are based on the initial weight of **1** used. Values in Figures 1, 2, and 4 are the result of single determinations. Those in Figures 3, 5, 6, and 7 are from triplicate determinations and the average values and maximum variations are shown. pH values for the buffered solutions showed only slight changes in most buffers during the course of the reactions. Final values were slightly lower (0.2 pH unit) in formate buffers. The only acetate buffer to show a change was 0.01 M, in which the pH decreased by 0.6 unit. Final pH values in phosphate buffers were 0.2 to 0.4 pH unit higher than the initial value. Iodide ion concentration in the experiments illustrated in Figure 2 was 4×10^{-3} M. The experiments illustrated in Figures 2 and 4 were performed in 0.1 M formate (pH 4), acetate (pH 5), succinate (pH 6), and phosphate (pH 7) buffers. For pH's 3 and below appropriate concentrations of HCl were used.

Pseudo-first-order rate constants in Figures 5 and 6 are for formation of the product mixture and were determined at 23 °C by monitoring the UV spectral changes of aliquots from 2×10^{-3} M solutions in 1-mm path-length cuvettes until the reactions were complete. The rate constants were calculated by a least-squares analysis from a plot of ln (OD_∞ − OD) at 290 nm vs. time. The plots were linear for at least 4 half-lives of the reaction, confirming that the reaction was pseudo-first-order at this wavelength. The major contributor to the UV spectrum of the product mixtues at 290 nm is uric acid; **5** is a minor contributor, while **4** exhibits little absorption at this wavelength.

3-Acetoxyxanthine Hydrochloride. A sample of 3-hydroxyxanthine, stirred overnight as a suspension in 0.01 N HCl, was collected and washed with water, acetone, and ether and then dried over P_2O_5 under vacuum. A portion of the dry, finely ground sample (1 g) was suspended in acetic acid (20 mL), acetic anhydride (20 mL), and

acetyl chloride (8 mL). The reaction mixture was stirred in a sealed flask at room temperature in the dark. Progress of the reaction was monitored by collecting a small sample of the precipitate, dissolving it in 0.05 N HCl, and chromatographing it quickly over a Dowex 50 [H^+], 200–400, mesh, column (9 × 100 mm) eluting with 0.05 N HCl;[14] **1** was eluted first, followed by **5**. After 1 week an additional 1 mL of acetyl chloride was added. The reaction was complete after 2 weeks. The precipitate was collected, washed with acetic acid and then with Et_2O, and then dried under vacuum over KOH: yield 1.14 g (78%); NMR (DMSO-d_6) δ 2.40 (s, 3, $COCH_3$), 8.048 (s, 1, CH), 11.604 (s, 1, NH). Anal. Calcd for $C_7H_6N_4O_4$·HCl: C, 34.09; H, 2.86; N, 22.72; Cl, 14.38. Found: C, 34.52; H, 2.90; N, 22.26; Cl, 14.24.

The extinction coefficient of **1** was determined by plotting the OD at 267 nm from a family of curves of a reacting solution of **1** at pH 4.0 against time and extrapolating to the initial OD value; λ_{max} (pH 4.0) 267 nm (ϵ 9200).

Chromatography of a weighted sample of **1**, as described previously, and calculation of the weight of **5** in the sample showed that the product contained, at most, 3% of **5**, part of which may be the result of hydrolysis of **1** during the chromatography.

8-Iodoxanthine. 8-Iodoguanine[51] was prepared from 8-iodoguanosine[16] by allowing a solution of the nucleoside in 50% aqueous CF_3CO_2H to be stirred overnight at room temperature, removing the solvents, and recrystallizing from H_2O. To a chilled solution of 8-iodoguanine (450 mg, 1.5 mmol) and 35 mL of CF_3CO_2H was added dropwise over a period of 90 min a solution of $NaNO_2$ (1 g) in 15 mL of water. After addition was complete the reaction was allowed to proceed at room temperature overnight. A silica gel GF TLC of the reaction mixture ($CHCl_3$–CH_3OH, 4:1) indicated the reaction was complete. The solvents were removed under vacuum and a solution of the residue in aqueous CH_3OH was applied to a 2 × 20 cm Dowex 50 [H^+], 200–400 mesh, column. Sixty percent aqueous CH_3OH eluted 8-iodoxanthine as well as a small amount of a second, unidentified product that was eluted just prior to the 8-iodoxanthine. The fractions containing 8-iodoxanthine were combined, the solvents were removed, and the sample was applied to the column and eluted as described. This procedure was repeated three times until all of the contaminant had been removed. The fractions containing 8-iodoxanthine from the final column were combined, the solvents were removed, and the product was recrystallized from CH_3OH/H_2O (C): yield 65 mg (15%); mp >300 °C, grad dec; pK_a's, determined from isosbestic spectra, 6.2 and 10.3; UV λ_{max} ($\epsilon \times 10^{-3}$) (pH 3.0) 215 (14.2), 278 (12.6), (pH 8.0) 213 (19.1), 280 (14.1) (pH 13.0), 245 sh (6.8), 289 (10.2) nm [lit.[15] (pH 1) 278 nm (pH 13), 288 nm]; NMR (DMSO-d_6) δ 11.59 (s, 1, NH), 10.85 (s, 1, NH), both exchangeable in D_2O; mass spectrum *m/e* (CI) 279 (M + 1). The analytical sample was dried over P_2O_5 at 120 °C for 3 h. Anal. Calcd for $C_5H_3N_4O_2I·H_2O$: C, 20.29; H, 1.69; N, 18.93; I, 42.88. Found: C, 20.41; H, 1.55; N, 18.75; I, 42.79.

Photolysis of 8-Iodoxanthine. The quantum yield for photoreduction of 8-iodoxanthine was determined by potassium ferrioxalate actinometry[52] in a Rayonet photochemical reactor equipped with 300-nm lamps with a 1×10^{-3} M solution of 8-iodoxanthine in 60% aqueous CH_3OH; $\Phi = 0.1$. Xanthine formation was determined by column chromatography and its identity was conformed by its characteristic UV absorption spectra[53] at three pH's and by paper chromatography in two solvent systems.

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Registry No.—**1**, 22052-01-3; **1**·HCl, 64761-25-7; 8-iodoguanine, 19690-21-2; 8-iodoxanthine, 64761-27-9.

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$$I^- + H_2NOSO_3H \rightarrow INH_2 + HSO_4^- \quad (I)$$

$$INH_2 + HI \rightarrow NH_3 + I_2 \quad (II)$$

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Stepwise Synthesis of *N*-Acetylneuraminic Acid and *N*-Acetyl[1-^{13}C]neuraminic Acid

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N-Acetylneuraminic acid (NANA) has been synthesized from 2-acetamido-2-deoxy-D-mannose by the stepwise extension of the carbon chain. Addition of nitromethane to 2-acetamido-2-deoxy-D-mannose gave 3-acetamido-1,3-dideoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol, which underwent a modified Nef reaction to yield 3-acetamido-3-deoxy-D-*glycero*-D-*galacto*-heptose. The heptose was converted to 3-acetamido-3-deoxy-4,5:6,7-di-*O*-isopropylidene-*aldehydo*-D-*glycero*-D-*galacto*-heptose via its isopropylidenated dimethyl dithioacetal derivative. The *aldehydo*-heptose was converted via a second nitromethane addition, and subsequent standard reactions, to 4-acetamido-1,2,4-trideoxy-1-nitro-D-*glycero*-D-*galacto*-octitol, which underwent a modified Nef reaction to yield 4-acetamido-2,4-dideoxy-D-*glycero*-D-*galacto*-octose. Treatment of the octose with aqueous sodium cyanide gave the expected nononic acid derivatives 5-acetamido-3,5-dideoxy-D-*erythro*-L-*manno*-nononic acid and 5-acetamido-3,5-dideoxy-D-*erythro*-L-*gluco*-nononic acid, which were selectively oxidized at C-2 to give 5-acetamido-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (NANA). Using Na^{13}CN in the synthesis gave [1-^{13}C]-NANA.

Acylneuraminic acids (sialic acids)[1,2] are important natural glycoses found in glycoproteins, glycolipids,[3,4] and microbial polysaccharides,[5-7] where they influence physicochemical, immunological, and other biological properties. These acids are N-acylated with acetyl or glycoloyl groups, and frequently *O*-acetyl substituents are present.

N-Acetylneuraminic acid (NANA), the most widely occurring member of the sialic acid family, was first obtained crystalline from submaxillary mucin,[8] and subsequent investigations showed NANA to be 5-acetamido-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid.[9] Chemical,[10] ^{1}H NMR,[11] and ^{13}C NMR[5,12] studies showed it to exist in aqueous solution as 5-acetamido-3,5-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranosonic acid[13] (Figure 1). The assigned structure of the acid is supported by x-ray analysis data.[14,15]

N-Acetylneuraminic acid has been synthesized in low yield by the reaction of oxalacetic acid with either 2-acetamido-2-deoxy-D-glucose[16,17] or 2-acetamido-2-deoxy-D-mannose,[18,19] and improved yields were reported by the condensation of di-*tert*-butyl oxaloacetate with the acetamidoglycoses or their 4,6-*O*-benzylidene derivatives.[20] Application of the Wittig reaction to 3-acetamido-2,4,5,6,7-penta-*O*-acetyl-3-deoxy-*aldehydo*-D-*glycero*-D-*galacto*-heptose has been used to effect the stereochemically defined synthesis of NANA.[21]

The aim of the present work was to develop a practical general method for the stepwise synthesis of NANA specifically labeled in the carbon chain with either ^{14}C or ^{13}C, which could also be adapted to the synthesis of configurational analogues of NANA.

The stepwise ascent procedure selected was the Fischer–Sowden nitromethane addition method.[22-24] It has been found that nitromethane did not always undergo base-catalyzed addition to glycoses. For example, while 2-acetamido-2-deoxy-D-mannose undergoes nitromethane addition, 2-acetamido-2-deoxy-D-glucose and 2-acetamido-2-deoxy-D-galactose fail to react with nitromethane under the usual experimental conditions. In other experiments, it was found that the latter glycoses readily underwent base-catalyzed addition of nitromethane to their protected acyclic aldehydo derivatives prepared by demercaptalation of their ketal-substituted dialkyl dithioacetal derivatives.[25] The use of the *aldehydo*-glycose derivatives to effect successful nitromethane additions appears to be of general application, and it was used in the present work when the conversion of the intermediate aldoheptose to the corresponding 1-deoxy-1-nitrooctitol derivatives could not be effected under the normal nitromethane addition conditions.

Discussion

2-Acetamido-2-deoxy-D-mannose (**1**) underwent base-catalyzed addition of nitromethane to yield 3-acetamido-1,3-dideoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol (**2**), with the formation of less than 1% of the corresponding D-*glycero*-D-*talo*-heptitol. The stereospecificity of this addition follows that found in the base-catalyzed nitromethane addition to D-mannose[26] and is that required for the introduction of the asymmetric center at C-4 of NANA. Heptitol **2** under modified[27] Nef[28] reaction conditions afforded 3-acetamido-3-deoxy-D-*glycero*-D-*galacto*-heptose (**3**), which was identical with an authentic sample prepared by reduction of the nitrile produced by the addition of hydrogen cyanide to 2-acetamido-2-deoxy-D-mannose.[29]

Heptose **3**, on treatment with methanethiol in concentrated hydrochloric acid, was converted in high yield to crystalline 3-acetamido-3-deoxy-D-*glycero*-D-*galacto*-heptose dimethyl dithioacetal (**4**), which on acid-catalyzed isopropylidenation gave crystalline 3-acetamido-3-deoxy-4,5:6,7-di-*O*-isopropylidene-D-*glycero*-D-*galacto*-heptose dimethyl dithioacetal (**5**), the assigned positional substitution of the isopropylidene groups being inferred from stereochemical considerations.[30] Demercaptalation of **5** produced 3-acetamido-3-deoxy-4,5:6,7-di-*O*-isopropylidene-*aldehydo*-D-*glycero*-D-*galacto*-heptose (**6**), which gave IR and NMR data consistent with the existence of the aldehydo function.

The substituted *aldehydo*-heptose **6** readily underwent base-catalyzed addition of nitromethane to give an almost theoretical yield of 4-acetamido-1,4-dideoxy-5,6:7,8-di-*O*-isopropylidene-1-nitro-D-*erythro*-L-*manno*-octitol (**7**), which on mild acid hydrolysis underwent deisopropylidenation to give crystalline 4-acetamido-1,4-dideoxy-1-nitro-D-*erythro*-L-*manno*-octitol (**8**). The nitromethane addition to **6** was stereospecific, giving only the octitol having the D-*erythro*-L-*manno* configuration, the assignment of the configuration of the new asymmetric center at C-7 being based on the observed positive Cotton effect at 340 nm in the ORD spectrum of **8**.[31,32] Acetylation of **8** afforded crystalline 4-acetamido-2,3,5,6,7,8-hexa-*O*-acetyl-1,4-dideoxy-1-nitro-D-*erythro*-L-*manno*-octitol (**9**), which on refluxing in benzene solution in the presence of sodium bicarbonate was converted to crystalline 4-acetamido-3,5,6,7,8-pentaacetoxy-D-*glycero*-D-*galacto*-1-nitro-1-octene (**10**). Octene **10** on reduction with sodium borohydride in ethanol solution afforded crystal-

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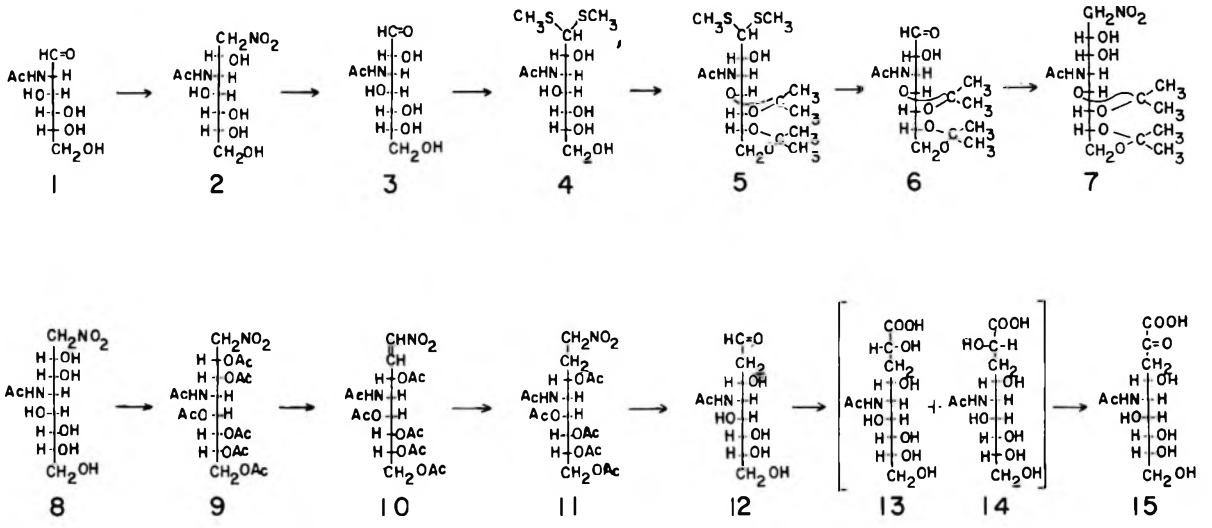

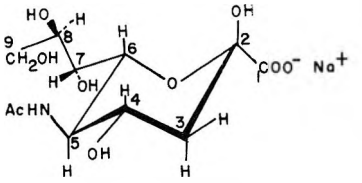

Figure 1. The assigned structure of NANA in aqueous solution.

line 4-acetamido-3,5,6,7,8-penta-*O*-acetyl-1,2,4-trideoxy-1-nitro-D-*glycero*-D-*galacto*-octitol (**11**), which underwent a modified Nef reaction to yield crystalline 4-acetamido-2,4-dideoxy-D-*glycero*-D-*galacto*-octose (**12**).

Octose **12**, which had the correct configuration for direct conversion to NANA, was converted to its epimeric nononic acid derivatives, 5-acetamido-3,5-dideoxy-D-*erythro*-L-*manno*-nononic acid (**13**) and 5-acetamido-3,5-dideoxy-D-*erythro*-L-*gluco*-nononic acid (**14**), by treatment with sodium cyanide. Acids **13** and **14** were formed in approximately equal proportions as evidenced by ^{13}C NMR and chromatographic analysis and were indistinguishable from the same acids produced in essentially the same proportion by the sodium borohydride reduction of the keto function of the salt of authentic NANA.

The mixed nononic acids **13** and **14** were oxidized with a vanadium pentoxide–potassium chlorate catalyst,[33-35] which effected the selective oxidation of the hydroxy groups at C-2 to yield 5-acetamido-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (NANA, **15**), which had identical physical, chromatographic, and NMR data with authentic NANA.

Starting from 2-acetamido-2-deoxy-D-mannose, the above synthetic route can give NANA in 17% overall yield. While most of the steps can be made in better than 90% yield, a significant loss of materials occurs in the nitromethane addition to 2-acetamido-2-deoxy-D-mannose, where it was observed that the unreacted material was mainly 2-acetamido-2-deoxy-D-glucose, which arises from the epimerization of the starting material in the alkaline medium. A second significant loss occurs in the isopropylidenation step, and it is possible that alternative protection groups would lead to improved yields. Although the synthesis of NANA using nitromethane-^{13}C or -^{14}C would not be practical under the described conditions, preliminary experiments have shown that nitromethane addition to some protected *aldehydo*-glycoses can be effected in excellent yield in *N,N*-dimethylformamide solvent using stoichiometric amounts of nitromethane catalyzed with 50% aqueous sodium hydroxide.[25] If this finding proves to be of general application, the use of nitromethane-^{13}C or -^{14}C in the synthesis of specifically labeled glycoses may be of practical value.

5-Acetamido [1-^{13}C]-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid was synthesized in 51% yield from the nononic acids **13** and **14** using Na^{13}CN and [1-^{13}C]NANA gave a ^{13}C NMR spectrum consistent with that expected. It is probable that the synthetic route could be used for the synthesis of configurational isomers of NANA.

All the compounds synthesized in the work had elemental analyses, IR, ^1H NMR, and ^{13}C NMR data consistent with the assigned structures.

Experimental Section

General Methods. Evaporations were performed under reduced pressure and below 40 °C. Melting points were determined on a Fisher-Johns apparatus and are corrected. Optical rotations were determined at 20 °C in 1-dm tubes using a Perkin-Elmer Model 141 polarimeter. Optical rotary dispersion (ORD) measurements were made using a Jasco Model ORD/UV-5 automatically recording spectrophotometer. Infrared (IR) spectra were obtained by the KBr disk technique using a Perkin-Elmer 237B Infracord.

Paper chromatography was performed by the descending method on Whatman No. 1 filter paper using the solvent systems (A) pyridine–ethyl acetate–water (2:5:5 v/v, top layer) and (B) 1-propanol–acetic acid–water (54:8:18 v/v). Compounds were detected with (a) 2% silver nitrate in acetone followed by 2% sodium hydroxide in ethanol,[36] (b) 2% *p*-anisidine hydrochloride in ethanol,[37] or (c) 0.02 M aqueous sodium metaperiodate followed by ethylene glycol–acetone–sulfuric acid (50:50:0.3 v/v) and 6% sodium 2-thiobarbiturate.[38] The rates of movement of the compounds are quoted relative to 2-acetamido-2-deoxy-D-mannose (R_M).

Thin-layer chromatography (TLC) was done on precoated 0.25-mm silica gel 60 plates (Merck) using (A) benzene–methanol (9:1 v/v) or (B) 1-butanol–acetone–water (4:5:1 v/v), and compounds were located by spraying with 10% sulfuric acid in ethanol and heating at 120 °C. Mobilities are quoted relative to the solvent front (R_f).

Gas chromatography (GC) was performed using a Hewlett-Packard 402 gas chromatograph with a hydrogen flame detector, fitted with glass U-tubes (4 ft × 6 mm × 3 mm i.d.) packed with (A) 3% (w/w) ECNSS-M on 100–120 mesh Gas Chrom Q or (B) 3% (w/w) OV-17 on 100–120 mesh Gas Chrom Q. Development was made with helium, and samples were injected directly onto the column packings without the use of the flash-heating system. Retention times of the compounds are quoted relative to 2-acetamido-2-deoxy-1,3,4,5,6-penta-*O*-acetyl-D-mannitol (T_{MA}).

Proton magnetic resonance (^1H NMR) spectra were recorded using a Varian EM-360 spectrometer at 60 MHz with tetramethylsilane as an internal standard. ^{13}C nuclear magnetic resonance (^{13}C NMR) spectra were measured on a Varian CFT-20 (20 MHz) spectrometer in 10-mm o.d. tubes, and the spectra were recorded with complete proton decoupling, spectra windows of 200 ppm, and digitization into 4K data points. Solvent deuterium resonance was used as a field frequency lock, and chemical shifts are expressed relative to tetramethylsilane contained in a coaxial 5-mm o.d. sample tube.

3-Acetamido-1,3-dideoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol (2). To a stirred suspension of 2-acetamido-2-deoxy-D-mannose (1, 20 g) in nitromethane (400 mL) was added dropwise over 20 min a solution of 1.7 M sodium methoxide in methanol (52 mL), followed by methanol (300 mL) to give a clear solution which was stirred at room temperature for 18 h. Following the addition of ether (1 L), the precipitated material was collected by filtration, and the ether-washed solid, dissolved in a minimum amount of cold water, was passed down a column of Rexyn 101 (H^+) ion-exchange resin (800 mL). The eluate and water washings from the column were concentrated under reduced pressure to yield a syrup which, on trituration with warm methanol, afforded crystalline **2** (14.62 g, 57.5%), which on paper chromatography (solvent A) gave a single silver nitrate positive spot with R_M 3.81. A sample of **2** recrystallized from methanol had mp 200–202 °C; $[\alpha]_D$ −59° (c 0.75, water); ORD $[\phi]_{350}$ +111° (c 0.2, water); IR 1560 cm^{-1} (NO_2); ^{13}C NMR (D_2O) δ 175.5 (C=O), 80.10 (CH_2NO_2), 71.89, 70.23, 68.57, 67.89, 64.37 (CH_2OH), 52.65 (CH–NHCOCH$_3$), 22.99 (CH_3CONH).

Anal. Calcd for $C_9H_{18}N_2O_8$: C, 38.29; H, 6.42; N, 9.92. Found: C, 38.40; H, 6.43; N, 9.97.

3-Acetamido-3-deoxy-D-*glycero*-D-*galacto*-heptose (3). Compound **2** (14.62 g) dissolved in a solution of $Ba(OH)_2 \cdot 8H_2O$ (15.9 g) in water (280 mL) was added dropwise with stirring to a cooled (0 °C) solution of concentrated sulfuric acid (32 mL) in water)170 mL), and the mixture was then stirred at 20 °C for 16 h. The reaction mixture was neutralized in the cold with saturated barium hydroxide solution (to pH 6); following the addition of barium carbonate (1 g), the mixture was filtered and the filtrate and water washings were passed through columns of Rexyn 101 (H^+) (6 mL) and Duolite A4 (OH^-) (5 mL) ion-exchange resins. Concentration of the eluate afforded **3** as a solid (11.8 g, 90%), which on paper chromatography (solvent A) gave a single silver nitrate and *p*-anisidine positive spot with R_M 0.52. A sample of **3** after two recrystallizations from ethanol had mp 215–216 °C and $[\alpha]_D$ +81.7° (4 min) → +116° (equilibrium) (*c* 1.2, water) (lit.[29] mp 223–225 °C, $[\alpha]_D$ +149.5 → +110.5° (water); the difference in melting point and mutarotation values is probably due to crystallization of **3** in different anomeric forms).

Anal. Calcd for $C_9H_{17}O_7N$: C, 43.02; H, 6.82; N, 5.58. Found: C, 43.31; H, 6.80; N, 5.51.

GC analysis (column A, 225 °C) of reduced and acetylated **3**[39] gave a single peak with T_{MA} 1.90, having the same retention time as authentic 3-acetamido-1,2,4,5,6,7-hexa-*O*-acetyl-3-deoxy-D-*glycero*-D-*galacto*-heptitol. Selective periodate oxidation and subsequent reduction of the methyl glycosides of **3** afforded 3-amino-3-deoxy-D-galactose hydrochloride with mp 180 °C and $[\alpha]_D$ +90° (c 0.4, water), which was chromatographically identical with an authentic sample of the aminoglycose.

3-Acetamido-3-deoxy-D-*glycero*-D-*galacto*-heptose Dimethyl Dithioacetal (4). Compound **3** (10.1 g) was dissolved in concentrated hydrochloric acid (20 mL) and cooled in an ice bath, and following the addition of methanethiol (20 mL) the stirred mixture was allowed to warm to 20 °C over 20 min. The reaction mixture was poured into ice water (300 mL) containing a few drops of 2-octanol, and the stirred solution was quickly neutralized by the addition of lead carbonate. Following filtration through a bed of Celite, the filtrate and washings were concentrated to dryness, and the residue, after extraction with boiling ethanol (400 mL), was filtered while hot (to remove $PbCl_2$). On cooling the ethanol solution to 0 °C, it gave crystalline **4** (10.5 g, 80%), which had mp 168–169 °C and $[\alpha]_D$ −34° (*c* 1.7, water), and on paper chromatography (solvent A) **4** gave a single silver nitrate positive spot with R_M 2.80.

Anal. Calcd for $C_{11}H_{23}NO_6S_2$: C, 40.11; H, 7.04; N, 4.25; S, 19.43. Found: C, 40.18; H, 7.07; N, 4.19; S, 19.31.

3-Acetamido-3-deoxy-4,5:6,7-di-*O*-isopropylidene-D-*glycero*-D-*galacto*-heptose Dimethyl Dithioacetal (5). Compound **4** (5 g) was added to a stirred solution prepared by the addition of 2,2-dimethoxypropane (20 mL) to acetone (7.5 mL) containing concentrated sulfuric acid (0.12 mL). After stirring at 20 °C for 90 min, the reaction mixture was neutralized by the addition of saturated barium hydroxide followed by barium carbonate (0.5 g). The neutralized mixture was filtered through Celite, and the filtrate, after the addition of three drops of pyridine, was concentrated to a syrup. The syrup was extracted with boiling hexane (3 × 150 mL), which on concentration and cooling gave crystalline **5** (2.37 g). Chromatographic separation of the residual hexane extract on a column of silica gel (3 × 50 cm) using a benzene–methanol mixture (10:1 v/v) as the mobile phase afforded further pure **5** (1.46 g, total yield 3.83 g, 62%).

Crystalline **5** gave a single spot on TLC (solvent A, R_f 0.29) and had mp 125–126 °C and $[\alpha]_D$ +61° (*c* 2.6, chloroform); ^1H NMR ($CDCl_3$) δ 5.98 (d, 1 H, NH), 4.8 (t, 1 H), 2.22 and 2.16 (2 s, 6 H, $2SCH_3$), 2.04 (s, 3 H, $COCH_3$), 1.42 (m, 12 H, CH_3 of isopropyl); D_2O exchange caused the signal at δ 5.98 to disappear and the triplet at δ 4.80 to collapse to a doublet.

Anal. Calcd for $C_{17}H_{30}NO_6S_2$: C, 49.86; H, 7.63; N, 3.42; S, 15.63. Found: C, 49.75; H, 7.61; N, 3.29; S, 15.51.

4-Acetamido-1,4-dideoxy-1-nitro-D-*erythro*-L-*manno*-octitol (8). A stirred solution of **5** (5.45 g) in an acetone–water mixture (10:1 v/v, 115 mL) was treated at 20 °C with mercuric oxide (9.5 g), followed by the addition of a solution of mercuric chloride (9.5 g) in an acetone–water mixture (10:1 v/v, 20 mL), and the mixture was stirred for 24 h. The reaction mixture was filtered through Celite into a flask containing a little mercuric oxide, and the filtrate was concentrated to a syrup. The syrup was extracted with chloroform (2 × 150 mL), and the extract, after filtration through Celite, was washed with 17% aqueous potassium iodide (150 mL), followed by water (2 × 50 mL). The dried (sodium sulfate) chloroform extract was concentrated to a syrup (2.75 g) and was combined with the syrup (0.83 g) obtained by back-extraction of the potassium iodide wash solution with chloroform to give 3-acetamido-3-deoxy-4,5:6,7-di-*O*-isopropylidene-*aldehydo*-D-*glycero*-D-*galacto*-heptose (**6**, total yield 3.58 g, 81%). The *aldehydo*-heptose **6** gave a single spot on TLC (solvent A, R_f 0.13); IR 1740 cm^{-1} (CHO); partial ^1H NMR ($CDCl_3$) δ 9.72 (s, 1 H, CHO), 6.1 (m, 1 H, NH), 1.82 (s, 3 H, $COCH_3$), 1.32 (m, 12 H, CH_3 of isopropyl). The syrup **6** was used in the next step without further purification.

To a stirred solution of **6** (3.28 g) in nitromethane (145 mL) was added dropwise 1.7 M sodium methoxide in methanol (11.9 mL), followed by the addition of methanol (70 mL) to dissolve the precipitated material, and the mixture was stirred at 20 °C for 48 h. The reaction mixture was saturated with carbon dioxide and was concentrated to a syrup. The syrup was extracted at 35 °C with chloroform (150 mL), and concentration of the filtered chloroform extract afforded essentially pure 4-acetamido-1,4-dideoxy-5,6:7,8-di-*O*-isopropylidene-1-nitro-D-*erythro*-L-*manno*-octitol (**7**, 3.64 g, 94%), which gave a single spot on TLC (solvent A, R_f 0.17) and was used in the next step without further purification.

A solution of **7** (3.5 g) in 0.02 N sulfuric acid (175 mL) was heated on a boiling water bath for 17 min, and the cooled solution was neutralized with barium carbonate and filtered. The filtrate was passed through a column of Rexyn 101 (H^+) (5 mL) and Duolite A4 (OH^-) (5 mL) ion-exchange resins, and the eluate was concentrated to yield **8** as a slightly yellow solid (2.57 g, 92%), which gave a single spot on TLC (solvent B, R_f 0.6) and on paper chromatography (solvent A, R_M 2.06). Recrystallization of the product (2.5 g) from methanol (20 mL) afforded pure crystalline **8** which had mp 173–174 °C; $[\delta]_D$ −22° (c 1.15, water); ORD $[\phi]_{340}$ +316° (c 0.19, water); IR 1545 cm^{-1} (NO_2); ^{13}C NMR (D_2O) δ 175.89 (CO), 80.19 (CH_2NO_2), 71.89, 70.52, 70.33, 69.85, 68.57, 64.45 (CH_2OH), 51.46 (CHNHCOCH$_3$), 23.06 (CH_3CO).

Anal. Calcd for $C_{10}H_{20}N_2O_9$: C, 38.45; H, 6.45; N, 8.97. Found: C, 38.29; H, 6.60; N, 8.76.

Reduced and acetylated **8**[39] on GLC (column A, 225 °C) gave a single peak with T_{MA} 3.87.

4-Acetamido-2,3,5,6,7,8-hexa-*O*-acetyl-1,4-dideoxy-1-nitro-D-*erythro*-L-*manno*-octitol (9). A solution of **8** (1.4 g) in acetic anhydride (60 mL) was treated with three drops of concentrated sulfuric acid, and the mixture was heated on a boiling water bath for 75 min. The cooled mixture was poured into ice water (600 mL) and, following extraction with chloroform (1 L), the chloroform solution was washed successively with saturated sodium bicarbonate solution (500 mL) and water (500 mL). Concentration of the dried (sodium sulfate) extract gave **9** (2.4 g, 95%), which was pure by TLC (solvent A, R_f 0.20) and was used directly in the next synthetic step.

An analytical sample of **9** obtained as rod-shaped crystals from a water–hexane–ethyl acetate mixture had mp 80–81 °C and $[\alpha]_D$ 0° (*c* 1.15, chloroform); IR 1560 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$) δ 2.02 (s, 3 H, $NHCOCH_3$), 2.12 (m, 18 H, CO_2CH_3).

Anal. Calcd for $C_{22}H_{32}N_2O_{15}$: C, 46.80; H, 5.71; N, 4.96. Found: C, 46.65; H, 5.89; N, 4.81.

4-Acetamido-3,5,6,7,8-pentaacetoxy-D-*glycero*-D-*galacto*-1-nitro-1-octene (10). A solution of **9** (2.4 g) in benzene (75 mL) was boiled under reflux for 3 h with sodium bicarbonate (2.7 g). The cooled reaction mixture was filtered, and the filtrate was concentrated to yield **10** as a solid (1.92 g, 90%), which gave a single spot on TLC (solvent A, R_f 0.19) and was used without further purification in the next synthetic step. An analytical sample of **10** obtained crystalline from an ether–petroleum ether (bp 65–110 °C) mixture had mp 149–150 °C and $[\alpha]_D$ +6.8° (*c* 0.80, chloroform); IR 1530 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$) δ 6.89 (m, 2 H, CH=CH), 2.18 (m, 15 H, CO_2CH_3), 1.90 (s, 3 H, $NHCOCH_3$); ^{13}C NMR ($CDCl_3$) δ 141.40 and 136.14 (C-1

and C-2).

Anal. Calcd for $C_{20}H_{28}N_2O_{13}$: C, 47.61; H, 5.59; N, 5.55. Found: C, 47.67; H, 5.60; N, 5.59.

4-Acetamido-3,5,6,7,8-penta-*O*-acetyl-1,2,4-trideoxy-1-nitro-D-*glycero*-D-*galacto*-octitol (11). A solution of **10** (2.4 g) in ethanol (100 mL) was treated with sodium borohydride (2 g), and after 8 min at 20 °C the cooled mixture was acidified with acetic acid. When no more hydrogen was evolved, the reaction mixture was concentrated, and the residue was evaporated with methanol (5 × 60 mL). The residue was extracted with chloroform (150 mL). Concentration of the filtered chloroform extract afforded **11** (1.05 g, 99%) as a glass, which gave a single spot on TLC (solvent A, R_f 0.16) and was used directly in the next step.

An analytical sample of **11** obtained crystalline from a benzene–petroleum ether (bp 60–110 °C) mixture had mp 137–138 °C and $[\alpha]_D$ +5.2° (c 0.59, chloroform); IR 1560 cm^{-1} (NO_2); ^{13}C NMR ($CDCl_3$) δ 29.20 (CH_2), and no signals at δ 141.40 or 136.14 (found in the spectrum of **10**).

Anal. Calcd for $C_{20}H_{30}N_2O_{13}$: C, 47.43; H, 5.97; N, 5.53. Found: C, 47.27; H, 5.87; N, 5.41.

4-Acetamido-2,4-dideoxy-D-*glycero*-D-*galacto*-octose (12). Compound **11** (0.81 g) was dissolved in 1 N sodium hydroxide (10.4 mL), and the solution was kept at 36 °C for 1 h. The cooled solution was added dropwise with stirring to an ice-cold solution of concentrated sulfuric acid (1.52 mL) in water (4 mL), and the reaction was allowed to proceed for 2 h at 20 °C. The reaction mixture was neutralized by the addition of saturated barium hydroxide solution, followed by barium carbonate (0.2 g), and the insoluble material was removed by filtration. The filtrate and water washings were passed down a column of Rexyn 101 (H^+) (14 mL) and Duolite A4 (OH^-) (6 mL) ion-exchange resins, and the eluate on concentration afforded **12** (0.40 g, 86%) as a glass, giving a single *p*-anisidine and silver nitrate positive spot on paper chromatography (solvent A, R_M 0.75). An analytical sample of crystalline **12** obtained from ethanol solution had mp 182–183 °C and $[\alpha]_D$ −26.6° (*C* 1.37, water); ^{13}C NMR (D_2O) δ 94.72 (C-1 β), 92.59 (C-1 α), 53.20 and 53.80 (CHNHAc), 41.00 and 38.60 (CH_2), 23.20 (CH_3CONH). GC (column A, 225 °C) of reduced and acetylated **12**[39] gave a single peak with T_{MA} 2.59.

Anal. Calcd for $C_{10}H_{19}NO_7$: C, 45.28; H, 7.22; N, 5.28. Found: C, 45.21; H, 7.16; N, 5.26.

5-Acetamido-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulosonic Acid (NANA, 15). Compound **12** (0.30 g) in water (2.5 mL) was treated with a fresh solution of sodium cyanide (0.15 g) in water (1.7 mL), and the mixture was kept at 4 °C for 7 days. The mixture was heated to 70 °C for 3 h while a slow stream of nitrogen was blown over the surface, and the cooled solution was then passed down a column of Rexyn 101 (H^+) ion-exchange resin (5 mL). The column eluate on concentration afforded almost equal amounts of 5-acetamido-3,5-dideoxy-D-*erythro*-L-*manno*-nononic acid (**13**) and 5-acetamido-3,5-dideoxy-D-*erythro*-L-*gluco*-nononic acid (**14**, 0.26 g, 79%), which gave a ^{13}C NMR spectrum indistinguishable from that of the mixed acids **13** and **14** obtained by the sodium borohydride reduction of a solution of the authentic potassium salt of NANA, and the product was used directly in the next synthetic step; ^{13}C NMR (D_2O) δ 22.60 and 22.98 ($NHCOCH_3$), 33.45 and 33.84 (CH_2), 52.19 and 53.47 (CHNHAc), 76.76 and 79.29 (C-2), 175.55 and 175.88 (CO_2H), 180.25 ($NHCOCH_3$), 64.33 (CH_2OH).

The mixture of nononic acids **13** and **14** (0.25 g) in water (6 mL) was adjusted to pH 8.5 with 0.1 N potassium hydroxide and was kept at 20 °C for 2 h while maintaining a pH of 8.5. The solution was treated with potassium chlorate (0.12 g), the oxidizing catalyst (5.4 mL), prepared by stirring vanadium pentoxide (75 mg) in concentrated hydrochloric acid (4.5 mL) at 0 °C and immediately adding pyridine (4.5 mL), was added, and the mixture was stirred at 20 °C for 20 h. The reaction mixture was diluted with water (15 mL) and was extracted with chloroform (15 mL). The water layer was then passed down a column of Dowex 50 (H^+) ion-exchange resin (14 mL), followed by Dowex 1-X8 (formate) ion-exchange resin (18 mL). The latter column was eluted with 5% (v/v) formic acid (50 mL), and the total eluate from the column was concentrated to a syrup (200 mg). The syrup, dissolved in water (1 mL), was chromatographed on a column of Dowex 1-X8 (formate) ion-exchange resin (1 × 24 cm) which was eluted with 300 mL of a 0–10% formic acid gradient. Fractions of the eluate found by paper chromatography to contain NANA were combined and concentrated under reduced pressure to yield crystalline NANA (**15**; 125 mg, 50%).

Crystalline NANA, mp 182–190 °C and $[\alpha]_D$ −32° (c 0.8, water) (lit.[20] mp 181–183 °C, $[\alpha]_D$ −32.1°), gave a single periodate–thiobarbiturate positive spot on paper chromatography (R_M 0.79, solvent B) and on TLC (R_f 0.44, 2-propanol–acetic acid–water, 54:8:18 v/v) having the same mobility as authentic NANA. Trimethylsilylated[40] (Me_3Si) **15** on GC (column B, 210 °C) gave a single peak (T_{MA} 0.49) having the same retention time as authentic Me_3Si–NANA. Compound **15** gave the following data: ^{13}C NMR (D_2O) δ 174.6 (C-1), 96.4 (C-2), 40.0 (C-3), 67.9 (C-4), 53.2 (C-5), 71.4 (C-6), 69.4 (C-7), 71.4 (C-8), 64.3 (C-9), 23.2 ($NHCOCH_3$), 176.0 ($NHCOCH_3$); the spectrum is indistinguishable from that of an authentic sample of NANA.

5-Acetamido[1-^{13}C]-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulosonic Acid. The reaction of **12** (0.30 g) with $Na^{13}CN$ (0.15 g, 90 atom % ^{13}C) and catalytic oxidation of the resulting nononic acids **13** and **14** as described above in the preparation of **15** gave crystalline [1-^{13}C]NANA (128 mg, 51%) having the same physical properties as **15**. The ^{13}C NMR spectrum (limited number of transients) showed a single signal at δ 174.6, and the full spectrum of the sample showed the same signals for C-(1–8) as those recorded for **15**.

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Registry No.—**1**, 3615-17-6; **2**, 38191-81-0; **3**, 28434-33-5; **4**, 64130-80-9; **5**, 64130-81-0; **6**, 64130-82-1; **7**, 64130-83-2; **8**, 64130-84-3; **9**, 64130-85-4; **10**, 64130-86-5; **11**, 64130-87-6; **12**, 64130-88-7; **13**, 64130-89-8; **14**, 64130-90-1; **15**, 131-48-6; [1-^{13}C]-**15**, 64162-77-2; 3-amino-3-deoxy-D-galactose hydrochloride, 64162-10-3.

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Reaction of Copper Enolates of Esters with Propargylic Systems. Facile Preparation of 3,4-Dienoic Esters, Stereoselective Rearrangement to (2*E*,4*Z*)- and (2*E*,4*E*)-Dienoic Esters, and Stereoselective Synthesis of a Fragrance from the Bartlett Pear

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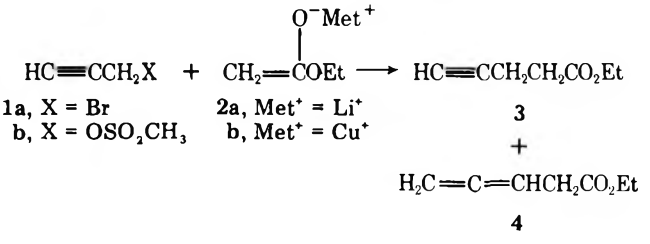
A copper enolate species derived by treatment of the lithium enolate of ethyl acetate with cuprous iodide has been found to react with propargyl bromide cleanly in an S_N2' manner to give ethyl 3,4-pentadienoate, a β-allenic ester. Under the same conditions, the lithium enolate gives only ethyl 4-pentynoate, the corresponding β-acetylenic ester, resulting from direct S_N2 displacement. The reaction of propargylic methanesulfonates having an alkyl group at the propargylic position shows the same remarkable effect of enolate counterion; with the copper enolate, higher homologues of the β-allenic esters can be synthesized efficiently. Copper can act in a catalytic fashion, as the reaction proceeds satisfactorily with only 0.2 equiv. Yields of β-allenic esters from reactions using the copper enolate derived from methyl propionate are lower. Extension of the reaction to a γ alkylation of a vinylogous copper enolate to produce a δ-allenic α,β-unsaturated ester succeeded in the case of 3,3-dimethylacrylic acid, but not with crotonic acid. When exposed to sodium ethoxide in ethanol, the β-allenic esters undergo rapid reconjugation to the 2,4-dienoates in excellent yield. The 2*E*,4*Z* isomer is the principal product upon reconjugation, and the reconjugation mixture can be equilibrated to predominantly the 2*E*,4*E* isomer by heating with thiophenol and 2,2′-azobis(isobutyronitrile). These reactions were used for the stereoselective preparation of ethyl (2*E*,4*Z*)-decadienoate, a component of the odoriferous principle of Bartlett pears.

It is well documented that the reaction of organometallic agents with propargylic electrophiles can lead to products having acetylenic as well as allenic structures (from S_N2 and S_N2' displacements, respectively).[1,2] Reaction with group 1 or 2 organometallic compounds generally produces mixtures of these products;[1] however, selective formation of allenic products is generally observed in reactions of organocopper reagents[2] and reactions catalyzed by ferric salts.[3] The reaction of propargylic electrophiles with stabilized anions such as enolates has not been reported, however.

We recently noted that in the reaction of allylic electrophiles with copper dienolates derived from the dianions of α,β-unsaturated acids, there appears to be an electronic preference for the allylic species to undergo transposition (S_N2' displacement).[4] In this report, we describe that certain propargylic bromides and methanesulfonates undergo S_N2' displacement in their reaction with copper enolates to produce exclusively β-allenic esters, while none of these products are found in reactions of the corresponding lithium enolates. Furthermore, these β-allenic esters provide convenient precursors for the selective preparation of either the 2*E*,4*Z* isomer (by base-catalyzed reconjugation) or the 2*E*,4*E* isomer of 2,4-dienoic esters (by reconjugation followed by radical-catalyzed equilibration). These reactions have been used in a stereoselective synthesis of ethyl (2*E*,4*Z*)-decadienoate, a component of the odoriferous principle of the Bartlett pear.[5]

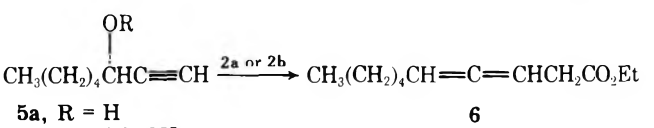
Results and Discussion

Formation of the β-Allenic Esters. In our initial observation of the effect of the enolate counterion in reactions with propargylic systems, the reaction of the lithium enolate of ethyl acetate (**2a**) with propargyl bromide (**1a**) was found to afford ethyl 4-pentynoate (**3**) (12% isolated yield); none of the allene product ethyl 3,4-pentadienoate (**4**) was produced, as indicated by both gas chromatography and infrared analysis of the crude reaction product. In contrast, reaction of propargyl bromide with the copper enolate **2b** provided only trace amounts of the acetylene product; essentially only a single volatile product characterized as the β-allenic ester **4** was formed in a 45% yield (39% isolated).



The reported use of sulfonate esters[2j,k] as leaving groups in propargylic rearrangements prompted us to prepare the methanesulfonate of propargyl alcohol (**1b**) as a substrate. Reaction of **1b** with the lithium enolate **2a** was very sluggish even when warmed to 0 °C. Small amounts of the acetylene product were formed, but the percent conversion was too low to permit a valid assessment of the yield. In contrast, the copper enolate reaction was complete within 15 min at −78 °C, affording **4** as essentially the only volatile product in a 34% yield (26% isolated). This material was identical with that obtained in the bromide reaction and only trace amounts of the acetylene were observed.

Extension of the reaction to higher homologues required the preparation of acetylenic carbinol derivatives substituted with alkyl groups in the propargylic position. These were prepared by the addition of an aldehyde to the acetylenic Grignard reagent at 0 °C. The methanesulfonate was formed in high yield with methanesulfonyl chloride in triethylamine–dichloromethane. Based on the use of propargylic acetates in reaction with organocuprates by Crabbe,[2d-h] the acetate **5c** was also prepared in 90% yield by reaction of **5a**



5a, R = H
b, R = SO_2CH_3
c, R = $C(O)CH_3$
d, R = $C(O)CF_3$

with acetic anhydride in pyridine. Attempted reaction of **5c** with the copper enolate **2b**, however, gave essentially no conversion of starting material, even after 16 h at room temperature. Use of a better leaving group, trifluoroacetate **5d**, gave complete consumption of starting material but afforded

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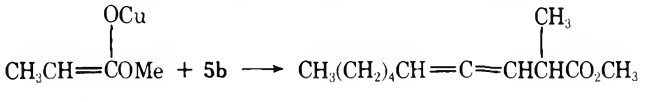
only the starting alcohol **5a**, presumably by a nucleophilic attack at the ester function.

Reaction of the copper enolate **2b** with methanesulfonate **5b** proceeds very cleanly to produce allene **6** in a 76% isolated yield. The reaction is complete within 15 min at −78 °C and affords only a single volatile product, with no evidence of the undesired acetylene product. In contrast, the lithium enolate **2a** gave poor conversion of starting material even after 1 h at 0 °C. Small amounts of allene **6** were detected, estimated at 1–2% of the volatile product; the presence of the acetylene product could not be confirmed without an authentic sample, but no peaks were present with the expected gas chromatographic retention time. Scale-up of the reaction for preparation of gram quantities of the allenes presents no difficulties. Multigram quantities of the alcohol **5a** were converted to the allene **6**, in 76% yield, without purification of the intermediate methanesulfonate. In summary, this reaction, combined with the high yield formation of the acetylenic carbinol, allows the net conversion of an aldehyde to a β-allenic ester having an alkyl chain four carbons longer. The process requires three steps and proceeds in good overall yield.

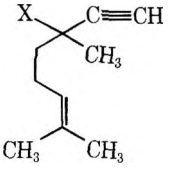
Having demonstrated the utility of the reaction for straight chain compounds, efforts were directed toward preparation of substituted derivatives. The preliminary results obtained thus far have not been encouraging. Branching at the C-2 carbon requires the use of esters other than acetates. However, reaction of the copper enolate of methyl propionate (**7**) with



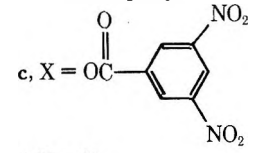
7 **8**

5b gave a disappointing yield of 13% for the corresponding allene **8**. Reaction was rapid (15 min) at −78 °C, but the crude product gave a multitude of peaks on gas chromatography and showed only a weak allene absorption in the infrared. Purification of **8** was difficult, as several unidentified products had very similar polarities.

Branching at the C-5 carbon requires the preparation of a tertiary acetylenic carbinol, conveniently made by reaction of ethynylmagnesium bromide with a ketone. Thus 6-methyl-5-hepten-2-one gives **9a** in high yield. Formation of



9a, X = OH
b, X = OSO_2CH_3

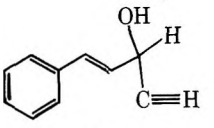


c, X = OC

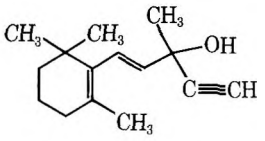
d, X = Br

the methanesulfonate **9b** was unsuccessful, as the product underwent a vigorous decomposition upon attempted isolation, presumably due to its tertiary and propargylic nature. This is somewhat surprising since secondary, propargylic methansulfonates, such as **5b**, can be purified by a bulb-to-bulb distillation at reduced pressure. The 3,5-dinitrobenzoate derivative **9c** was successfully formed in 94% yield. However, reaction of this substrate with the copper enolate **2b** afforded a dark purple product having no allene peak in the infrared. Reduction of the nitro groups by the organocopper may have been responsible for the formation of the intensely colored product and the resulting failure of the reaction. Preparation of the bromide derivative **9d** using triphenylphosphine dibromide[6] was unsuccessful.

As might be anticipated from the preceding discussion, problems with electrophile stability were also encountered with the extension to unsaturated aldehydes and ketones, substrates that would provide access to triene esters. In these cases, the potential leaving group is both propargylic and allylic and is either secondary or tertiary depending on the choice of an aldehyde or a ketone. Attempted bromination of **10** using the triphenylphosphine dibromide failed to give any



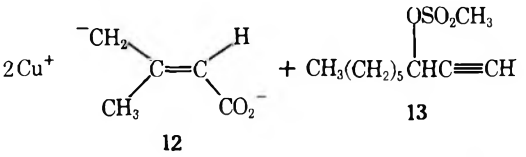
10



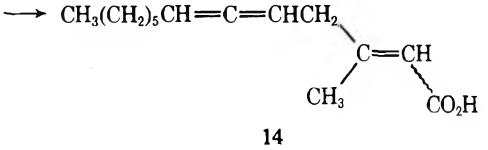
11

product that possessed an acetylene function, as indicated by both ^1H NMR and infrared spectra. Likewise, the methanesulfonate derived from **11** was too unstable for isolation, presumably undergoing facile elimination reactions.

The other access to triene esters, namely the reaction of vinylogous copper enolates with a methanesulfonate such as **5b**, has met with mixed success. The copper dianion of 3,3-dimethylacrylic acid (**12**) reacts with the methanesulfonate



12 **13**



14

13 at the γ position[4] to give allene **14**, isomeric at the α,β bond, in a 36% yield. However, reaction of **13** with the copper enolates derived from both crotonic acid and its ethyl ester failed to give the desired allene.

Mechanistic Considerations. Throughout this discussion, the reactive species has been termed a "copper enolate", but in fact the actual character of the organometallic has not been elucidated in detail. The copper species is generated by the addition of 1 equiv of cuprous iodide to the lithium enolate, preformed by the addition of the ester to lithium diisopropylamide (LDA) in tetrahydrofuran at −78 °C. The mixture is stirred for 1 h at −78 °C to ensure ample time for formation of the reactive species; at this point, it is a pale yellow heterogeneous mixture. If this material is allowed to warm to −30 °C, it becomes nearly homogeneous, but turns dark brown. Reaction of this brown species with the propargylic derivatives is not as clean as with the reagent prepared and used at −78 °C. This procedure for generating copper enolates has been modified somewhat from a literature method[7] (LDA addition to the ester in the presence of cuprous iodide at −110 °C), but it was felt the same species should be generated in each case. Despite the uncertainty as to the precise nature of the "copper enolate", it is obvious that copper is participating in the reaction, judging by the dramatic change in reaction course in going from a lithium enolate to the copper species. Some insights into the species present and the mechanism involved may be obtained from the following studies.

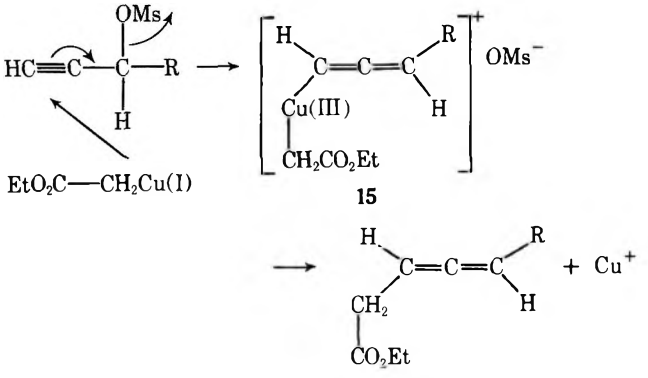
The oxidative dimerization of organocoppers using molecular oxygen is a well-recognized process,[8] and Kuwajima and Doi[7] were able to demonstrate that their copper species,

designated ethoxycarbonylmethylcopper, did in fact undergo oxidative dimerization to give diethyl succinate. Although our reactant (**2b**) was generated in a slightly different manner, introduction of molecular oxygen at −50 °C to the organocopper yielded diethyl succinate, although in lower yield (29% isolated) than that reported in the literature (73%).[7] This result would substantiate the claim that the reactive species is some type of organocopper derivative.

It was also determined that the copper can function in a catalytic role. When **5b** was reacted with the lithium enolate of ethyl acetate in the presence of 0.2, 0.5 and 1.0 equiv of cuprous iodide, the isolated yields of allene were 77, 77, and 76%, respectively. The 0.2 equiv of cuprous iodide may be approaching the lower limit, as small amounts of starting material persisted in the reaction mixture, but the reaction rate is not detectably slower (still complete within 15 min at −78 °C). This result also demands that any mechanism which proposes changes in the oxidation state of the copper must, in the end, return the metal to the Cu(I) state. It might also be mentioned that product isolation from reactions using catalytic amounts of cuprous iodide is much simpler because smaller amounts of insoluble salts remain after the reaction mixture is quenched.

The major mechanistic question which needs to be addressed is the difference in reactivity of the lithium and copper enolates. A possible explanation may be based on differences in the mode of reaction; the lithium enolates undoubtedly react via a nucleophilic attack on the substrate whereas cuprates,[9] and potentially other organocoppers, are generally thought to react by an electron transfer mechanism. Such reactions occur by an initial transfer of a single electron, followed by a coupling of the resulting radical ions.

Following the prevailing view of the involvement of copper(III) intermediates in conjugate addition and coupling reactions, we propose the following mechanism, which is analogous to one proposed by Brandsma[2j] for copper-catalyzed Grignard additions to propargylic electrophiles. The postulated copper enolate species **2b** attacks at the terminal acetylenic carbon leading to a propargylic rearrangement with loss of the methanesulfonate anion. The intermediate copper(III) species **15** (which is formulated as a C-copper enolate,



but may be an O-copper species) then undergoes a rapid rearrangement with transfer of the ester function and reduction of the copper(III) to the cuprous oxidation state, yielding the allene product.

The major departure of this mechanism from those proposed by Crabbe[2g] and Brandsma[2j] is the rapid transfer of the ester group in **15** to give the product. Both of these workers reported that in the reaction of organocopper reagents with propargylic systems, the unsubstituted allene (the hydrolysis product of the copper(III) intermediate analogous to **15**) was isolated if a protic quench was carried out at low temperatures. It is not surprising that in our case the ester group, with its greater capacity to bear negative charge, appears to undergo more rapid rearrangement to give the alkylated product.

Table I. Isomer Ratios Obtained after Reconjugation of β-Allenic Esters[a]

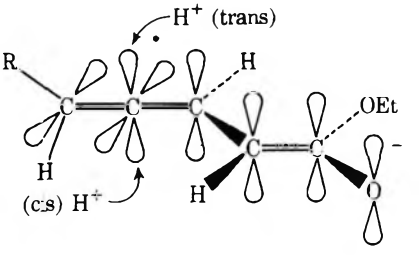
Allene	Conditions	Diene ester[b] 2Z,4Z	2Z,4E	2E,4Z	2E,4E
4	(NaOEt)			100	
6	(NaOEt)		6	63	31
6	(PhSH,AIBN)		(——16——)[c]		84

[a] Reconjugation was effected by NaOEt in EtOH; equilibration, by PhSH and AIBN subsequent to NaOEt (see text). [b] Isomer ratios determined by GLC analysis. [c] The isomers were not sufficiently well resolved to allow for an accurate determination of quantities formed. Fourth isomer (2Z,4Z) not formed in the reconjugation step is now present in small amounts.

Formation of the Diene Esters. The reconjugation of a variety of β-allenic carbonyl compounds has been studied, including ketones,[10] aldehydes,[11] amides,[12] and esters.[13] In most cases, base catalysis was used to accomplish the formation of the fully conjugated system. Table I presents the isomer ratios obtained by reconjugation of the β-allenic esters **4** and **6** with sodium ethoxide in ethanol at 0 °C. Treatment with base was at least 30 min in duration in each case, frequently longer. Variation in reaction times did not appear to substantially affect the product ratios.

$$\mathbf{6} \xrightarrow[\text{EtOH}]{\text{NaOEt}} \underset{\mathbf{16}}{CH_3(CH_2)_4CH{=}CHCH{=}CHCO_2Et}$$

As can be seen from the data, the predominant geometry at the α,β double bond in **16** after reconjugation is the expected *E* configuration. However, the unexpected *Z* geometry predominates at the γ,δ double bond, standing in a 2:1 ratio over the 4*E* geometry. Such a result can be rationalized by visualizing the enolate **17**, presumed to be the intermediate

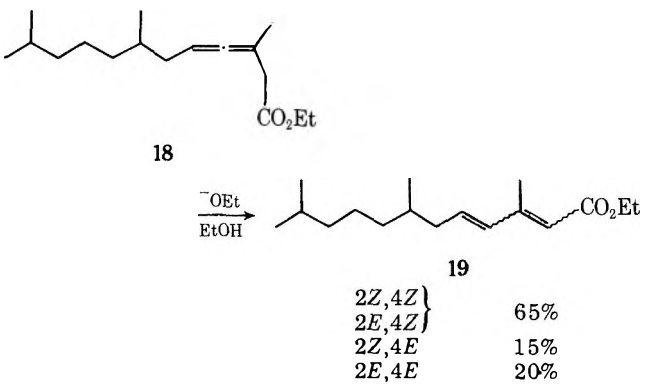


17

in the reconjugation. Approach of the proton to the digonal carbon of the allene would be expected to occur from the less hindered side (cis), attacking the π lobe opposite the bulky R group. The net result is the *Z* geometry at the γ,δ bond. The configuration of the other double bond is determined by the more stable rotamer of the α,β bond in the extended enolate. The conformation having the bulky groups trans to one another (s-trans) is more stable and affords the *E* geometry.

The formation of the 2*E*,4*Z* isomer (**16**) (the major isomer upon reconjugation) represents the synthesis of a natural product, a component of the odoriferous principle of Bartlett pears.[5] The desired isomer was separated from the 2*Z*,4*E* and 2*E*,4*E* isomers by means of preparative thin layer chromatography. Multiple developments using a low polarity solvent were required to achieve the separation.

It should be noted that Henrick and co-workers[13] observed but provided no explanation for this same propensity for 4*Z* isomer formation in their reconjugation studies on more highly substituted dienoates. In their case reconjugation of the β-allenic ester **18** gave the isomeric dienoates **19** in the ratios noted. The lowered stereoselectivity at the α,β site presumably results from the fact that the methyl substituent at C-3 makes the s-cis and s-trans conformers (about the C-2–C-3 bond of



the corresponding enolate intermediate: cf. **17**) of more comparable energy.

Equilibration of the Diene Esters. The predominance of the 2*E*,4*Z* isomer of **16** in the reconjugation of **6** and the stability of the product ratios indicate that the reconjugation is a kinetically controlled process, sodium ethoxide not being a sufficiently strong base to lead to any equilibration of the dienoates formed. Since the 2*E*,4*E* isomer is expected to be thermodynamically most stable, it should be possible to increase the proportion of this isomer by equilibration of the reconjugation mixture.

The use of catalytic amounts of thiophenol and 2,2′-azobis(isobutyronitrile) (AIBN) has been reported to give equilibration of dienoate isomers.[13,14] Presumably the isomerization occurs by a reversible addition of a benzenethiyl radical to the dienoate system. No thiol adducts were isolated, nor was there any tendency toward polymerization.[14] Thus, treatment of the reconjugation isomer mixtures of **16** with 5 mol % of thiophenol and 1 mol % of AIBN gave isomer equilibration to predominantly the *E*,*E* compound (see Table I). The 2*E*,4*E* isomer of **16** was separated in isomerically pure form by preparative thin layer chromatography.

Both the reconjugation and equilibration steps proceed in high yield, allowing an effective conversion of β-allenic esters to the dienoates. The reconjugation of allene **6** affords the diene ester isomer mixture in a 93% yield after purification by silica gel chromatography. Further equilibration of the crude reconjugation product proceeds in an 86% isolated yield (overall for the two steps).

Conclusion

The reaction of copper enolates derived from esters with propargylic electrophiles provides a convenient route to β-allenic esters. In contrast, the lithium enolates under the same conditions are either unreactive or react sluggishly to give mainly the acetylenic products. The copper enolate route to β-allenic esters parallels and complements another method for preparation of such systems, the Claisen rearrangement of propargylic orthoesters.[13,15] While our method works on easily prepared methanesulfonate derivatives, the orthoester rearrangement operates successfully on tertiary propargylic systems whose corresponding methanesulfonates are very unstable.

The rearrangement of the β-allenic esters to 2,4-dienoates is also of synthetic value, particularly with the recognition that the 2*E*,4*Z* isomer is favored under kinetic conditions and the 2*E*,4*E* isomer under equilibrating conditions. While many other methods for the preparation of dienoates are known,[16] few of these offer control over the stereochemistry of the double bond in the γ,δ position.

Experimental Section

General. Analytical thin layer chromatography was performed using 0.25 mm silica gel glass-backed plates with F-254 indicator (Merck). Visualization was by ultraviolet light, iodine, or phosphomolybdic acid. Preparative plates were from Merck or were prepared using Merck Silica Gel 60 PF-254 + 366.

Analytical gas chromatography (GLC) utilized a Hewlett-Packard 5750 instrument equipped with flame ionization detectors and using a 20 ft × 0.125 in. SE-30, 5% on Gas-Chromosorb Q, 80/100 column (to establish isomer compositions) and a 5 ft × 0.125 in. OV-17, 3% on Supelcoport, 100/120 (to follow reactions), with nitrogen (30 mL/min) as carrier gas. Determinations were made in either an isothermal mode or using programmed runs at 15 °C/min with a 2 min postinjection delay. Peak areas, where determined, were obtained by planimetry based on the average of three consecutive runs.

Proton magnetic resonance (^{1}H NMR) spectra were recorded on Varian Associates spectrometers, Models T-60, A-60, EM-390, and HR-220; chemical shifts are reported in ppm downfield from a tetramethylsilane internal standard (δ scale). The ^{1}H NMR data are presented in the form: δ value of signal (peak multiplicity, coupling constant (if any), integrated number of protons). Infrared spectra were recorded on either a Perkin-Elmer Model 137 spectrometer or a Beckman Model IR-12 instrument. Unless otherwise noted, spectra were obtained on neat compounds held between sodium chloride plates. Data are presented in cm^{-1} and only the important diagnostic bands are reported.

Mass spectra were obtained from a Varian MAT CH-5 spectrometer and were at 70 eV ionization voltage unless otherwise indicated. Data are presented in the form: *m/e* (intensity relative to base peak). Elemental analyses were provided by the microanalytical service laboratory of the University of Illinois.

Chemicals were obtained from the following sources: Aldrich Chemical Co.: hexanal, β-ionone, benzophenone, tetrahydrofuran, triethylamine, diisopropylamine, propargyl alcohol, propargyl bromide, thiophenol, methyl propionate, 3,3-dimethylacrylic acid, crotonic acid, methanesulfonyl chloride, trifluoroacetic anhydride, 2,2′-azobis(isobutyronitrile). Fisher Scientific Co.: cuprous iodide, dichloromethane. J. T. Baker Chemical Co.: ethyl bromide. Fluka: 6-methyl-5-hepten-2-one. Linde: acetylene. Mallinckrodt: ethyl acetate, diethyl ether, acetic anhydride, magnesium metal. Ventron: *n*-butyllithium.

The acetylene gas was passed through an alumina scrubbing tower, a dry ice–acetone trap, concentrated sulfuric acid, and finally a tube containing sodium carbonate. Tetrahydrofuran was distilled from sodium–benzophenone by use of a recirculating still, maintaining a deep blue coloration at all times. Diisopropylamine and triethylamine were refluxed over calcium hydride and then distilled to ensure dryness. Ethyl acetate was dried by distillation from phosphorus pentoxide. The hexanal was distilled from anhydrous sodium sulfate, discarding the initial forerun.

The organolithium reagent was titrated periodically to determine the organic base present, using either the double titration method[17] or the single titration method[18] with 1,10-phenanthroline as an indicator. All values used were the average of at least three separate determinations.

Glassware for all reactions involving moisture-sensitive compounds was dried for a minimum of 2 h at 120 °C. Such reactions were run under a positive pressure nitrogen atmosphere, predried by use of a Drierite drying tower. Transfers involving moisture- or air-sensitive liquids were performed using hypodermic syringes, added via rubber septa on the side arm of the reaction flask.

Reaction products were dried over anhydrous magnesium sulfate unless otherwise stated. All yields reported are isolated products after purification unless indicated otherwise. Silica gel chromatography was performed using 0.05–0.2 mm silica gel with weight ratios usually in the range 30:1 to 50:1 silica gel/crude product. Close separations required ratios as high as 200:1. Elution solvent mixtures are given as volume percentages.

1-Octyn-3-ol (5a). Magnesium metal turnings, 2.67 g (0.11 mol), were added to a hot, dry three-necked flask equipped with addition funnel and reflux condensor. The entire system was flushed with dry nitrogen, and 50 mL of dry tetrahydrofuran was added. A solution of 11.99 g (0.11 mol) of ethyl bromide in 5 mL of solvent was added over a 1-h period, while the temperature was maintained at 25–30 °C by means of a water bath. The dark mixture was stirred for 1 h following the addition to ensure complete formation of the ethylmagnesium bromide. A small amount of magnesium metal remained.

A second flask, equipped with a side arm and addition funnel, was filled with 50 mL of dry tetrahydrofuran and purified acetylene was bubbled through for 5 min. The above Grignard solution was then transferred slowly through Teflon tubing under nitrogen pressure. The addition required 45 min and the temperature was held at 15–20 °C. A constant stream of acetylene was maintained during the addition and for 5 min afterwards.

After cooling to 0 °C, the hexanal, 10.02 g (0.1 mol), in 5 mL of solvent was added dropwise. The cooling produced some precipitate, presumably the Grignard reagent, but it did not interfere with the reaction. Following the addition, the mixture was stirred 30 min at 0 °C and a similar length of time at room temperature. The reaction was quenched with saturated ammonium chloride (with cooling), the solvent was removed under reduced pressure, and the product was extracted with ether and dried. Silica gel chromatography (20% ether/hexane) gave 10.71 g (85%) of pure product: ^{1}H NMR (CCl_4) δ 4.10–4.40 (m, 1 H), 2.92 (broad s, 1 H, D_2O exchangeable), 2.30 (d, J = 2 Hz, 1 H), 1.15–1.85 (m, 8 H), and 0.70–1.15 (m, 2 H); IR 3360 (OH), 3310 (C≡CH), and 2120 (C≡C) cm^{-1}; mass spectrum (10 eV) m/e (rel intensity) 125 (0.8), 111 (1.3), 97 (13), 93 (27), 83 (32), 79 (35), and 43 (100). Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.35; H, 11.20.

Methanesulfonate of 1-Octyn-3-ol (5b). Acetylenic carbinol **5a**, 5.05 g (40 mmol), was added to 50 mL of dichloromethane, followed by 6.07 g (60 mmol) of triethylamine. After cooling to 0 °C, 5.73 g (50 mmol) of methanesulfonyl chloride was added dropwise. The resulting yellow reaction mixture was stirred at 0 °C for 3 h. A white precipitate formed soon after the addition was complete. After dilution with ether, the mixture was washed with half-saturated brine containing 20 mL of 3 N hydrochloric acid and with saturated sodium bicarbonate. The product was dried and chromatographed on silica gel (25% ether/hexane) to give 7.63 g (93%) of product: ^{1}H NMR (CCl_4) δ 5.03 (dt, J = 2, 6 Hz, 1 H), 3.01 (s, 3 H), 2.67 (d, J = 2 Hz, 1 H), 1.75–2.20 (m, 2 H), 1.20–1.75 (m, 6 H), and 0.75–1.20 (m, 3 H). Anal. Calcd for $C_9H_{16}O_3S$: C, 52.92; H, 7.89; S, 15.70. Found: C, 53.05; H, 8.10; S, 15.92.

The homologous methanesulfonate **13** was prepared in an analogous fashion starting from heptanal.

Methanesulfonate of Propargyl Alcohol (1b). The above precedure was followed using 3.36 g (60 mmol) of propargyl alcohol, 7.56 g (66 mmol) of methanesulfonyl chloride, and 7.08 g (70 mmol) of triethylamine. Purification by silica gel chromatography (50% ether/hexane) afforded 6.98 g (87%) of product: ^{1}H NMR (CCl_4) δ 4.80 (d, J = 2 Hz, 2 H), 3.10 (s, 3 H), and 2.70 (t, J = 2 Hz, 1 H). Anal. Calcd for $C_4H_6O_3S$: C, 35.81; H, 4.51; S, 23.90. Found: C, 35.86; H, 4.55; S, 24.06.

Ethyl 3,4-Decadienoate (6). Diisopropylamine, 0.51 g (5 mmol), was added to 20 mL of dry tetrahydrofuran and cooled to −10 °C. n-Butyllithium, 2.13 mL of a 2.35 M solution (5 mmol), was then added. After stirring 10 min at −10 °C, the mixture was cooled to −78 °C and 0.44 g (5 mmol) of ethyl acetate in 3 mL of solvent was added. Stirring was continued for 30 min at −78 °C to ensure complete formation of the enolate. Cuprous iodide, 0.95 g (5 mmol), was added and stirred for 1 h at −78 °C. The mixture never became homogeneous but did assume a pale yellow–tan coloration. Methanesulfonate **5b**, 1.02 g (5 mmol), in 2 mL of solvent was added dropwise at −78 °C. The mixture turned green during the addition but reverted to the yellow–tan color after the addition was complete. TLC indicated the reaction was complete within 15 min at −78 °C. Saturated ammonium chloride was used to quench the reaction, and the solvent was removed under reduced pressure. The product was extracted with ether and dried. Silica gel chromatography (5% ether/hexane) gave 0.74 g (76%) of product: ^{1}H NMR (CCl_4) δ 4.90–5.30 (m, 2 H), 4.07 (q, J = 7 Hz, 2 H), 2.89 (dd, J = 6, 3 Hz, 2 H), 1.75–2.20 (m, 2 H), 1.10–1.75 (m, 6 H), 1.24 (t, J = 7 Hz, 3 H), and 0.70–1.10 (m, 3 H); IR 1970 (C=C=C), 1745 (C=O), and 1170 (C–O) cm^{-1}; mass spectrum m/e (rel intensity) 196 (M$^+$, 9.7), 167 (6), 151 (5), 140 (16), 139 (10), 123 (3), 112 (23), 111 (20), 108 (13), 98 (11), 93 (12), 83 (53), and 67 (100). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.34; H, 10.20.

Reactions run using a catalytic amount of cuprous iodide were conducted in the same manner, with 0.2 and 0.5 equiv of cuprous iodide both giving 77% isolated yields. A larger scale reaction using 5.11 g (25 mmol) of methanesulfonate **5b** (used without purification) and comparable amounts of all other reagents gave a 76% isolated yield. Reactions run with the lithium enolate were conducted in a similar manner, omitting the use of cuprous iodide. Warming to 0 °C was required to observe reaction with these enolates and even then reaction was slow and gave several products.

Ethyl 2,4-Pentadienoate (4). The above procedure was followed using 1.34 g (10 mmol) of methanesulfonate **1b** and the corresponding amounts of all other reagents. GLC yield of the product (internal standard) was 34% and silica gel chromatography (10% ether/hexane) gave 323 mg (26%) of product. Only trace amounts of the acetylene product **3** were evident in the GLC trace: ^{1}H NMR (CCl_4) δ 5.20 (p, J = 7 Hz, 1 H), 4.69 (td, J = 3, 7 Hz, 2 H), 4.07 (q, J = 7 Hz, 2 H), 2.94 (td, J = 3, 7 Hz, 2 H), and 1.23 (t, J = 7 Hz, 3 H); IR 1960 (C=C=C), 1745 (C=O), and 1165 (C–O) cm^{-1}; mass spectrum (10 eV) m/e (rel intensity) 126 (M$^+$, 1.18), 125 (1), 124 (3), 98 (100), 81 (18), 70 (62), 55 (15), and 53 (50). Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.85; H, 8.01.

Reaction under similar conditions with propargyl bromide **1a** gave a GLC yield of 45% for **4**, with 488 mg (39%) isolated after purification by silica gel chromatography. Again only trace amounts of the acetylenic product **3** were detected in the GLC trace.

Methyl 3-Methyl-2,5,6-tridecatrienoate (Methyl Ester of 14). The above procedure was followed using 2 equiv of lithium diisopropylamide and cuprous iodide for each equivalent of 3,3-dimethylacrylic acid and methanesulfonate **13**. The mixture was stirred for 3 h at −78 °C before quenching with saturated ammonium chloride. The solvent was removed, followed by acidification of the aqueous layer with 3 N hydrochloric acid and extraction with ether. After drying the product, silica gel chromatography (1% HOAc/15% ether/84% hexane) gave 160 mg (36%) of a viscous yellow oil.

The above product was esterified by the addition of 138 mg of the acid to 10 mL of HMPA, followed by 1 mL of 20% sodium hydroxide. After stirring 1 h, 0.75 mL of methyl iodide was added and the mixture was stirred 16 h at room temperature. The product was poured into dilute hydrochloric acid and then extracted with ether, washing the extracts with brine to remove the HMPA. After drying, the product was purified by silica gel chromatography (5% ether/hexane): ^{1}H NMR (CCl_4) δ 5.50–5.65 (m, 1 H), 4.80–5.15 (m, 2 H), 3.60 (s, 3 H), 3.15–3.30 and 2.60–2.80 (m, 2 H, E and Z isomers), 2.12 and 1.85 (d, J = 1.5 Hz, 3 H, E and Z isomers), 1.75–2.10 (m, 2 H), 1.10–1.60 (m, 8 H), and 0.70–1.10 (m, 3 H); IR 1960 (C=C=C), 1720 (C=O) and 1645 (C=C) cm^{-1}; mass spectrum m/e (rel intensity) 236 (M$^+$, 10.9), 221 (4), 205 (6), 177 (34), 166 (15), 165 (25), 152 (41), 151 (28), 138 (21), 137 (10), and 93 (100). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 75.94; H, 10.00.

Ethyl 4-Pentynoate (3). Diisopropylamine, 1.52 g (15 mmol), was added to 30 mL of dry tetrahydrofuran and cooled to −10 °C. n-Butyllithium, 6.09 mL of a 2.46 M solution (15 mmol), was then added, and after stirring for 10 min, the mixture was cooled to −78 °C. Ethyl acetate, 1.32 g (15 mmol), was then added dropwise to form the enolate. After 30 min at −78 °C, 1.78 g (15 mmol) of propargyl bromide was added dropwise. Following 1 h at −78 °C, the mixture was warmed to 0 °C for 2 h. The yellow solution was quenched with saturated ammonium chloride, the solvent was removed under reduced pressure, and the product was extracted with ether and dried. Silica gel chromatographic separation (10% ether/hexane) of the most mobile component afforded 0.22 g (12%) of product. GLC and infrared analysis showed no evidence of allene **4**; ^{1}H NMR (CCl_4) δ 4.09 (q, J = 7 Hz, 2 H), 2.45 (d, J = 2 Hz, 4 H), 1.80–1.90 (m, 1 H), and 1.24 (t, J = 7 Hz, 3 H); IR 3300 (HC≡C), 2120 (C≡C), 1740 (C=O), and 1175 (C–O) cm^{-1}; mass spectrum m/e (rel intensity) 126 (M$^+$, 4.5), 98 (75), 97 (18), 81 (87), 70 (39), and 53 (100). Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.47; H, 7.96.

The use of methanesulfonate **1b** in this reaction led to a very slow consumption of starting material, even at 0 °C, and gave a mixture of products of which starting material was the major component. Both the acetylene (**3**) and the allene (**4**) products appeared to be present in this case, but no attempt was made to determine yields as the percent conversion of the methanesulfonate was very low.

Ethyl 2,4-Decadienoate (16). Allene **6**, 1.50 g (7.64 mmol), was added to 40 mL of absolute ethanol and cooled to 0 °C. Sodium ethoxide solution, 2.29 mL of a 1 M solution in ethanol (2.29 mmol), was added to give a brownish-yellow solution. After stirring for 30–40 min at 0 °C, the mixture was quenched with 3 N hydrochloric acid by adding the acid until the color faded to a pale yellow. The ethanol was removed under reduced pressure, and the product was extracted and dried. GLC analysis of the product indicated an isomer ratio of 6:63:31 for the 2Z,4E/2E,4Z/2E,4E isomers of **16**, respectively, in order of elution of the products.

This mixture was equilibrated by the addition of 42 mg (0.38 mmol) of thiophenol and 13 mg (0.076 mmol) of 2,2′-azobis(isobutyronitrile) to the above crude product. No solvent was used, and the mixture was heated at 80 °C for 2 h under a nitrogen atmosphere. After cooling, the product was diluted with ether, washed with 3 N sodium hydroxide, and then dried. Silica gel chromatography (5% ether/hexane) gave 1.29 g (86%) of purified isomer mixture. GLC analysis now showed the 2E,4E isomer constituted 84% of the mixture, with the other three isomers contained in the remaining 16%. These isomers were not sufficiently well resolved on GLC analysis to allow determination of their relative quantities.

The 2E,4Z and 2E,4E isomers were separated from the reconjugation and equilibration products respectively by means of preparative TLC. Eight developments using 3% ether/97% hexane were required to achieve a separation, taking in each case only a portion of

the band to ensure purity. Each plate was spotted with 40 mg of product and a total of 34 mg of 2*E*,4*Z* and 26 mg of 2*E*,4*E* was obtained. A silver nitrate (20% by weight) coated silica gel column failed to produce any separation of the isomers. 2*E*,4*Z* isomer: ^{1}H NMR (CCl_4) δ 7.43 (dd, J = 10, 15 Hz, 1 H), 6.03 (t, J = 10 Hz, 1 H), 5.55–5.95 (m, 1 H), 5.71 (d, J = 15 Hz, 1 H), 4.12 (q, J = 7 Hz, 2 H), 2.15–2.50 (m, 2H), 1.10–1.70 (m, 6 H), 1.24 (t, J = 7 Hz, 3 H), and 0.75–1.10 (m, 3 H). 2*E*,4*E* isomer: ^{1}H NMR (CCl_4) δ 7.10 (ddd, J = 15, 6, 3 Hz, 1 H), 5.95–6.20 (m, 2 H), 5.62 (d, J = 15 Hz, 1 H), 4.09 (q, J = 7 Hz, 2 H), 1.95–2.30 (m, 2 H), 1.10–1.65 (m, 6 H), 1.24 (t, J = 7 Hz, 3 H), and 0.70–1.10 (m, 3 H).

Ethyl (*E*)-2,4-Pentadienoate. Reconjugation of allene **4** under the same conditions as described above gave essentially a single product as indicated by GLC analysis. Although TLC did give a very faint indication of a higher R_f spot, no other product could be isolated. The reduced yield (50%) resulted from the volatility of the product: ^{1}H NMR (CCl_4) δ 7.14 (dd, J = 15, 11 Hz, 1 H), 6.39 (dt, J = 17, 10 Hz, 1 H), 5.10–5.95 (m, 3 H), 4.10 (q, J = 7 Hz, 2 H), and 1.27 (t, J = 7 Hz, 3 H); IR 1720 (C=O), 1647, 1605, 1010, and 925 (C=C) cm^{-1}; mass spectrum *m/e* (rel intensity) 126 (M^+, 17), 111 (2), 98 (20), 97 (12), 81 (100), 70 (8), 53 (58), and 43 (10). Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.77; H, 8.05.

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Registry No.—**1a**, 106-96-7; **1b**, 16156-58-4; **2a**, 56579-97-6; **2b**, 64706-02-1; **3**, 63093-41-4; **4**, 30332-99-1; **5a**, 818-72-4; **5b**, 64706-03-2; **6**, 36186-28-4; **12**, 64714-94-9; **13**, 64706-04-3; *E*-14 Methyl ester, 64706-05-4; *Z*-14 Methyl ester, 64706-06-5; (2*E*,4*Z*)-**16**, 3025-30-7; (2*E*,4*E*)-**16**, 7328-34-9; (2*Z*,4*E*)-**16**, 3025-31-8; ethyl bromide, 74-96-4; *hexanal, 66-25-1; methanesulfonyl chloride, 124-63-0; propargyl* alcohol, 107-19-7; ethyl (*E*)-2,4-pentadienoate, 13369-23-8.

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An Efficient Synthesis of γ-Methylene-γ-butyrolactone (α′-Angelicalactone). Application to the Synthesis of Deoxyobtusilactone and Deoxyisoobtusilactone

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The mercury(II)-catalyzed cyclization of 4-pentynoic acid proceeds efficiently to give γ-methylene-γ-butyrolactone (α′-angelicalactone). The enolate of this lactone reacts with 11-dodecenal producing separable diastereomeric β-hydroxylactones. The corresponding methanesulfonate derivatives undergo partially selective elimination to afford deoxyobtusilactone and deoxyisoobtusilactone.

Introduction

γ-Methylene-γ-butyrolactone or α′-angelicalactone (**1**) forms the basic ring structure of two newly described classes of natural products, the obtusilactones (**2a–f**)[1] and the fimbrolides (**3**).[2,3] Obtusilactone (**2a**) was the first-discovered member of a series of cytotoxic natural products (**2b–f**) isolated from the plant *Lindera obtusiloba* by Yamamura and workers.[1] The fimbrolides are marine natural products with antimicrobial (including antifungal) activity that have been isolated from the red alga *Delisea fimbriata* by Wells[2] and Sims.[3] Because of the demonstrated biological activity of these compounds, the synthesis of γ-methylene-γ-butyrolactones is of interest. In this report, we describe a method for the facile synthesis of γ-methylene-γ-butyrolactone and the application of this method to the preparation of the deoxy analogs of obtusilactone (**2a**) and isoobtusilactone (**2b**).

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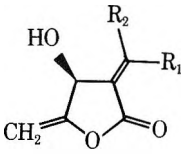
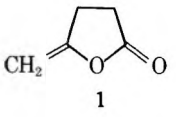


2a, $R_1 = -(CH_2)_9CH{=}CH_2$; $R_2 = H$
b, $R_1 = H$; $R_2 = -(CH_2)_9CH{=}CH_2$
c, $R_1 = -(CH_2)_{12}CH_3$; $R_2 = H$
d, $R_1 = H$; $R_2 = -(CH_2)_{12}CH_3$
e, $R_1 = -(CH_2)_5CH{=}CH(CH_2)_7CH_3$; $R_2 = H$
f, $R_1 = H$; $R_2 = -(CH_2)_5CH{=}CH(CH_2)_7CH_3$



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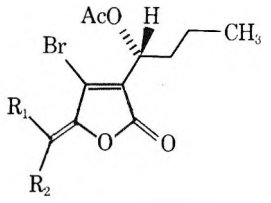
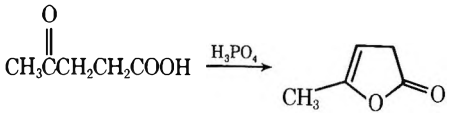


3, R_1R_2 = H,Cl,Br,I

Results and Discussion

Routes to Angelicalactones. The preparation of enol lactones has been well studied, with some of the work dating back to the late 1800's. Two major routes exist to these compounds, cyclization of either a keto acid or an acetylenic acid. The acid-catalyzed cyclization of levulenic acid to give α-angelicalactone (**4**) was first observed by Wolff[4] and further



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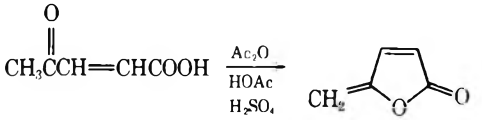
explored by Helberger.[5] The only reported case of formation of the exocyclic double bond by this approach is the synthesis of protoanemonin (**5**) by a similar cyclization of acetylacrylic



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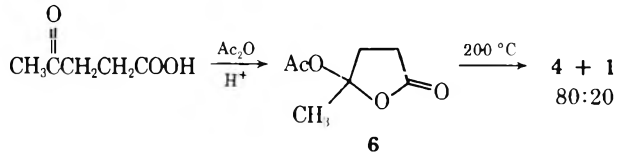
acid.[6] In this case, however, the presence of the conjugated double bond ensures the formation of the exocyclic enol ester. It is apparent that acid-catalyzed cyclization of keto acids is not an appropriate method for the preparation of γ-methylene-γ-butyrolactones since isomerization to the more stable endocyclic olefin would be expected under the acidic conditions.

Swern[7] has recently modified this procedure by trapping the intermediate lactol **6**; subsequent pyrolytic elimination

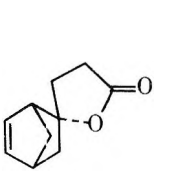


6

gave unfavorable mixtures of the α- and α′-angelicalactones.

Other pyrolytic approaches recently reported involve the retro-Diels–Alder reaction of **7** to give 1[8] and the rearrangement of **8** to a substituted analog of 1.[9]

The well-precedented Markownikoff addition of carboxylic acids across terminal acetylenes[10] would appear to provide ready access to γ-methylene-γ-butyrolactones. In fact, the iodolactone corresponding to **1** is formed upon treatment of



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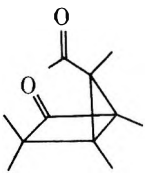

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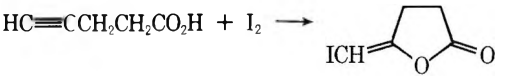
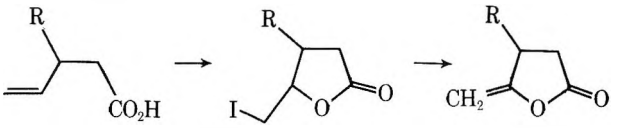
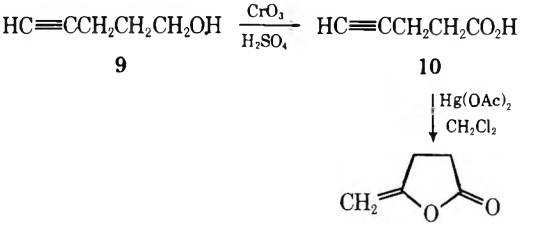
4-pentynoic acid with iodine.[11] Two other reported cyclizations have given endocyclic double bond isomers of the parent compound, however.[12,13]



A very recent report of Jäger and Günther[14] describes a selective preparation of γ-methylene-γ-butyrolactones by iodolactonization of 4-pentenoic acids, followed by dehydroiodination.[15]



Selective Preparation of α′-Angelicalactone. We have found that treatment of 4-pentynoic acid (**10**) in dichloromethane with a catalytic amount of mercuric acetate (4.5 mol %) gave the desired cyclization product γ-methylene-γ-butyrolactone (**1**) in 74% yield. This compound was the sole



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isolable product from the reaction with no evidence of either α- or β-angelicalactones or the corresponding δ-lactone that would result from an anti-Markownikoff addition. As 4-pentynoic acid is prepared in good yield by chromic acid oxidation of commercial 4-pentyn-1-ol (**9**),[16] this two-step synthesis represents a very short and efficient route to a compound that has been prepared only with difficulty by most previous routes.

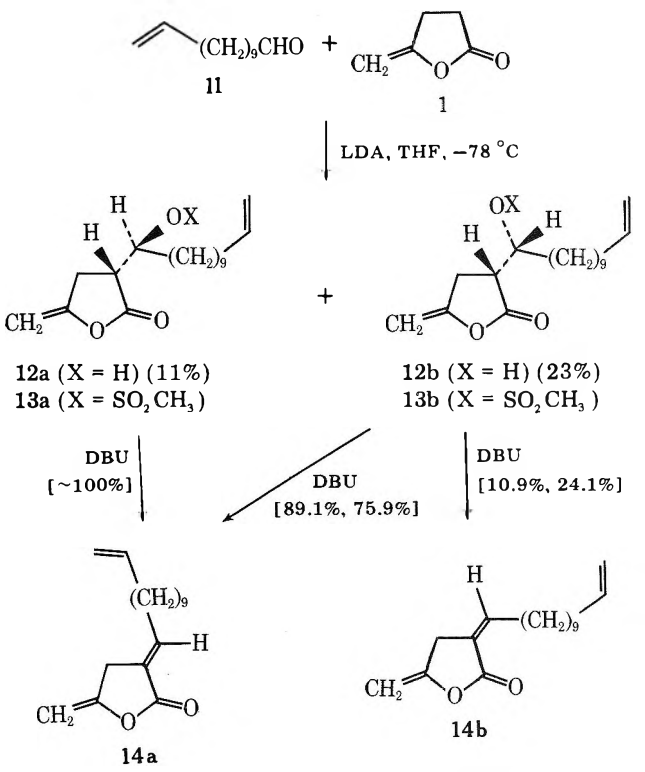
Synthesis of Deoxyobtusilactone and Deoxyisoobtusilactone. The approach we have taken to the deoxyobtusilactones is outlined in Scheme I.

Although the required aldehyde **11** is not commercially available, the lower homologous alcohol 10-undecen-1-ol (**15a**) is available. Homologation of **15a** was effected by displacement of the methanesulfonate **15b** (prepared from **15a** and used without purification) with sodium cyanide in dimethyl sulfoxide (92% yield), followed by controlled reduction with diisobutylaluminum hydride in benzene at room temperature, to give the aldehyde **11** (75% yield).[17] Homologation of the corresponding tosylate **15d** was equally efficient.

Several methods have been developed for condensing carbonyl compounds with lactones, although most of these represent syntheses of α-methylene lactones[18] rather than α-alkylidene lactones; phosphonium ylides,[19] α-silyl carbanions,[20] or α-thiomethylene intermediates[21] have been utilized. These approaches give predominantly or exclusively the *E*-alkylidene isomers and thus are not suitable for generating the *Z* geometry in obtusilactone.

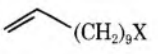
The reaction of lactone enolates with various electrophiles has constituted an important route to α-methylene lactones.[22]

Scheme I[a]



[a] Yields in parentheses are isolated; yields in brackets are product ratios. Where two numbers are given, the first is from reaction in ether, the second in hexane (see text).

Application of this method to aldehydes other than formaldehyde has not been well studied, but Zimmer[23] has reported the condensation of both alkyl and aryl aldehydes with lac-



15a, X = OH
b, X = OSO_2CH_3
c, X = CN
d, X = $OSO_2C_6H_4CH_3$

tones using weak bases, diethylamine or sodium methoxide. To minimize self-condensation of the aldehyde, we considered it desirable to modify Zimmer's procedure by preforming the lactone enolate stoichiometrically.

As indicated in Scheme I, the enolate of α'-angelicalactone (**1**) was generated by the addition of the lactone to a tetrahydrofuran solution of lithium diisopropylamide (LDA) at −78 °C. The aldehyde **11** was then added at low temperature, giving complete consumption of starting material within 10 min. Two major products were formed having substantially different R_f's on thin layer chromatography. The isolated compounds had essentially identical mass and infrared spectra and elemental analyses, and their spectra differed only in the resonances assigned to the hydrogens α to the carbonyl and on the carbon bearing the hydroxyl; thus, they appeared to be the diastereomeric β-hydroxy lactones **12a** and **12b**. The pronounced chromatographic separation between these species is presumably due to differences in intramolecular hydrogen bonding, although construction of models of **12a** and **12b** does not allow any definite conclusion as to why one diastereomer should show more effective intramolecular bonding than the other. Nevertheless, it was possible to assign structures to the more and less polar components based on the stereochemistry of their elimination products (vide infra).

The conventional method for the elimination of α-hydroxymethyl lactones is conversion of the alcohol to the methanesulfonate, followed by elimination in refluxing pyridine. This method was applied to a model compound, the condensation product between the enol lactone **1** and hexanal, and was found to proceed quite slowly. To avoid these rather strenuous conditions, we used the stronger base 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU). Compared to bases such as pyridine, these amidine bases (DBU and DBN) are particularly effective in promoting elimination reactions.[24]

The methanesulfonates **13a** and **13b** were formed by treatment of the corresponding alcohols with excess methanesulfonyl chloride in a triethylamine–dichloromethane solvent. Isolated but not purified, the methanesulfonates were treated with DBU in an ether solvent, giving an immediate reaction at 0 °C as evidenced by a rapid clouding of the solution and an eventual (2–3 min) precipitation of a viscous oil.

Methanesulfonate **13a**, derived from the less polar diastereomer **12a**, gave the deoxyisoobtusilactone **14a** in 75% yield with only faint traces of the other olefin isomer present by thin layer chromatography. The *E* configuration for the trisubstituted double bond was assigned on the basis of the lower field ^{1}H NMR resonance at δ 6.61 for the vinyl proton β to the carbonyl.[19a] Methanesulfonate **13b**, derived from the more polar diastereomer **12b**, gave a mixture of 63% of **14a** and 8% of **14b** (deoxyobtusilactone), the latter being assigned the *Z* configuration on the basis of the higher field ^{1}H NMR resonance at δ 6.12 for the vinyl proton β to the carbonyl.[19a]

The eliminations are not highly stereoselective. Presumably, this results from the fact that the elimination is proceeding by both ElcB and E2 mechanisms. Under the ElcB mechanism, both methanesulfonates undergo predominant elimination to the more stable *E* isomer (**14a**), with **13a** giving only this isomer. However, since **13b** does give small amounts of the *Z* isomer (**14b**), some of this isomer must react by an E2 mechanism; otherwise, if the distribution of *E* and *Z* isomers from **13b** were thermodynamic, then **13a** would be expected to produce some **14b**. Thus, from the antiperiplanar geometry of the E2 mechanism, we can assign the stereochemistries of **12a** (less polar diastereomer) and **12b** (more polar diastereomer) as shown in Scheme I.

As the E2 and ElcB mechanisms appear to be operating in competition, it was anticipated that a change to a less polar solvent, one less capable of stabilizing the intermediate carbanion, might increase the extent of E2 elimination and improve reaction stereoselectivity. Indeed, when **13b** was treated with DBU in hexane at 0 °C, the yields of **14b** and **14a** were 16.0% and 50.4%, as compared to 7.7% and 63.2% from the ether reaction. The stereoselectivity expressed in terms of the isomeric composition of the alkylidene lactone products is even better; hexane as solvent afforded 24.1% and 75.9% of **14b** and **14a**, respectively, while ether gave 10.9% and 89.1%.

Experimental Section

General. Analytical thin layer chromatography was performed using 0.25-mm silica gel glass-backed plates with F-254 indicator (Merck). Visualization was by ultraviolet light, iodine, or phosphomolybdic acid. Preparative TLC plates were from Merck or were prepared using Merck silica gel 60 PF-254 + 366.

Proton magnetic resonance ^{1}H NMR spectra were recorded on Varian Associates spectrometers, Models T-60, A-60, EM-390, and HR-220; chemical shifts are reported in ppm downfield from a tetramethylsilane internal standard (δ scale). The ^{1}H NMR data are presented in the form: δ value of signal (peak multiplicity, coupling constant (if any), integrated number of protons). Infrared spectra were recorded on either a Perkin-Elmer Model 137 spectrometer or a Beckman Model IR-12 instrument. Unless otherwise noted, spectra were obtained on neat compounds held between sodium chloride plates. Data are presented in cm^{-1} and only the important diagnostic bands are reported.

Mass spectra were obtained from a Varian MAT CH-5 spectrometer

and were at 70 eV ionization voltage unless otherwise indicated. Data are presented in the form: *m/e* (intensity relative to base peak). Elemental analyses were provided by the microanalytical service laboratory of the University of Illinois.

Chemicals were obtained from the following sources: Aldrich Chemical Co., tetrahydrofuran, triethylamine, diisopropylamine, 10-undecen-1-ol, methanesulfonyl chloride, *p*-toluenesulfonyl chloride, 1,5-diazabicyclo[5.4.0]undec-5-ene; Fisher Scientific Co., dichloromethane; J. T. Baker Chemical Co., mercuric acetate; Chem. Samples, 4-pentyn-1-ol; Mallinckrodt, dimethyl sulfoxide, diethyl ether, chromium trioxide; Ventron, *n*-butyllithium, diisobutylaluminum hydride.

Tetrahydrofuran was distilled from sodium benzophenone by use of a recirculating still, maintaining a deep blue coloration at all times. Diisopropylamine and triethylamine were refluxed over calcium hydride and then distilled to ensure dryness. The organolithium reagents were titrated periodically to determine the organic base present, using either the double titration method[25] or the single titration method[26] with 1,10-phenanthroline as an indicator. All values used were the average of at least three separate determinations.

Reaction products were dried over anhydrous magnesium sulfate unless otherwise stated. All yields reported are isolated products after purification unless indicated otherwise. Silica gel chromatography was performed using 0.05–0.2 mm silica gel with weight ratios usually in the range 30:1 to 50:1 silica gel–crude product. Close separations required ratios as high as 200:1. Elution solvent mixtures are given as volume percentages.

4-Pentynoic Acid (10). This was prepared in 74% yield from 4-pentyn-1-ol according to the method of Holland and Gilman.[16] Recrystallization from hexane–THF gave white crystalline plates: mp 53–55 °C; lit.[16] 54.5–56.5 °C; ^{1}H NMR ($CDCl_3$) δ 11.30 (s, 1 H), 2.45–2.70 (m, 4 H), 1.99 (t, J = 2 Hz, 1 H).

Anal. Calcd for $C_5H_6O_2$: C, 61.22; H, 6.16. Found: C, 60.95; H, 6.07.

Dihydro-5-methylene-2(3*H*)-furanone (γ-Methylene-γ-butyrolactone; α′-Angelicalactone) (1). 4-Pentynoic acid (**10**), 1.47 g (15 mmol), was dissolved in 100 mL of dichloromethane, followed by 0.21 g (0.66 mmol) of mercuric acetate. Initially, the mixture was cloudy but it cleared during the course of the reaction. After 24 h at room temperature, TLC showed the complete consumption of starting material with a single spot of R_f slightly higher than the acid. The product was stirred with saturated sodium bicarbonate for 5 to 10 min and was then extracted thoroughly and dried. Silica gel chromatography (40% ether–hexane) removed the remaining mercury salts and gave 1.08 g (74%) of pure product: ^{1}H NMR (CCl_4) δ 4.55–4.75 (m, 1 H), 4.15–4.30 (m, 1 H), 2.35–3.10 (m, 4 H); IR 1815 (C=O), 1675 (C=C), 1130 (CO), and 885 (C=CH_2) cm^{-1}; mass spectrum (10 eV) *m/e* (rel intensity) 98 (M^+, 100), 70 (32), 56 (48), 55 (10), 42 (30), 28 (23).

Anal. Calcd for $C_5H_6O_2$: C, 61.22; H, 6.16. Found: C, 61.25; H, 6.19.

***p*-Toluenesulfonate of 10-Undecen-1-ol (15d).** Alcohol **15a**, 17.03 g (0.10 mol), was added to a solvent mixture of 12.14 g (0.12 mol) of triethylamine in 50 mL of dichloromethane. After cooling to 0 °C, 20.02 g (0.105 mol) of *p*-toluenesulfonyl chloride was added. A precipitate of the amine hydrochloride salt appeared rapidly, but 4 days at 0 °C was required for consumption of the alcohol. When TLC indicated the reaction to be essentially complete, it was diluted with 200 mL of ether, stirred over saturated sodium bicarbonate for 4 h at 25 °C, washed with brine and 3 N hydrochloric acid, and dried. Removal of the solvent gave an essentially quantitative yield of **15d** sufficiently pure for the subsequent reactions. The analytical sample was purified by silica gel chromatography (30% ether–hexane): ^{1}H NMR (CCl_4) δ 7.72 (d, J = 8 Hz, 2 H), 7.28 (d, J = 8 Hz, 2 H), 5.78 (ddt, J = 9.5, 17, 6 Hz, 1 H), 4.75–5.10 (m, 2 H), 3.95 (t, J = 6 Hz, 2 H), 2.43 (s, 3 H), 1.80–2.20 (m, 2 H), 1.25 (broad s, 14 H).

Anal. Calcd for $C_{18}H_{28}O_3S$: C, 66.63; H, 8.70; S, 9.88. Found: C, 66.69; H, 8.65; S, 9.87.

The corresponding methanesulfonate (**15b**) was prepared by this procedure but was not purified and characterized.

11-Dodecenenitrile (15c). Sodium cyanide, 0.74 g (15 mmol), was added to 15 mL of dry dimethyl sulfoxide with only a portion dissolving in the solvent. Tosylate **15d**, 3.24 g (10 mmol), was then added dropwise. The mixture was stirred 24 h at room temperature during which time the crystals of sodium cyanide gradually dissolved. The mixture was diluted with 200 mL of water and extracted several times with ether. These extracts were washed with saturated brine and dried. Silica gel chromatography (30% ether–hexane) afforded 1.75 g (98%) of product.

The compound was also prepared on a larger scale (8.24 g of product) by reaction of the sodium cyanide with the corresponding methanesulfonate, **15b**. The methanesulfonate appeared to be less reactive than the *p*-toluenesulfonate but afforded an overall yield of 92% for the two steps: ^{1}H NMR (CCl_4) δ 5.71 (ddt, J = 17, 10, 7 Hz, 1 H), 4.75–5.10 (m, 2 H), 2.23 (t, J = 6 Hz, 2 H), 1.80–2.20 (m, 2 H), 1.20–1.80 (m, 14 H); IR 3080 (C=CH_2), 2245 (C≡N), 1640, 990, 910 (C=CH_2) cm^{-1}. mass spectrum (10 eV) *m/e* (rel intensity) 179 (M^+, 2.2), 178 (4), 164 (6), 150 (34), 136 (89), 122 (100), 108 (30), 94 (31).

Anal. Calcd for $C_{12}H_{21}N$: C, 80.38; H, 11.81; N, 7.81. Found: C, 80.35; H, 11.88; N, 8.00.

11-Dodecenal (11). Nitrile **15c**, 8.07 g (45 mmol), was added to 90 mL of dry benzene, followed by the dropwise addition of diisobutylaluminum hydride, 9.12 mL (7.11 g, 50 mmol). The addition required 15 min, during which time the reaction temperature was maintained at 20–25 °C by means of a water bath. After 1 h at room temperature, TLC showed no evidence of starting material. The mixture was cooled to 0 °C, and methanol was added slowly until all foaming ceased. The product was diluted with ether and 3 N hydrochloric acid was added with cooling until the aqueous layer was just acid. The organic layer was then separated and dried. Silica gel chromatography (10% ether–hexane) gave 6.15 g (75%) of pure aldehyde: ^{1}H NMR (CCl_4) δ 9.64 (t, J = 1 Hz, 1 H), 5.70 (ddt, J = 17, 10, 6 Hz, 1 H), 4.75–5.05 (m, 2 H), 2.33 (t, J = 6 Hz, 2 H), 1.80–2.20 (m, 2 H), 1.15–1.80 (m, 14 H). IR 3080 (C=CH_2), 2720 (CHO), 1730 (C=O), 1640, 990, 910 (C=CH_2) cm^{-1}; mass spectrum (10 eV) *m/e* (rel intensity) 182 (M^+, 2.5), 180 (4), 164 (35), 153 (4), 139 (9), 135 (35), 125 (15), 121 (60), 98 (100).

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.96; H, 11.94.

3-(1-Hydroxy-11-dodecenyl)dihydro-5-methylene-2(3*H*)-furanone (Diastereomers 12a and 12b). The diisopropylamine, 0.81 g (8 mmol), was added to 50 mL of dry tetrahydrofuran and cooled to −10 °C. *n*-Butyllithium, 3.23 mL of a 2.30 M solution (7.44 mmol), was then added. After 10 min, the mixture was cooled to −78 °C and 0.73 g (7.44 mmol) of lactone **1** was added dropwise. The homogeneous mixture was stirred 30 min at −78 °C, and then 1.36 g (7.44 mmol) of aldehyde **11** was added dropwise. The reaction was stirred 30 min at −78 °C (TLC indicated the reaction was essentially complete within 10 min) and then was quenched with saturated ammonium chloride. The solvent was removed under reduced pressure, and the product was extracted into ether, washed with saturated ammonium chloride, and dried. Silica gel chromatography (25% ether–hexane) yielded two pure components: 239 mg (11%) of a nonpolar material (**12a**) (R_f ≈ 0.4 in 50% ether–hexane) and 489 mg (23%) of a polar material (**12b**) (R_f ≈ 0.2); nonpolar diastereomer (**12a**): ^{1}H NMR (CCl_4) δ 5.70 (ddt, J = 17, 10, 7 Hz, 1 H), 4.75–5.05 (m, 2 H), 4.55–4.70 (m, 1 H), 4.14–4.30 (m, 1 H), 3.90–4.14 (m, 1 H), 2.60–3.10 (m, 4 H, 1 D_2O exchangeable), 1.80–2.20 (m, 2 H), 1.10–1.75 (m, 16 H); IR 3500 (OH), 3085 (C=CH_2), 1805 (C=O), 990, 910, 840 (C=CH_2) cm^{-1}; mass spectrum (10 eV) *m/e* (rel intensity) 280 (M^+, 15), 262 (2), 235 (3), 219 (4), 205 (2), 191 (2), 177 (3), 163 (3), 149 (3), 98 (100).

Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 73.09; H, 10.11.

Polar diastereomer (**12b**): ^{1}H NMR (CCl_4) δ 5.70 (ddt, J = 17, 10, 7 Hz, 1 H), 4.75–5.05 (m, 2 H), 4.55–4.75 (m, 1 H), 4.15–4.30 (m, 1 H), 3.50–3.80 (m, 1 H), 3.07 (broad s, 1 H, D_2O exchangeable), 2.50–2.95 (m, 3 H), 1.75–2.20 (m, 2 H), 1.10–1.70 (m, 16 H); IR 3500 (OH), 3080 (C=CH_2), 1800 (C=O), 980, 910, 840 (C=CH_2) cm^{-1}; mass spectrum (10 eV) *m/e* (rel intensity) 280 (M^+, 9), 262 (3), 235 (15), 219 (5), 205 (3), 191 (3), 177 (5), 163 (6), 149 (4), 98 (100).

Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 73.10; H, 10.10.

3-(11-Dodecenylidene)dihydro-5-methylene-2(3*H*)-furanone (*E* and *Z* Isomers, 14a and 14b, Respectively, or Deoxyisoobtusilactone and Deoxyobtusilactone, Respectively). The enol lactone **12b**, 486 mg (1.73 mmol), was added to 10 mL of dichloromethane, followed by 228 mg (2.25 mmol) of triethylamine. After cooling to 0 °C, 238 mg (2.08 mmol) of methanesulfonyl chloride was added dropwise, followed by stirring for 3 h at 0 °C. The reaction was quenched with saturated sodium bicarbonate, diluted with ether, washed again with the bicarbonate, and dried. After removal of solvents, the crude product was added to 10 mL of ether, cooled to 0 °C, and then 343 mg (2.25 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) was added dropwise. Formation of an oily precipitate was immediate, and TLC after 15 min showed complete consumption of starting material. The product was diluted with ether, washed with brine, and dried. Silica gel chromatography (5% ether–hexane) gave 35 mg (8%) of **14b** and 287 mg (63%) of **14a**.

A similar procedure on 239 mg of **12a** afforded 167 mg (75%) of **14a** with only faint traces of **14b**. Compound **14b**: ^{1}H NMR (CCl_4) δ 6.12

(tt, J = 7, 2 Hz, 1 H), 5.70 (ddt, J = 17, 10, 7 Hz, 1 H), 4.75–5.05 (m, 2 H), 4.55–4.68 (m, 1 H), 4.05–4.15 (m, 1 H), 3.30–3.50 (m, 2 H), 2.50–2.80 (m, 2 H), 1.80–2.20 (m, 2 H), 1.15–1.70 (m, 14 H); IR 3080 (C=CH_2), 1788 (C=O), 968, 910, 835 (C=C) cm^{-1}; mass spectrum m/e (rel intensity) 262 (M^+, 9), 219 (5), 205 (3), 191 (2), 177 (4), 163 (3), 110 (72), 43 (100).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.53; H, 10.14.

Compound **14a:** ^1H NMR (CCl_4) δ 6.61 (tt, J = 7, 2.5 Hz, 1 H), 5.70 (ddt, J = 17, 10, 7 Hz, 1 H), 4.74–5.03 (m, 2 H), 4.60–4.74 (m, 1 H), 4.10–4.20 (m, 1 H), 3.25–3.45 (m, 2 H), 1.70–2.35 (m, 4 H), 1.15–1.70 (m, 14 H); IR 3080 (C=CH_2), 1795 (C=O), 955, 910, 837 (C=C) cm^{-1}; mass spectrum m/e (rel intensity) 262 (M^+, 11), 234 (4), 219 (7), 205 (7), 191 (5), 177 (9), 163 (9), 110 (78), 41 (100).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.97; H, 10.07.

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Registry No.—**1,** 10008-73-8; **10,** 6089-09-4; **11,** 51148-68-6; **12a,** 64215-99-2; **12b,** 64216-00-8; **13a,** 64235-92-3; **13b,** 64235-93-4; **14a,** 64216-01-9; **14b,** 64216-02-0; **15a,** 112-43-6; **15b,** 52355-50-7; **15c,** 5048-44-2; **15d,** 51148-67-5; p-toluenesulfonyl chloride, 98-59-9; sodium cyanide, 143-33-9; methanesulfonyl chloride, 124-63-0.

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Thermolysis and Photolysis of Unsaturated Ketones. 26. Preparation of Bicyclo[2.2.2]octan-2-ones and Bicyclo[2.2.1]heptan-2-ones by Thermal Cyclization of Unsaturated Ketones. A Facile Synthesis of (+)-Camphor from (+)-Dihydrocarvone[1]

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Bicyclo[2.2.2]octan-2-ones **4a** and **4b** have been synthesized in yields of 85 and 50%, respectively, by the thermal cyclization of the appropriate 3-alkenylcyclohexanone at 390 °C. The monoterpene (+)-camphor (**10**) has been prepared in 55% yield and 90% optical purity by cyclization of (+)-dihydrocarvone (**9**) at 400 °C. An explanation for the formation in these thermolyses of a number of side products such as 2-cyclohexenones and alkylbenzenes is offered. Thermal fragmentation of bicyclo[2.2.2]octan-2-ones via a retro-Diels–Alder reaction gives an alkene and a 2-cyclohexenone, which is then converted into an alkylbenzene. It is suggested that these latter transformations may be related to the formation of some petroleum hydrocarbons from terpenoid precursors.

The thermal cyclization of unsaturated ketones has been used to prepare a wide variety of cycloalkyl ketones and cycloalkanones.[2] Bridged systems such as bicyclo[3.2.1]- and -[3.3.1]alkanes have been prepared in high yield using this technique.[2] In this report we describe the preparation of two bicyclo[2.2.2]octan-2-ones and a strained bicyclo[2.2.1]heptan-2-one, the monoterpene (+)-camphor, using this cyclization procedure. The formation of side products in these

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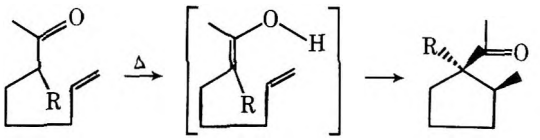
thermolysis reactions will also be rationalized.

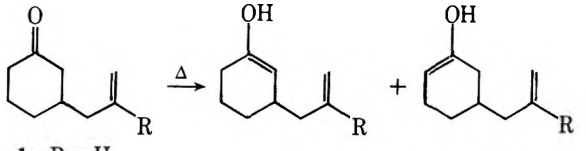
These cyclizations proceed via the enol tautomer in a manner analogous to the intramolecular ene reaction with the enol hydrogen being transferred to the terminus of the double bond and the new carbon–carbon bond formed as illustrated in eq 1. When epimerization of the product is not possible (e.g.,



(1)

eq 1, R = alkyl), the stereochemistry of the product may be reliably predicted.[2]

In the present investigation, employing 3-alkenylcyclohexanones such as **1**, two different enols (**2** and **3**) may be

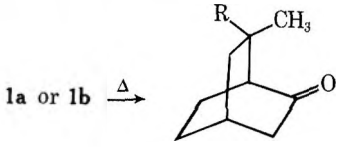


1a, R = H
b, R = CH_3 **2** **3**

formed initially. Enol **2** would lead to a strained cyclobutyl ketone under the usual thermolysis conditions (in fact, the reverse reaction occurs in such cases[3]), while **3** should lead to the desired bridged products.

When 3-allylcyclohexanone (**1a**)[4,5] was heated for 16 h at 390 °C in the vapor phase, a crystalline product, *endo*-6-methylbicyclo[2.2.2]octan-2-one (**4a**), was formed in 85% yield along with 2-cyclohexenone (**5**, 8%). The infrared spectrum exhibited carbonyl absorption at 1725 cm^{-1}, as expected for this ring system,[6] and the NMR spectrum showed a methyl doublet at τ 9.11 and a rather sharp four-proton multiplet (4-Hz width at half height) at τ 7.91, characteristic of bicyclo[2.2.2]octan-2-ones.[7] Ketone **4a** was previously synthesized[8] by a lengthy route from a Diels–Alder adduct, and the melting point and carbonyl absorption in the infrared spectrum were in agreement with the values reported here. The endo configuration of the C_6 methyl group is that predicted from the cyclization mechanism discussed above.

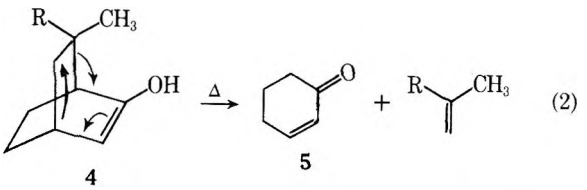
Similarly, when 3-methallylcyclohexanone (**1b**)[9] was heated



4a, R = H
b, R = CH_3

for 16 h at 390 °C, crystalline 6,6-dimethylbicyclo[2.2.2]-octan-2-one (**4b**) was formed in 50% yield along with 2-cyclohexenone (39%) and benzene (6%). The bicyclic ketone **4b** possessed a camphor-like odor, and its NMR spectrum exhibited a sharp four-proton multiplet at τ 7.95 (5-Hz width at half height)[7] and two singlet methyl resonances (τ 8.92 and 9.10), as anticipated for the cyclized product. **4b** has not been reported previously, but the related 4,6,6-trimethylbicyclo[2.2.2]octan-2-one exhibits singlet methyl resonances at τ 8.93, 9.08, and 9.11.[10]

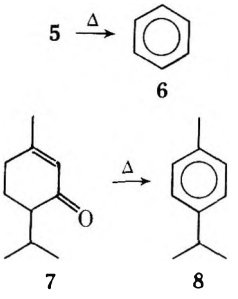
The side products formed in the thermolysis of both **1a** and **1b** deserve comment. 2-Cyclohexenone (**5**) was formed in both reactions, and we propose it originates from a retro-Diels–Alder reaction of the enol tautomer of **4** (eq 2). In the mass spectra of many bicyclo[2.2.2]octenes, the base peak is formed as a result of such a fragmentation.[11] When a pure sample of **4a** was heated under the same thermolysis conditions (390 °C,



4 **5** (2)

16 h), 2-cyclohexenone was formed in low yield, showing that bicyclo[2.2.2]octan-2-ones may serve as precursors to 2-cyclohexenones. Thus, in the thermolysis of both **1a** and **1b**, there is a critical balance between the rate of cyclization of the unsaturated ketones and the rate of fragmentation of the bicyclic product (**4**). The lower yield of ketone **4b** appears to result from its more facile fragmentation and suggests that additional alkyl substitutents facilitate this retro-diene reaction. A more detailed study of this retro reaction of bicyclo[2.2.2]octan-2-ones in which the number and positions of substituents are varied could provide useful insights into both the retro and the Diels–Alder reaction itself. From the limited investigation of these two systems (**4a** and **4b**), we conclude that the more substituted ethylene is expelled in the fragmentation process. A similar preference is found in the mass spectral fragmentations of these systems.[11]

The mechanism of formation of the aromatic hydrocarbons in these thermolyses is not obvious. We suggest that the precursors to these aromatics are the 2-cyclohexenones which are formed in the retro-diene reaction described above. Thus, benzene would be derived from 2-cyclohexenone and toluene from a methylcyclohexenone. In support of this proposal, it was found that thermolysis of 2-cyclohexenone (**5**) at 400 °C for 20 h (Table I, expt 4) resulted in a 7% conversion to benzene (**6**), with the remainder of the enone being recovered. The



6 **7** **8**

same conditions resulted in a 53% conversion of piperitone (**7**) to a variety of products (expt 5), the major one being *p*-cymene (**8**). These two examples confirm the cyclohexenone → benzene transformation and suggest that alkyl substituents facilitate the reaction. Further support for this conclusion will be offered later. It is important to note that these transformations involve no change in the oxidation level of the starting enone. In its simplest terms, the conversion may involve enolization of the enone followed by a series of [1,5] sigmatropic hydrogen shifts[12] to give a cyclohexadienol, which dehydrates to the aromatic system. A related transformation, conversion of cyclohexanane to 1,3-cyclohexadiene, has been investigated.[13,14]

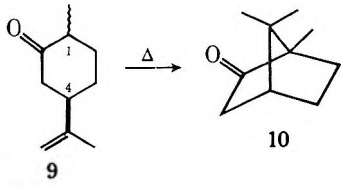
Having established that thermal cyclization was an effective method for the preparation of bicyclo[2.2.2] systems, we investigated next the possible preparation of a strained bicyclo[2.2.1]alkanone. (+)-Dihydrocarvone (**9**) was chosen as the substrate for two reasons: (i) successful cyclization of this ketone would result in a facile synthesis of (+)-camphor,[15] and (ii) the use of an optically active substrate might provide additional mechanistic information concerning these thermal reactions. **9**, prepared from (−)-carvone by reduction with lithium in liquid ammonia,[16] exists as a mixture of C_1 epimers in a 3:1 ratio. This ratio, and consequently the specific rotation of **9**, varies with the method of preparation,[17] but the mixture

Table I. Thermolysis Experiments

Expt	Ketone substrate	Registry no.	Thermolysis conditions Temp, °C	Time, h	% conversion to products	Cyclized product, % yield	% yield of other products[a,b] 5	6	16	13	Others
1	**1a**	20498-05-9	390	16	100	**4a**, 85	8	3	4		
2	**1b**	937-44-0	390	16	95	**4b**,[g] 50	39	6			
3	**4a**	25578-20-5	390	16	5		40		40		
4	**5**	930-68-7	400	20	7			100			
5	**7**	89-81-6	400	20	53				11		50,[c] 32[d]
6	**9**	5524-05-0	400	20	80	**10**, 55			12	21	7[e]
7	**10**	464-49-3	400	20	5					20	80[f]

[a] Yields are calculated on the basis of reacted material. [b] Where total yield does not equal 100%, other minor components of undetermined structure were also detected. [c] A 3:2 mixture of 3- and 5-methyl-2-cyclohexenone, respectively. [d] *p*-Cymene. [e] A 4:3 mixture of 2- and 6-methyl-2-cyclohexenone, respectively. [f] Dihydrocarvone (**9**). [g] Registry no.: **4b**, 64235-42-3.

was of no concern in our synthetic approach as C_1 is involved in the enolization step prior to cyclization. Thermolysis of **9** at 400 °C for 20 h in the vapor phase resulted in an 80% conversion and gave as the major product (55%) (+)-camphor (**10**)



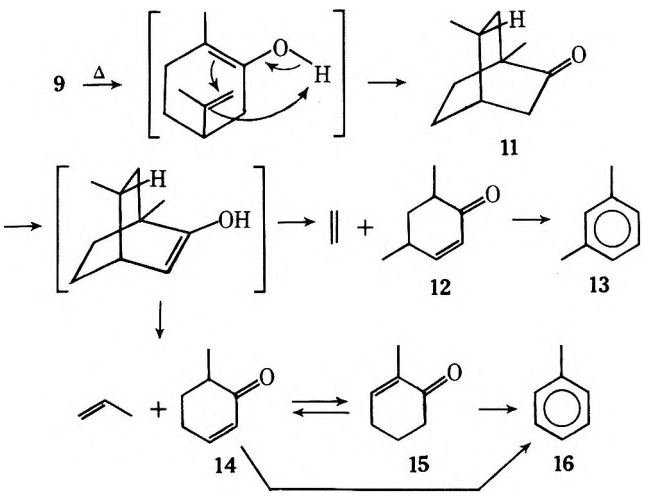
9 **10**

of 80% optical purity. Unreacted **9**, recovered by GC after the thermolysis, was found to be a 3:1 mixture of C_1 epimers and had an optical purity of only 58%. Other products that formed in the thermolysis of **9** are indicated in Table I, expt 6.

The synthesis of camphor in high yield by the BF_3-catalyzed cyclization of an enol acetate of (+)-dihydrocarvone has recently been reported, but the product was found to be racemic.[17] It was assumed that the chiral center at C_4 in **9** must have been racemized either by double bond migration or 1,2-hydrogen shifts. Under our thermolysis conditions, a similar process must have occurred but fortunately only to a minor extent. A lower optical purity of recovered **9** relative to **10** is consistent with partial racemization taking place before cyclization. This conclusion is supported also by the fact that thermolysis of (+)-camphor (**10**)[18] under the same conditions (expt 7) employed for **9** resulted in the recovery of 95% of the starting camphor of 96% optical activity.

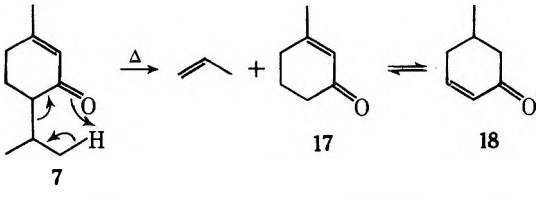
The origin of the other products formed in the thermolysis of **9** is not obvious and suggests the possibility of some novel transformations. We propose that the bicyclo[2.2.2]octan-2-one **11** is the common intermediate of all five side products, **12**, **13**, **14**, **15**, and **16** (Scheme I). In the introduction it was noted that in thermal cyclization of unsaturated ketones the new carbon–carbon bond is always formed between the carbon α to the carbonyl group and the *nonterminal* end of the alkene substituent.[2] A molecular model of **9** indicates that bond formation between the α carbon and the *terminal* end of the double bond via a 6-membered transition state is not only possible but would result in the less strained bicyclo[2.2.2] system **11**, as compared with the bicyclo[2.2.1] system in **10**. Apparently, under the thermolysis conditions required to effect the reaction of **9**, the enol of **11** (Scheme I) is converted completely to enones **12** and **14** via retro-Diels–Alder reactions. Subsequently, **12** is transformed to the major side product *m*-xylene (**13**) while **14** undergoes thermal isomerization to **15**, and then both **14** and **15** are partially converted to toluene (**16**).[19] Our study of the bicyclo[2.2.2]octan-2-ones described above provides precedents for both the fragmentation of **11**[20] and the conversion of the resultant enones to alkylated benzenes. The fact that dimethylcyclohexenones (e.g., **12**) were not isolated (only the transformation product **13**) while methylcyclohexenones **14** and **15** were isolated

Scheme I



provides additional support for the suggestion that alkyl substituents facilitate the conversion to the substituted benzenes.

Thermal isomerization of enone **14** to **15**, possibly via a [1,5] sigmatropic hydrogen shift in the enol of **14**, further illustrates the lability of the double bonds at these temperatures. An additional example of this type of enone isomerization was found upon thermolysis of piperitone (**7**) (Table I, expt 5). In



7 **17** **18**

addition to the 32% yield of *p*-cymene described above, it was expected that a McLafferty-type rearrangement in **7** would yield **17**. Instead, a mixture of **17** and **18** was formed in 50% yield of converted material, with **18** arising by thermal isomerization of **17**.

In conclusion, we have shown that thermolysis of 3-alkenylcyclohexanones at 390–400 °C is an effective method for the preparation of substituted bicyclo[2.2.2]octan-2-ones and bicyclo[2.2.1]heptan-2-ones. Specifically, we have synthesized the monoterpene (+)-camphor in good yield and high optical purity. In addition, we believe that certain other transformations described here may be related to the formation of petroleum hydrocarbons. Terpenoids have long been thought to be important precursors of petroleum products,[21] but the details of these transformations have not been clear in most instances.[22] In this report we have shown that monoterpenes (e.g., **7** and **9**) may be converted by thermolysis[23,24] to toluene

and/or *m*-xylene, which are two of the most abundant aromatic hydrocarbons in petroleum.[25]

Experimental Section

Melting points were determined on a Mettler FP 51 automatic apparatus, infrared spectra were recorded on a Perkin-Elmer 457G spectrophotometer, ultraviolet spectra on a Unicam SP 1800 spectrophotometer, and mass spectra on a Varian M-66 spectrometer operating at 70 eV. Optical rotations were determined on a Perkin-Elmer 141 automatic polarimeter at 25 °C with absolute ethanol as the solvent, and ^{1}H NMR spectra were recorded on a Perkin-Elmer R12A 60-MHz spectrometer using the internal standard tetramethylsilane (τ 10.0) and the following designations: s, singlet; d, doublet; m, multiplet. Gas chromatographic (GC) analyses and collections were done on an Aerograph Model A-90P with hydrogen as the carrier gas and the following columns: A, 3.5 m × 8 mm, 20% Carbowax 20M on 45–60 mesh Chromosorb P; B, 4.0 m × 8 mm, 20% SE30 on 45–60 mesh Chromosorb P. Peak areas were determined by triangulation and were not corrected for differences in thermal response.

The thermolyses were conducted in a 500-mL evacuated (<0.025 Torr) glass reactor, using the apparatus previously described.[26] The samples to be thermolyzed were routinely collected by preparative GC prior to reaction, and the sample size was normally 300–350 mg. The thermolysis products were immediately distilled into a cold finger cooled in liquid nitrogen and analyzed. In none of the thermolyses described was there any significant polymerization or tar formation, and thus the product recoveries were nearly quantitative. Where the thermolysis products were known compounds, their structures were confirmed by comparison of NMR, IR, and GC retention times on both columns A and B with authentic samples. The per cent conversion and the product distribution of the compounds thermolyzed are summarized in Table I.

***endo*-6-Methylbicyclo[2.2.2]octan-2-one (4a).** A 320-mg sample of 3-allylcyclohexanone (1a)[4,5] was placed in the thermolysis reactor at 390 °C for 16 h. Distillation of the product gave 300 mg of a pale yellow oil which darkened after several hours at room temperature. GC analysis (column A, 176 °C; column B, 145 °C) gave the product distribution indicated in Table I, expt 1. The major peak was collected by preparative GC and identified as **4a**: mp 52 °C (lit.[8] 50–52 °C); IR (neat) 2930, 2870, 1725, 1455, 1095 cm^{-1}; IR (CCl_4) 1729 cm^{-1} (lit.[8] 1729 cm^{-1}); NMR (CCl_4) τ 9.11 (3 H, d, J = 6.0 Hz), 8.89 (1 H, m), 8.28 (4 H, m), 8.05 (2 H, m), 7.91 (4 H, m, 4-Hz width at half-height); mass spectrum, *m/e* (rel intensity) 138 (M^+, 100), 123 (10), 95 (4), 94 (9).

Anal. Calcd for $C_9H_{14}O$: *m/e* 138.104. Found: *m/e* 138.104.

6,6-Dimethylbicyclo[2.2.2]octan-2-one (4b). A 200-mg sample of 3-methallylcyclohexanone (1b)[9] was thermolyzed at 390 °C for 16 h and distilled to give a pale yellow oil which was analyzed by GC (column A, 185 °C; column B, 155 °C) to give the product distribution reported in Table I, expt 2. The major product, which had a retention time slightly shorter than 1b on column B, was collected on this column. It was found to possess a camphor-like odor and was identified as **4b**: mp 117 °C; IR (melt) 2920, 2870, 1725, 1450, 1220 cm^{-1}; IR (CCl_4) 1730 cm^{-1}; NMR (CCl_4) τ 9.10 (3 H, s), 8.92 (3 H, s), 8.15–8.68 (6 H, m), 7.95 (4 H, m, 5-Hz width at half-height); mass spectrum, *m/e* (rel intensity) 152 (M^+, 100), 138 (25), 137 (22), 109 (5), 95 (8).

Anal. Calcd for $C_{10}H_{16}O$: *m/e* 152.120. Found: *m/e* 152.123.

(+)-Camphor (10). (+)-Dihydrocarvone (**9**), α_D +10.9° (*c* 3.0), was prepared[16] from (−)-carvone, α_D −62° (Fluka), and purified by preparative GC. A 350-mg sample of **9** was thermolyzed at 400 °C for 20 h and analyzed by GC (Table I, expt 6). All the major peaks were collected by GC and compared with authentic samples. The synthetic (+)-camphor was found to have α_D +32° (*c* 3.3), while a natural (+)-camphor sample which was collected and analyzed in the same number was found to have α_D +40° (*c* 3.8). The recovered **9** at the end of the thermolysis was found to have α_D +6.3° (*c* 1.9).

References and Notes

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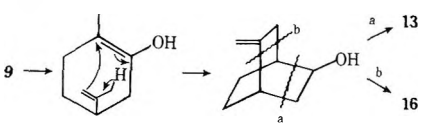
(19) An ene reaction of the enol of **9** followed by fragmentation and dehydrogenation also would account for the formation of **13** and **16** but not **14** and **15**. A study is under way to distinguish between these possible mechanisms.



(20) In the fragmentations of **4a** and **4b** the more substituted ethylenes were expelled, while with **11** approximately the same amounts of ethylene and propylene were expelled to give **13** (21%) and **14** + **15** + **16** (19%), respectively.
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Photochemistry of Phenyl Alkyl Ketones in the Presence of Organophosphorus(V) Compounds

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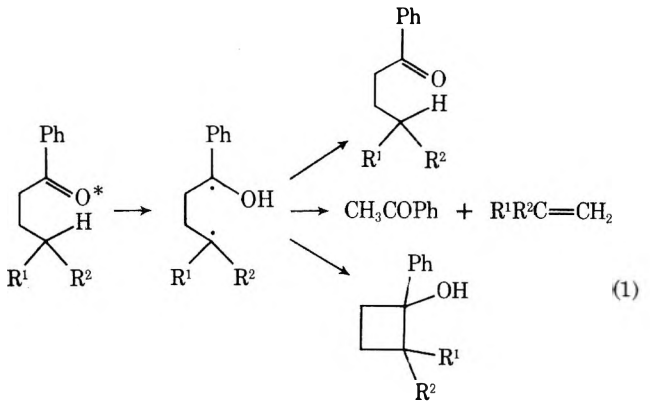
Triphenylphosphine oxide, as well as organic phosphates [$(MeO)_3PO$, $(PrO)_3PO$, and $(PhO)_3PO$], interact with the biradicals produced in the photochemistry of phenyl alkyl ketones (e.g., valerophenone), increasing the yields of photofragmentation and cyclization. The effect is presumed to result from the formation of a complex between the organophosphorus substrate and the intermediate biradical.

When a solution of a phenyl alkyl ketone bearing γ-hydrogen atoms is irradiated with UV light, it undergoes fragmentation and cyclization processes, known as the Norrish type II reaction.[2] The intermediacy of biradicals in the reaction from the triplet state has been proposed from studies of solvent effects and the photochemistry of optically active molecules.[2-5] This proposal was confirmed by Wagner,[5-6] who successfully trapped the biradicals from valerophenone and γ-methoxyvalerophenone, and by a series of examples of biradical interception which followed this report.[7-13] More recently the biradicals of reaction have been detected directly in laser photolysis experiments.[14]

The biradicals have lifetimes in the range of 30–100 ns, depending on the solvent.[12,14]

During a study of the quenching ability of several group 5 organometallics, we observed evidence indicating that P–O double bonds interact efficiently with the biradicals produced in the photochemistry of phenyl alkyl ketones bearing γ-hydrogen atoms.[15] For example, while organophosphines and organic phosphates are efficient quenchers of carbonyl triplets,[15-17] triphenylphosphine oxide causes an increase in the yield of photofragmentation of valerophenone in benzene. The effect is proposed to result from the interaction of the intermediate biradical (see reaction 1) with the organophosphorus substrate.



(1)

R^1, R^2 = H or Me

The effect on the quantum yields is similar to that of polar solvents[18] and oxygen,[8] where it has been proposed to result from bonding interactions (hydrogen bonding in the case of alcohols) which prevent the reabstraction reaction.

We report in this paper a study of the photochemistry of valerophenone in the presence of triphenylphosphine oxide and trimethyl, tri-*n*-propyl, and triphenyl phosphates. Butyrophenone and γ-methylvalerophenone have also been examined in the case of trimethyl phosphate.

Results and Discussion

Figure 1 shows the effect of trimethyl phosphate on the quantum yields of photofragmentation of butyrophenone and γ-methylvalerophenone. For comparison we have also included a plot showing the effect of *tert*-butyl alcohol in the case of γ-methylvalerophenone calculated from literature parameters.[18] The effect on the cyclobutanols is similar but relatively smaller (see below).

Scheme I shows the mechanism proposed to account for the effect. It is the same type of mechanism proposed for the effect of alcohols and oxygen.[8,18] We note that no assumptions are made regarding the structure of the intermediate BP or the nature of the molecular interactions involved.

In the absence of triplet quenching, eq 2 is expected to represent the behavior of the system, where τ_B is the biradical lifetime, P_{II}^0 and P_{II}^∞ are the probabilities of fragmentation from ^1B and BP, and Φ_{II} and Φ_{II}^0 are the quantum yields of

Scheme I

$$K \xrightarrow{h\nu} {}^1K \rightarrow {}^3K$$

$${}^3K \xrightarrow{k_1} {}^3B$$

$${}^3K + P \xrightarrow{k_2} K + P$$

$${}^3B \xrightarrow{k_3} {}^1B$$

$${}^1B \xrightarrow{k_4} K$$

$${}^1B \xrightarrow{k_5} ACP + \text{olefin}$$

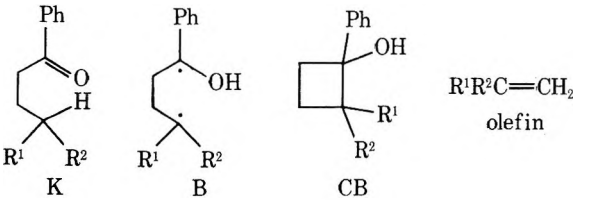
$${}^1B \xrightarrow{k_6} CB$$

$${}^3B + P \xrightarrow{k_7} BP$$

$$BP \xrightarrow{k_8} K + P$$

$$BP \xrightarrow{k_9} ACP + \text{olefin} + P$$

$$BP \xrightarrow{k_{10}} CB + P$$



R^1, R^2 = H or Me

$X_3P{=}O$ P

CH_3COPh ACP

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Table I. Effect of 0.02 M Organophosphorus Compounds on the Photochemistry of Phenyl Alkyl Ketones in Benzene at 30 °C

Ketone	Registry no.	Substrate	Registry no.	Φ_{II}/Φ_{II}^0	Φ_{CB}/Φ_{II}	$k_7\tau_B$[a]	k_7[b]	r^2[c]
Valerophenone	1009-14-9	Ph_3PO	791-28-6	1.48	0.16	18	5.3×10^8	0.995
		$(MeO)_3PO$		1.35	0.19	12	3.5×10^8	0.993
		$(PrO)_3PO$	513-08-6	1.44	0.18	16	4.7×10^8	0.989
		$(PhO)_3PO$	115-86-6	1.06	~0.22[d]	1.7	5.0×10^7	0.999_9
Butyrophenone	495-40-9	$(MeO)_3PO$	512-56-1	1.37	*e*	16	5.0×10^8[f]	0.999
γ-Methylvalerophenone	2050-07-9	$(MeO)_3PO$		1.42	*e*	6	1.7×10^8	0.999_6
Valerophenone		*t*-BuOH[g]		1.03		0.63	1.8×10^7	
		Pyridine[g]		1.15		4.4	1.3×10^8	
		None[g]		1.0	0.22			

[a] In units of M^{-1}. [b] In units of $M^{-1}\ s^{-1}$, based on lifetimes from ref 8c. [c] Coefficient of determination from the least-squares treatment of eq 2. [d] $k_6\tau_B$ too small to allow an accurate measurement. [e] Not measured. [f] Based on τ_B = 33 ns, obtained in oxygen-scavenging studies (R. D. Small, Jr., and J. C. Scaiano, *J. Am. Chem. Soc.*, in press. [g] From ref 18.

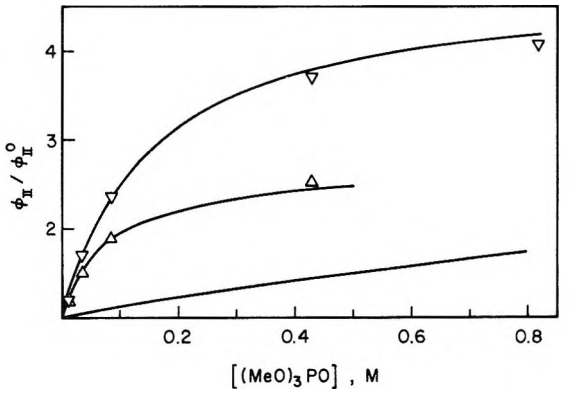

Figure 1. Effect of trimethyl phosphate on the yields of photofragmentation of butyrophenone (△) and γ-methylvalerophenone (▽). The lower curve corresponds to *tert*-butyl alcohol and γ-methylvalerophenone (see text).

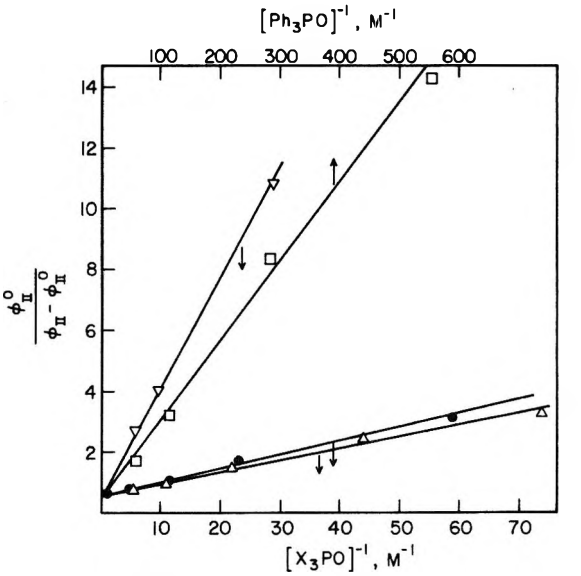

Figure 2. Results according to eq 2 for valerophenone in benzene interacting with $(MeO)_3PO$ (●, lower scale), $(PrO)_3PO$ (△, lower scale), $(PhO)_3PO$ (▽, lower scale), and Ph_3PO (□, upper scale).

fragmentation in the presence and absence of P.

$$\frac{\Phi_{II}^0}{\Phi_{II}-\Phi_{II}^0} = \frac{P_{II}^0}{P_{II}^\infty - P_{II}^0}\left(1 + \frac{1}{k_7\tau_B[P]}\right) \qquad (2)$$

Figure 2 shows the plots of $\Phi_{II}^0/(\Phi_{II} - \Phi_{II}^0)$ vs. $[P]^{-1}$ for several organophosphorus compounds reacting with the biradicals from valerophenone.[19] The same type of plots can be made for the cyclobutanols [plotting $\Phi_{CB}^0/(\Phi_{CB} - \Phi_{CB}^0)$ instead of $\Phi_{II}^0/(\Phi_{II} - \Phi_{II}^0)$]. These plots lead to the same values of $k_7\tau_B$; however, since the effect on the yields of cyclobutanols is smaller and they are more difficult to measure experimentally, the points are subject to considerably more error than the fragmentation data.

We have carried out a number of experiments trying to detect new products and/or consumption of the organophosphorus compound. We have failed to detect any consumption of reagent or formation of any products other than the fragmentation and cyclization products which are characteristic of the Norrish type II process. For example, in the case of $(MeO)_3PO$ with valerophenone, $\Phi_{products}/\Phi_{-P} \geq 200$, where Φ_{-P} is the yield of consumption of $(MeO)_3PO$ and $\Phi_{products}$ is the yield of acetophenone plus cyclobutanols, which, within experimental error, agrees with the consumption of valerophenone.

Table I shows a comparison of the effect on fragmentation and cyclobutanols for 0.02 M organophosphorus compounds, as well as the values of $k_7\tau_B$ calculated using eq 2 and k_7 values based on experimental lifetimes.[12-14] The mechanism of Scheme I assumes that the overall process is kinetically controlled, that is, that reaction 7 is not reversible. Alternatively we could propose an equilibrium-controlled process. In this case $k_7\tau_B$ would be replaced by $K_{eq}\tau_B(k_8 + k_9 + k_{10})$. As in the case of alcohols,[18] it is impossible to decide from quantum yields studies which is the mechanism that best represents the behavior of the system.

Up to this point our discussion of the results has been limited to kinetic arguments. An interesting question is which type of interaction is the cause of the changes in quantum yields observed. In the case of alcohols,[18] hydrogen bonding is believed to be responsible for the enhancement of quantum yields; i.e., the engagement of the hydroxylic group in the biradical in hydrogen bonding prevents the reverse hydrogen transfer to produce the parent ketone, resulting in an increase of the yields of fragmentation and cyclization.

In principle, one could invoke the same type of interactions in the case of X_3PO compounds, which are known to form hydrogen bonds efficiently.[20] However, we believe that the alkyl end of the biradical is also involved in the process. The dependence of $k_7\tau_B$ values (and k_7) on γ substitution (see Table I) seems to support this idea. Further, an interaction of this type could be to a certain extent responsible for the large differences in reactivity between some of the X_3PO compounds and alcohols (e.g., Ph_3PO is nearly 30 times more efficient than *tert*-butyl alcohol).[21]

The values of $k_7\tau_B$ follow the order butyrophenone > valerophenone > γ-methylvalerophenone and should reflect the order of k_7 values since direct[12,14] and indirect[13] measure-

ments of τ_B show that it is largely independent of the substitution at the τ position. If the alkyl end of the biradical were to add to the P–O double bond or interact in such a way as to decrease the P–O bond order, we could expect the rate of this process to follow the inverse order of that observed in the α cleavage of phosphoranyl radicals, which follow the order primary < secondary < tertiary,[22,23] in agreement with our experiments. Although no detailed study has been reported on the addition of radicals to the P=O bond, Levin et al.[24] have reported evidence that the process occurs when methyl radicals are generated in the presence of $(EtO)_3PO$. We have made several attempts to detect the presence of phenyl radicals (in the case of Ph_3PO, see Experimental Section) in the hope that BP would undergo α cleavage. All our experiments produced negative results, suggesting that either BP does not have a phosphoranyl-type structure or it is too short-lived for the process of α cleavage to compete with other modes of decay.

A few experiments with other phosphorus(V) compounds are worth mentioning. $(PhO)_2P(O)OH$ and $(MeO)_2P(O)OH$ do not seem to have any significant effect on the quantum yields. Presumably, intramolecular hydrogen bonding tends to make them inefficient.

A series of experiments was carried out with Ph_3PSe and Ph_3PS in the case of valerophenone. The latter does not seem to have much effect on the yields of fragmentation; however, the ratio of fragmentation-to-cyclization yields is increased slightly. For example, for 0.06 M Ph_3PS, the value of $(\Phi_{II}\Phi_{CB}^0)/(\Phi_{CB}\Phi_{II}^0) = 1.08$, suggesting that the substrate is in fact interacting with the biradical. It seems likely that some quenching of the triplet state tends to compensate the effect. In the case of Ph_3PSe, extensive quenching and the difficulties in obtaining very pure samples make any conclusion highly speculative.

The interaction of the biradical produced in the Norrish type II reaction with good hydrogen bonding solvents such as alcohols and wet acetonitrile has been frequently used to measure limiting quantum yields for the type II reaction,[18,25] a parameter which for simple ketones measures the quantum yield of biradical production. The high efficiency of organophosphorus compounds can probably extend the applicability of these techniques to systems where high concentrations of hydroxylic compounds are not desirable, as is the case of polymers, where the type II process plays an important role in photodegradation.[26]

In conclusion, phosphine oxides and trisubstituted organic phosphates interact efficiently with type II biradicals, producing a marked increase in the yields of fragmentation and a small increase in the case of cyclization. In all the examples examined (see Table I), the yields extrapolated at infinite substrate concentration add, within experimental error, to one. The kinetics of the reaction are consistent with a mechanism involving the formation of a complex between the intermediate biradical and the organophosphorus compound. While the involvement of hydrogen bonding in the biradical–X_3PO interaction cannot be discounted, it seems certain that the alkyl end plays an important role.

Experimental Section

Materials. Butyrophenone and valerophenone were Aldrich products. γ-Methylvalerophenone was a generous gift from Dr. K. U. Ingold. Triphenylphosphine oxide (K & K), triphenyl phosphate (Aldrich), and triphenylphosphine sulfide (Aldrich) were recrystallized. Tri-*n*-propyl phosphate (Matheson), trimethyl phosphate (Aldrich), and dimethyl phosphate (ICN) were distilled under vacuum. TLC and/or VPC checks were carried out in all cases. Benzene was a Fisher (Certified, ACS) product. Dodecane and mesitylene (Aldrich, Gold Label) were distilled prior to use and carbon tetrachloride (Mallinckrodt, spectroquality) was distilled twice.

Irradiations. The samples (1 cm^3) were contained in matched Pyrex tubes made of precision bore tubing (i.d. 0.2500 ± 0.0002 in, made of Corning 7740 glass, Lab Crest Scientific). They were degassed by three freeze–pump–thaw cycles to a residual pressure of ca. 10^{-5} Torr. The samples were irradiated in a merry-go-round apparatus, using a Rayonet reactor fitted with 16 RPR-3500 lamps. Conversions (based on parent ketone) were kept below 2%, except during the attempts to detect consumption of the organophosphorus compound.

Analyses. Quantitative analyses of type II products were carried out by gas chromatography, using 5% DC-11 silicone oil on a Chromosorb W column and FID. This and other columns, as well as TLC, were used in a number of unsuccessful attempts to detect new products.

Search for Evidence of Phenyl Radicals. A number of experiments were carried out with the valerophenone–Ph_3PO system in an attempt to trap phenyl radicals. We looked in vain for the formation of benzene, using *n*-dodecane and mesitylene as solvents, or chlorobenzene, using carbon tetrachloride as solvent.

Spectra. The UV spectra of all the ketone–organophosphorus compound pairs were examined using a Cary 14 spectrophotometer. No evidence for association in the ground state was observed.

Actinometry. Whenever necessary, the photofragmentation of valerophenone in benzene [Φ(acetophenone) = 0.30][18] was used as an actinometer.

Registry No.—$(PhO)_2P(O)OH$, 838-85-7; Ph_3PS, 3878-45-3; $(MeO)_2P(O)OH$, 813-78-5.

Supplementary Material Available: Tables II–IV showing quantum yields (4 pages). Ordering information is given on any current masthead page.

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Methoxyphosphonium Ions: Intermediates in the Arbuzov Reaction

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Compounds of the form ABR'P$^+$OR X$^-$ (I) are believed to be intermediates in the Arbuzov reaction. Several compounds of this sort, with X = $^-O_3SCF_3$ and R = R' = CH_3, have now been isolated. Evidence is presented for the phosphonium salt structure. The compound $CH_3P^+(OCH_3)_3$ is a rapid methylating agent; it reacts quantitatively and too fast to measure with water, and with I$^-$ with a second-order constant of 900 M^{-1} s^{-1} at 0 °C in acetone. Various compounds of type I with A and B = CH_3O, aryl, aryloxy, and alkyl have been isolated and characterized.

When trimethyl phosphite is treated with methyl iodide, the first detectable product is dimethyl methylphosphonate, and the methyl iodide is recovered. This example of the Arbuzov reaction is believed[1-3] to go through the intermediate iodide salt of the methyltrimethoxyphosphonium ion 1 (eq 1 with X = I)

$$P(OCH_3)_3 + CH_3X \rightarrow \underset{1}{CH_3P^+(OCH_3)_3} + X^- \quad (1)$$

which rapidly decomposes yielding the phosphonate and methyl iodide (eq 2).

$$\underset{1}{X^- + CH_3P^+(OCH_3)_3} \rightarrow XCH_3 + \underset{3}{OP(CH_3)(OCH_3)_2} \quad (2)$$

This plausible intermediate has not been isolated, and the reaction has not been adequately studied in dilute solution by modern kinetic methods. Nevertheless, the failure to observe the postulated intermediate requires that the attack of I$^-$ on 1 must be very fast. The mechanism is rendered more plausible by the isolation of salts of the form 2, $CH_3P(OAr)_3^+$ X$^-$, where the presumed second step becomes the very unfavorable nucleophilic attack on aryl carbon.[4] Similarly, the compound $CH_3P^+[OCH_2C(CH_3)_3]_3$ I$^-$ has been reported.[5] Recently methyltriphenoxyphosphonium trifluoromethanesulfonate has been prepared[6] and has been shown to be a strong electrolyte in acetonitrile, although the compound with X = I has been reported[7,8] to be a weak electrolyte because the reaction with silver nitrate is slow.[4] There is a report of the isolation of Et_2MeP^+OMe I$^-$ as a reasonably stable crystalline material.[7] Other workers have been able to isolate trialkoxyphosphonium fluoroborates obtained by interaction of $Et_3O^+BF_4^-$ or $Ph_3C^+BF_4^-$ with phosphites.[9]

Because the presumed reaction of the intermediate is a nucleophilic substitution reaction, we guessed that if we could provide a methylating agent with a very weakly nucleophilic leaving group, the phosphonium salt might be isolable even with the most reactive examples. This has proved to be the case using the reaction of methyl trifluoromethanesulfonate with trimethyl phosphite. In hexane or ether, a white crystalline product is rapidly precipitated to which we assign the structure 1 triflate. The compound is not highly stable and is contaminated with a small amount of the Arbuzov product 3, but it is adequately characterized by the proton NMR in $CDCl_3$ (PCH_3, δ 2.18, doublet, J_{PH} = 17 Hz, area 1.0; OCH_3, δ 4.05, doublet, J_{PH} = 11 Hz, area = 3.0), the ^{31}P NMR (proton decoupled, δ +53.1 from H_3PO_4, the new convention[10] for the sign of the chemical shift is used throughout), and the yield of acid produced very rapidly on hydrolysis (97%, based on $C_6H_{12}O_6PSF_3$). Since it was not easily obtained in a much purer state, it was not characterized by elemental analysis.

The salt showed three fast reactions: hydrolysis, yielding triflic acid, dimethyl methylphosphonate, and (presumably) methanol; a reaction with sodium iodide in acetone, yielding methyl iodide and the phosphonate ester; and a reaction with trimethyl phosphite, also yielding the phosphonate ester. We did not attempt to measure the hydrolysis rate.

The reaction with sodium iodide in acetone was very fast and exothermic. The rate was followed in quite dilute solutions by the change of temperature with time, with the data treated as described by Bell.[11] The rate constant for iodide ion attack so obtained at 0 °C (with a temperature rise of about 0.1 °C) is 9×10^2 M^{-1} s^{-1}. This rate constant is quite large enough to account for the failure to detect an intermediate in the methyl iodide catalyzed rearrangement of trimethyl phosphite.

The reaction of the salt with trimethyl phosphite is extremely exothermic, and we were unable to measure a rate constant by Bell's method in our simple apparatus. The rate constant is apparently greater than that for iodide attack. The reaction is the simple methyl transfer, reaction 3.

$$CH_3P^+(OCH_3)_3 + P(OCH_3)_3 \rightarrow CH_3\underset{\underset{O}{\|}}{P}(OCH_3)_2 + CH_3P^+(OCH_3)_3 \quad (3)$$

The high but unknown rate of this reaction suggests that it may play an important role in the Arbuzov rearrangement of trimethyl phosphite catalyzed by methyl iodide, since the rate constant for (3) is higher than for iodide attack, and the nucleophile is present at higher concentration. Reaction 3 has been previously described as a part of the "autocatalytic mechanism."[3,12] It is the high rate of (3) which accounts for the contamination of 1 triflate by 3.

The low reactivity of 1 triflate can either be attributed to the low rate of nucleophilic attack of the triflate ion on 1 (reaction 4)

$$1 + OTf^- \rightleftarrows 3 + MeOTf \quad (4)$$

or to a possibly unfavorable equilibrium for this reaction. The latter is certainly true, for we were able to synthesize 1 triflate by treatment of 3 with methyl triflate, a synthesis about as convenient as that from trimethyl phosphite although not as conspicuously exothermic. Indeed, the facility of the reverse reaction 4, together with that of reaction 3, suggests that in the synthesis of 1 triflate, 3 may be an intermediate. Since we hope to generalize this reaction to some of preparative value, it is important that the general reaction 5

$$ABPOR + CH_3OTf \rightarrow ABP^+CH_3(OR) + OTf^- \quad (5)$$

goes directly rather than via an Arbuzov product, OPABR, which would give an *O*-methyl compound, $ABP^+R(OCH_3)$, rather than an OR compound. We have therefore treated triethyl phosphite with methyl triflate and find only the direct product, $(CH_3CH_2O)_3P^+CH_3$ OTf^-, not contaminated at the level of the proton NMR spectrum with P-ethylated or O-methylated material.

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Table I. $MeP^+(OMe)AB^-OSO_2CF_3$

Registry no.	A	B	^1H NMR δ[a]	^1H NMR Multiplicity	^1H NMR J, Hz	^{31}P NMR,[b] δ	Mp, °C
64294-66-2	OMe	OMe	4.05	d	11	+53.1	28–32
			2.18	d	17		
64294-67-3	OMe	Ph	7.6	m		+78.5	Oil
			4.0	d	10		
			2.38	d	14		
64294-69-5	Ph	Ph	7.8	m		+74.5	34–37
			4.0	d	13		
			2.8	d	15		
64294-70-8	OPh	OPh	7.0	m		+41.5	Oil
			3.7	d	11		
			2.53	d	17		
64294-72-0	Et	OMe	3.96	d	11	+99.0	~0
			2.12	d	14		
			1.7	m			
64294-74-2	Et	Et	3.95	d	11	+103.5	~0
			2.35	m			
			2.1	d	12		
64315-07-7	o-$C_6H_4O_2$		7.1	m		+49.6	Oil[d]
			3.71	d	12		
			3.22	d	8		
64294-75-3	$(EtO)_3P^+CH_3$[c]		4.4	m	6		
			2.17	d	17		
			1.45	t	6		

[a] Chemical shifts relative to Me_4Si; spectra taken in $CDCl_3$ on a Varian A-56/60. [b] Chemical shifts relative to 85% H_3PO_4; spectra taken in $CDCl_3$ on a Varian XL-100. [c] This compound is not structurally described by the table heading. [d] At times a crystalline compound could be obtained which was a solid at 0 °C.

Several other substances identified as alkoxyphosphonium triflates have been made by the same method. They are presented in Table I, which shows the proton and phosphorus chemical shifts. The major contaminant is the Arbuzov product, shown by both proton and phosphorus NMR. They have not yet been otherwise characterized, but the wide range of compounds suggests that this reaction is both general and practical for the preparation of alkoxyphosphonium triflates.

The phosphorus chemical shifts shown in Table I fall in the range believed to be characteristic of phosphonium salts rather than phosphoranes, but a study of the various compounds used to establish this rule suggests that a structural ambiguity might exist in the original compounds,[13] as well as in ours; thus, the NMR chemical shift is not a totally unequivocal method for structure assignment. In a similarly ambiguous way, the phosphorane in its stable conformation would have one apical and two equatorial methoxyls of presumably different chemical shift. The observed presence of only one methoxy doublet argues compellingly either for the phosphonium structure or for a rapidly pseudorotating pentacovalent system. However, rapid pseudorotation is sufficiently prevalent in phosphoranes so that it cannot be reasonably eliminated. The observation of high electrical conductivity of methyltriphenoxyphosphonium triflate is convincing evidence for the ionic structure;[3,4] yet, exactly the same cation as the iodide salt was reported to react only slowly with silver ion in ethanol solution,[4] which was widely interpreted as implying a phosphorane structure.[7,8] We have repeated this experiment and find that we can explain the slow iodide precipitation by the following reaction sequence (eq 6–8).

$$MeP^+(OPh)_3 + EtOH \rightarrow PhOH + MeP^+(OPh)_2(OEt) \quad (6)$$

$$MeP^+(OPh)_2(OEt) + I^- \rightarrow OP(Me)(OPh)_2 + EtI \quad (7)$$

$$EtI + Ag^+ \rightarrow AgI \quad (8)$$

The slow reaction with silver nitrate is presumably the reaction with ethyl iodide. Curiously, this series of reactions was well understood by Landauer and Rydon,[4] who proposed making alkyl iodides in this way. The widespread alternate interpretation as evidence for a nonionic phosphorane is apparently a consequence of an initial misreading, followed by numerous quotations[7,8,15–17] of secondary sources. We have not yet studied further the kinetics of this reaction, but a fairly rapid formation of ethyl iodide in this system is readily observable by NMR. Thus there remains no evidence of a stable or slowly equilibrated phosphorane in these systems with reasonably stable counterions. We therefore recommend that the term "quasiphosphonium ion" be abandoned in favor of the unqualified phosphonium ion.

A report of the reaction of methyl diethylphosphinite with methyl iodide to yield a stable methyldiethylmethoxyphosphonium iodide[7] is the only case we have found reported of a true Arbuzov intermediate, except for a few cases where the ester group is a highly branched alkyl.[5,18,19] This report is apparently inconsistent with the very fast reaction of the ion 1 with iodide ion, but it is possible that the substitution of two ethyl groups for two of the methoxy groups inductively decreases the rate so much that the iodide salt is isolable, especially if it is not very soluble. We have therefore repeated this experiment and isolated methyldiethylmethoxyphosphonium iodide at −10 °C but found it quite unstable in our hands. Decomposition to diethylmethylphosphine oxide occurs in about 20 min at room temperature and in about 24 h at −78 °C.

Conclusion

Compounds of the type $ABP^+(OR)(CH_3)^-OSO_2CF_3$ are readily prepared by the reaction of ABPOR with $CH_3O_3SCF_3$. They are ionic, they are powerful alkylating agents, and the cations are both intermediate in and catalytic for the Arbuzov reaction.

Experimental Section

A presumed serious hazard connected with this study is that of the toxicity of methyl trifluoromethanesulfonate. By analogy to the slightly less reactive methyl fluorosulfonate which has been found to be a lethal inhalation hazard,[20] all operations should be carried out in a good hood and with scrupulous care in handling this powerful

methylating agent. It is also now classified as a cancer suspect agent.

Methods. The phosphonium salts are moisture sensitive; therefore, precautions were taken to ensure that all reagents and glassware were thoroughly dried. Commercial anhydrous ethyl ether was used without further purification. In two cases the starting materials for the phosphonium salts (methyl diethylphosphinite and dimethyl ethylphosphonite) were pyrophoric, and all transfers of these compounds were performed in a glovebag purged with nitrogen. ^{31}P NMR spectra were obtained on a Varian XL-100 spectrometer, and chemical shifts are reported relative to 85% phosphoric acid;[10] proton spectra were obtained on a Varian A-56/60 spectrometer at 60 MHz with tetramethylsilane reference. Melting and boiling points are uncorrected.

Materials. A general method was employed to make methyl esters of phosphonous and phosphinous acids. This involved the reaction of methanol with a chlorophosphorous compound in the presence of *N,N*-diethylaniline to absorb the hydrochloric acid formed. A typical example of the method is the synthesis of dimethyl phenylphosphonite.

Dimethyl phenylphosphonite was prepared by the dropwise addition of 25.1 g (0.14 mol) of phenyldichlorophosphine (Strem Chemicals) to 8.96 g (0.28 mol) of methanol and 33.94 g (0.28 mol) of *N,N*-diethylaniline in about 100 mL of anhydrous ether. The reaction was conducted in an ice bath and under a nitrogen atmosphere. The mixture was allowed to stir for several hours, and then the *N,N*-diethylaniline hydrochloride was filtered and washed with anhydrous ether. The combined filtrate and washings were distilled under vacuum with a nitrogen bleed. The clear product was collected at 95–97 °C (16 mm) [lit.[21] 94.5 °C (13 mm)]: yield, 53%; ^{31}P NMR ($CDCl_3$) δ +159 (lit.[22] +159).

Methyl diphenylphosphinite was prepared in a similar manner using diphenylchlorophosphine (Strem Chemicals) and 1 equiv each of methanol and *N,N*-diethylaniline: bp 140–143 °C (88 mm) [lit.[23] 151–152 °C (10 mm)]; yield, 85%; proton NMR ($CDCl_3$) δ 3.53 (d, J_{HP} = 15 Hz, $POCH_3$), 7.3 (m, aromatic); ^{31}P NMR ($CDCl_3$) δ +155.2 (lit.[24] +115.6).

Diphenylmethyl Phosphite. Methanol (1 equiv) and 1 equiv of *N,N*-diethylaniline and diphenyl phosphorochloridite were used to prepare diphenylmethyl phosphite: bp 158–162 °C (9 mm) [lit.[25] 169.5–170.5 °C (11 mm)]; yield, 75%; proton NMR (CDCl) δ 3.57 (d, J_{HP} = 9 Hz, $POCH_3$), 6.9 (m, aromatic); ^{31}P NMR ($CDCl_3$) δ +128. The diphenyl phosphorochloridite was prepared in low yield (30%) by the reaction of 2 equiv of phenol with phosphorus trichloride: bp 102–105 °C (0.5 mm). Diphenyl phosphorochloridite was prepared in an alternate manner from triphenyl phosphite and propionyl chloride:[26] bp 122–123 °C (0.7 mm) [lit.[26] 115 °C (0.5 mm)]; yield, 60%.

Dimethyl Ethylphosphonite. Similarly, dimethyl ethylphosphonite was prepared from methanol, *N,N*-diethylaniline, and dichloroethylphosphine (Strem Chemicals). This compound is pyrophoric and was always handled in a nitrogen atmosphere: bp 103–105 °C (760 mm) [lit.[27] 73.5–74.5 °C (225 mm)]; yield, 34%; proton NMR ($CDCl_3$) δ 1.1 (m, PCH_2CH_3), 3.43 (d, J_{HP} = 11 Hz, $POCH_3$); ^{31}P NMR ($CDCl_3$) δ +190.

Methyl diethylphosphinite was prepared by the reaction of methyl phosphorodichloridite with ethylmagnesium bromide similar to that described for propyl dipropylphosphinite.[28] A purged apparatus was charged with 13.3 g (0.1 mol) of methyl phosphorodichloridite and 34.8 g (0.44 mol) of pyridine in about 150 mL of anhydrous ether. The flask was kept at dry ice–acetone temperatures while 0.22 mol of ethylmagnesium bromide was added dropwise. The mixture was allowed to stir for several hours and then warmed to room temperature. The solution with suspended pyridine salt was filtered and the precipitate washed with ether in a thoroughly purged glovebag. The filtrate and washings were distilled with a nitrogen bleed: bp 48–50 °C (60 mm); yield, 60%.

The above preparation required the difficult separation of pyridine from the desired product so an alternate method was used to prepare methyl diethylphosphinite. Methanol and *N,N*-diethylaniline (1 equiv each) were allowed to react with diethylchlorophosphine (Strem Chemicals) as before. Again all transfers were done in a nitrogen atmosphere: bp 124–126 °C (760 mm); yield, 85%; proton NMR ($CDCl_3$) δ 1.2 (m, PCH_2CH_3), 3.4 (d, J_{HP} = 13 Hz, $POCH_3$); ^{31}P NMR ($CDCl_3$) δ +139.4.

Methyl *o*-phenylene phosphite was prepared following the method of Crofts et al.:[29] bp 80–82 °C (17 mm); yield, 90%; proton NMR ($CDCl_3$) δ 3.22 (d, J_{HP} = 10 Hz, $POCH_3$), 7.0 (m, aromatic); ^{31}P NMR ($CDCl_3$) δ +128.

Trimethyl phosphite obtained commercially was distilled under nitrogen: bp 109–110 °C; ^{31}P NMR ($CDCl_3$) δ +140 (lit.[22] 140).

Preparation of Phosphonium Salts. A typical preparation of a methylphosphonium triflate is described. Methyl triflate (Aldrich, 5 g, 0.03 mol) was placed in a flask thoroughly purged with nitrogen in 25 mL of anhydrous ether. The reaction vessel was cooled to 0 °C. Trimethyl phosphite (3.7 g, 0.03 mol) was added dropwise. The mixture was allowed to stir for about 1 h. A fine white precipitate was present. The mixture was filtered rapidly under a nitrogen stream, and the solid was stored in a vacuum desiccator at 0 °C.

All of the phosphonium salts were prepared in a similar manner, the only difference being the nature of the product. In some cases, the phosphonium salt was an oil which resisted crystallization. Where the product was an oil, the solvent was removed at 0 °C using a vacuum pump with a nitrogen bleed. All of the phosphonium salts prepared were sensitive compounds and had limited lifetimes shown by liquefaction of the crystals; methyltrimethoxyphosphonium triflate would last for about 1 week, while diethylmethoxymethylphosphonium triflate only lasted for several hours at −10 °C. In particular, 2-methoxy-2-methyl-1,3,2-benzodioxaphospholium triflate and diphenoxymethoxymethylphosphonium triflate showed a tendency to undergo further reaction to the Arbuzov product (i.e., loss of the *O*-methyl group) unless the temperature was maintained at 0 °C during reaction. Furthermore, longer reaction time (overnight stirring) is necessary in these two cases involving methyl *o*-phenylene phosphite and diphenylmethyl phosphite.

Measurement of Rates of Reactions. The method employed to determine the rate of reaction of methyltrimethoxyphosphonium triflate with iodide was similar to that of Bell.[11] The methyltrimethoxyphosphonium triflate (0.029 g, 0.0001 mol) in 30 mL of dried spectroqualilty acetone was placed in a test tube shaped glass container equipped with a sealed stirrer, an inert gas inlet, and a sealed thin-walled bulb containing sodium iodide (0.015 g, 0.0001 mol) in 2 mL of acetone on the end of a movable glass rod located over a spike in the bottom of the tube. A glass sealed thermistor was also in the solution for measuring temperature. The solution was purged by passing nitrogen through, and the whole apparatus was placed in an ice–water bath. When temperature equilibrium was obtained, as shown by the thermistor resistance, the glass bulb was broken on the spike. The temperature rise was observed on a potentiometric recorder attached to the thermistor via a Wheatstone bridge circuit. This reaction showed a temperature rise of about 0.1 °C attained in approximately 12–18 s. The method was limited by the time constants of the thermistor and the recorder.

When the reaction was done in a more concentrated solution, the NMR spectrum corresponded to that of an approximately 1:1 mixture of methyl iodide and dimethyl methylphosphonate.

A similar method was used to follow the reaction of methyltrimethoxyphosphonium triflate with trimethyl phosphite. This reaction proved to be too fast to follow in this manner. The product was again identified by both the proton and phosphorus NMR spectra.

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Registry No.—Dimethyl phenylphosphonite, 2946-61-4; methyl diphenylphosphinite, 4020-99-9; diphenylchlorophosphine, 1079-66-9; diphenylmethyl phosphite, 3577-87-5; diphenyl phosphorochloridite, 5382-00-3; dimethyl ethylphosphonite, 15715-42-1; dichloroethylphosphine, 1498-40-4; methyl diethylphosphinite, 13506-71-3; methyl phosphorodichloridite, 3279-26-3; ethyl bromide, 74-96-4; methyl *o*-phenylene phosphite, 20570-25-6; trimethyl phosphite, 121-45-9; methyl triflate, 333-27-7.

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Studies on Vitamin D (Calciferol) and Its Analogues. 13. 3-Deoxy-3α-methyl-1α-hydroxyvitamin D_3, 3-Deoxy-3α-methyl-1α,25-dihydroxyvitamin D_3, and 1α-Hydroxy-3-epivitamin D_3. Analogues with Conformationally Biased A Rings[1,2]

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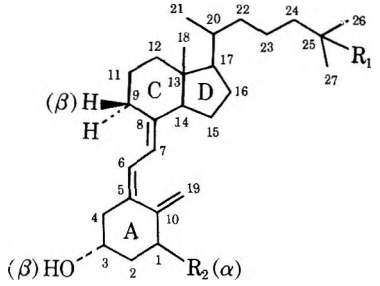
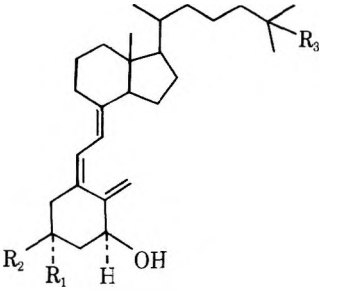
Lithium dimethylcuprate reacts with high stereoselectivity from the α face at C_3 of each of the three steroids: the 3β-tosylate (**10b**) of 1α-hydroxycholesterol (**10a**) to give inversion product **11a**; cholesta-2,5-dien-1-one (**14**) or its presumed equivalent **13** (3β-benzoyloxycholest-5-en-1-one) to afford the 1,4-addition product **12a**; and 1α-acetoxycholesta-3,5-dien-7-one (**23**) to produce mainly the 1,6-addition compound **24a**. The diol **10a** was also epimerized stereoselectivity at the 3 position to afford **26a**. The alcohol **11a**, its 25-hydroxy counterpart **11c**, and **26a** were converted by conventional methods to 3-deoxy-3α-methyl-1α-hydroxyvitamin D_3 (**7**), 3-deoxy-3α-methyl-1α,25-dihydroxyvitamin D_3 (**8**), and 1α-hydroxy-3-epivitamin D_3 (**9**). The intermediates **12a** and **24a** could also be utilized for preparing intermediates leading to **7**, and the 3α-methyl configuration for the various intermediates was rigorously established by chemical and spectral correlations. High-resolution ^1H NMR studies at 300 MHz revealed that the A ring of **7** is locked into a single chair conformer with both 1α-hydroxyl and 3α-methyl equatorially oriented. By contrast, **9**, which differs from **7** only in the replacement of the 3α-methyl by hydroxyl, exists predominantly (~70%) in the opposite chair conformer. All three analogues, **7**, **8**, and **9**, possess an ability to elicit in vivo intestinal calcium absorption and bone calcium mobilization in the chick.

Before vitamin D_3 (**1**) elicits its physiological action (calcium transport), it must be metabolized to 25-hydroxyvitamin D_3 (**2**) and then to 1α,25-dihydroxyvitamin D_3 (**3**). The latter (**3**), the most biologically potent calciferol known, is now



1, $R_1 = R_2 = H$
2, $R_1 = OH$; $R_2 = H$
3, $R_1 = R_2 = OH$

considered to be a steroid hormone both from a structural as well as a functional point of view. Its metabolic precursors **1** and **2** can be defined as prohormones.[4] Unlike the classical steroid hormones[5] such as estradiol, aldosterone, and dihydrotestosterone, which possess the fully intact cyclopentanoperhydrophenanthrene nucleus, vitamin D is unique inasmuch as it lacks the B ring. Recent ^1H NMR studies have shown that the A ring of **3**,[6a-c] as well as that of other related calciferols,[6] is partitioned between two rapidly equilibrating chairlike conformations.[7] We have considered the interesting possibility that one of the two unique chair forms of vitamin D might be involved in selective binding to various receptor



4, $R_1 = OH$; $R_2 = R_3 = H$
5, $R_1 = R_2 = H$; $R_3 = OH$
6, $R_1 = R_2 = R_3 = H$
7, $R_1 = R_3 = H$; $R_2 = CH_3$
8, $R_1 = H$; $R_2 = CH_3$; $R_3 = OH$
9, $R_1 = R_3 = H$; $R_2 = OH$

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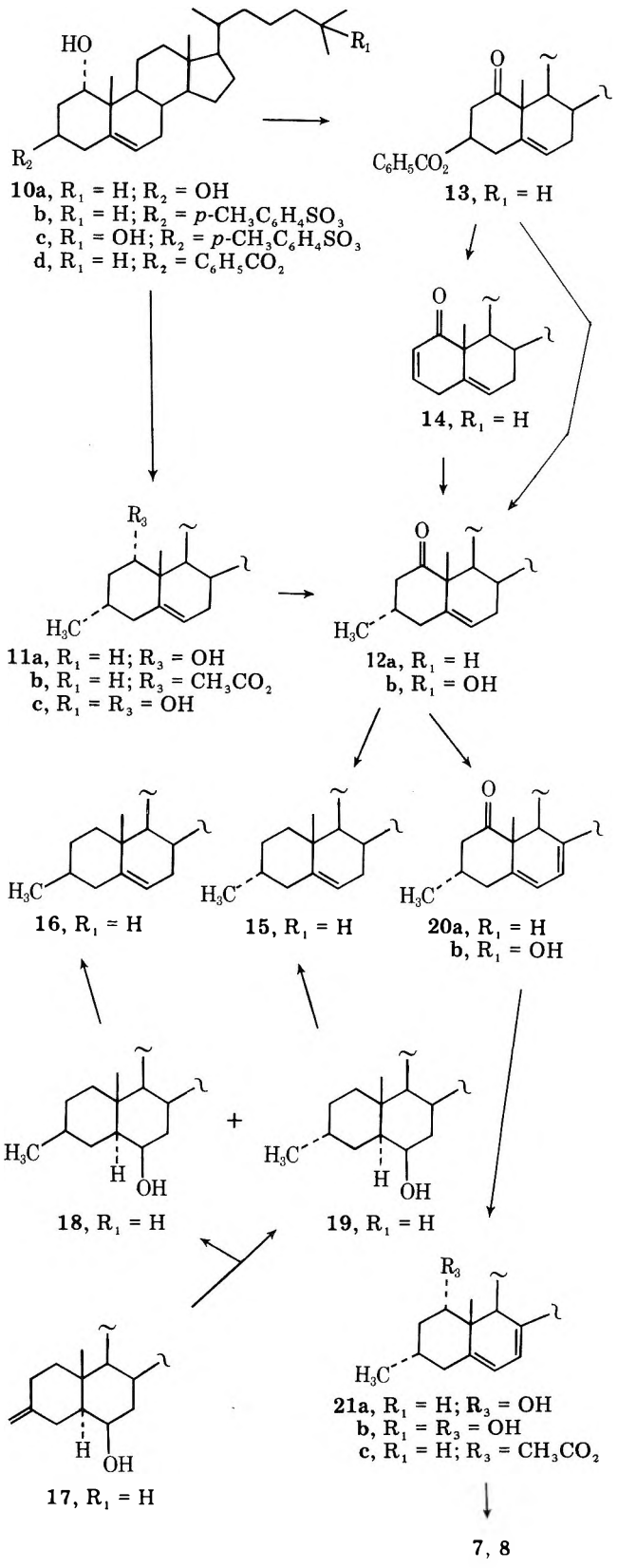
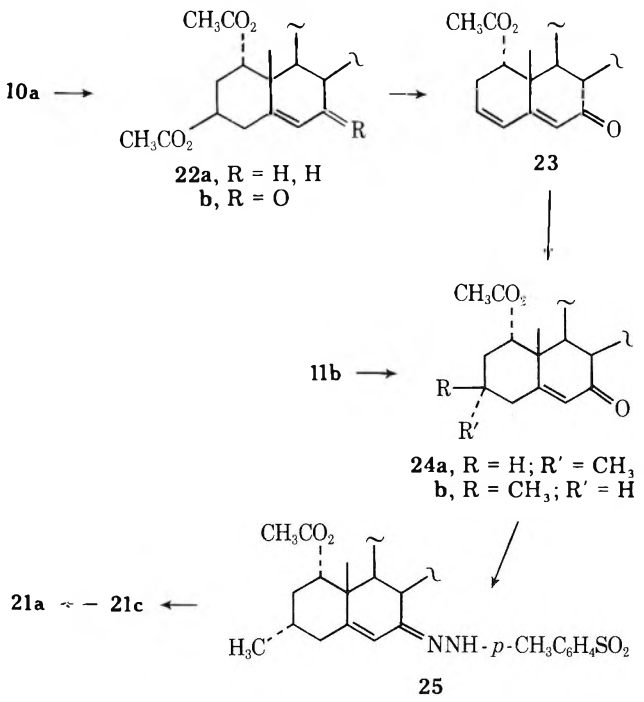
Scheme I



Scheme II



proteins.[8] Thus, it became of interest to prepare conformationally locked A-ring analogues of vitamin D. Apparently, for calciferols to possess relatively significant biological activity (e.g., for intestinal calcium absorption), a 1α-OH group is of unusual importance. We have observed, for example, that the 3β-OH of **3** or that of 1α-hydroxyvitamin D_3 (**4**),[9] a potent synthetic analogue of **3**, can be removed to produce substances 3-deoxy-1α,25-dihydroxyvitamin D_3 (**5**)[10] and 3-deoxy-1α-hydroxyvitamin D_3 (**6**),[11] respectively, which still possess significant biological potency in both in vivo (intestinal calcium absorption) and in vitro assays (intestinal receptor). Thus, a seemingly appropriate place for conformationally biasing substituents is the 3 position of **5** and **6**. Whereas **3** is the most biologically potent substance known for its ability to elicit both intestinal calcium absorption (ICA) and bone calcium mobilization (BCM), our laboratories have recently observed that 3-deoxy-1α,25-$(OH)_2D_3$ (**5**) exhibits a similar in vivo ICA activity but shows only a minimal BCM ability.[12] This selectivity in biological action served as an added stimulus for synthesizing analogues of **3** modified at the 3 position.

This paper describes studies directed toward modifying the now readily available 1α-hydroxycholesterol (**10a**) at its 3 position. The resulting intermediates have been converted to two 3-substituted derivatives of **6**, namely 3-deoxy-3α-methyl-1α-hydroxyvitamin D_3 (**7**) and 1α-hydroxy-3-epivitamin D_3 (**9**).[1a,6e] By a parallel scheme, the 25-OH derivative of **7** (**8**) was also synthesized. Conformational analyses by ^1H NMR studies of **7** and **9** are described.

Results and Discussion

Schemes I–III summarize the various synthetic transformations carried out in this study. It was our initial goal to synthesize both the 3α-methyl- and 3β-methyl-1α-hydroxy steroids.[8] The strategy was to react lithium dimethylcuprate with the sulfonate ester **10b**[11b] we reported earlier (i, Scheme I), the known 2-en-1-one **14** (ii, Scheme I),[13] and the previously unknown 3,5-dien-7-one **23** (iii, Scheme II). From steric considerations[14] and/or literature precedents,[15] we had expected that i and iii should give predominantly 3β-methyl incorporation products while ii should give mainly 3α-methyl product. Only one of these predictions (ii) was borne out by experiment. All three reactions produced predominantly, if not exclusively, 3α-methyl incorporation products.

It is known that cholesteryl tosylate (**28**) reacts with lithium dimethylcuprate to afford **16** (retention of configuration) along with an equal amount of **29**.[15] Simple lithium dialkylcuprates normally react with secondary alkyl tosylates with inversion of configuration.[16] In the case of **10b**, the axially oriented 1α-OH (actually as its alkoxide under the reaction conditions) might have been expected to hinder α attack at

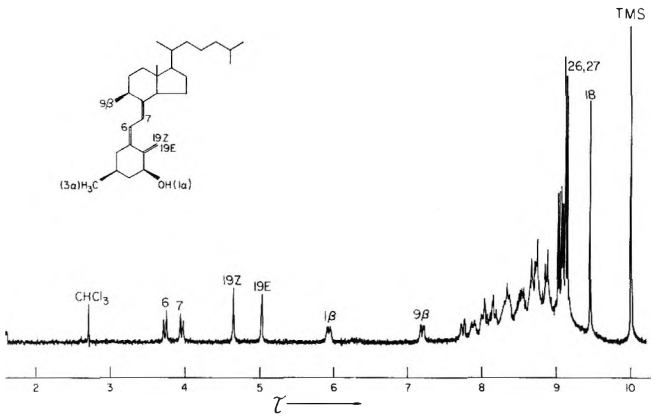
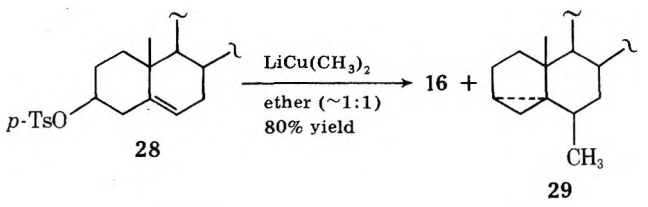
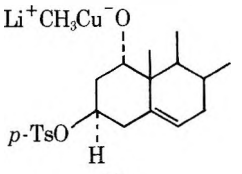


Figure 1. The 300-MHz ^1H NMR spectrum of 3-deoxy-3α-methyl-1α-hydroxyvitamin D_3 in $CDCl_3$, containing $CHCl_3$ and Me_4Si as internal standards 2180 Hz apart.



28 29

C_3 such as to give the C_3 epimer of **11a** instead. Since **11a** is in fact produced, we conjecture that the 1α-OH might be providing a directing influence through the intermediacy of a mixed cuprate species such as **30.**[17] There appears to be no



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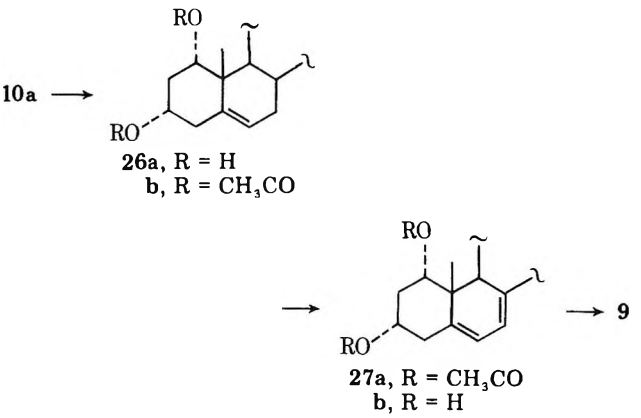
previous example of this kind of intramolecular alkyl transfer in organo cuprate chemistry, and it would be of interest to see whether this type of reaction can be used strategically in solving a stereochemical problem in synthesis. The fact that dienone **23,** which possesses a 1α-acetoxy group that survives the reaction conditions,[17] also gives predominantly 3α-methyl product may simply reflect the possibility that the 1α group does not shield the α face of the dienone terminus (C_3). A molecular model of **23** reveals that in one A-ring conformation the 1α-OAc is pseudoaxial, and it appears that it should hinder 3α attack; in the other conformation (1α-OAc pseudoequatorial) it does not. The former pseudoaxial conformation should dominate.[18] Thus, the observation that 3α methylation dominates might be due to a kinetic preference via α-face attack by the cuprate for the less stable pseudo-1α-equatorial conformation or that the acetoxyl group itself also is capable of coordinatively directing syn addition. A third alternative is that C_3 attack from the α face may be so inherently favored over β-face attack that steric hindrance by an axial C_1 oxygen substituent is simply overcome.[14] Oxidation of **11a** afforded ketone **12a** (Scheme I), which was also obtained from **14.**[13] Rather than react **14** with lithium dimethylcuprate, it was later found expeditious to treat its precursor **13** directly with excess cuprate. The stereochemistry at C_3 of **12a** was established by its Wolff–Kishner reduction to 3α-methylcholest-5-ene (**15**), which proved to be identical to a sample prepared by the regioselective dehydration of alcohol **19.**[19] Catalytic reduction of the known **17** gave mixtures of epimers **18** and **19;**[19] the isomer which predominated depended on the catalyst (Pd or Rh) employed.[20] Dehydration[21] of **18** afforded the

Scheme III



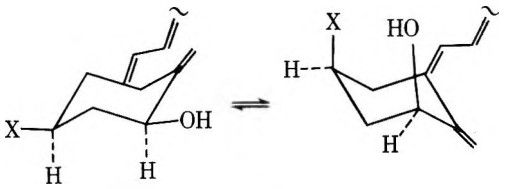
known 3β-methylcholest-5-ene[22] (**16**); **15** and **16** are clearly distinguishable by thin-layer chromatography ($AgNO_3$–silica gel) and by comparison of their 300-MHz ^1H NMR spectra. The acetate (**11b**) of **11a** could not be brominated and then dehydrobrominated[23] to the 5,7-diene; major amounts of the 4,6-diene and other products of unknown constitution were produced. The ketone **12a,** however, was convertible to **20a,** which was reduced directly to the provitamin **21a.**

An alternative synthesis of **21a** is given in Scheme II, and it utilizes Dauben's method for introducing the Δ^7 double bond regioselectively.[24] The key steps include the dehydroacetylation of **22b** to **23,** the chemospecific 1,6 addition[25] of dimethylcuprate to **23,** and the stereoselectivity (80% **24a,** 7% **24b**) of the latter process. In fact, the small amount of **24b** produced in this experiment was our only observation of detectable amounts of 3β-methyl-1-oxygenated steroid in the entire study. The configuration of **24a** was established by independent synthesis from **11b,** while the conversion of **24a** to **21a** occurred without significant incident using Dauben's method.[24]

The overall yield of **21a** from **10a** (6 steps) was 13% by Scheme I. The 8-step Scheme II afforded an overall yield of 20% for the identical net transformation. On a large scale, Scheme II would likely be more efficient because the provitamin produced by Dauben's method is uncontaminated by its $\Delta^{4,6}$ isomer. Photochemical irradiation followed by mild thermolysis of **21a** afforded the desired 3-deoxy-3α-methyl-1α-hydroxyvitamin D_3 (**7**). By an analogous sequence of steps, the 25-hydroxy tosylate[10] **10c** was converted (**10c** → **11c** → **12b** → **20b** → **21b** → **8**) to the 25-OH form of the vitamin **8.** For the synthesis of **9,**[1a,6e] the requisite provitamin **27b** was prepared as outlined in Scheme III. The key step was the finding that 1α-hydroxycholesterol (**10a**) could be cleanly epimerized at C_3 by treatment with diethyl azodicarboxylate/triphenylphosphine/formic acid.[26] The provitamin was converted by conventional procedures to **9.**

The ^1H NMR spectra of **7** (see Figure 1) and **9** were in good accord with the assigned structures. The calciferols **7, 8,** and **9** exhibited UV spectra characteristic of all other vitamins possessing the same triene stereostructure (λ_{max} ~263, λ_{min} 228 nm).[27] They also revealed the characteristic mass spectral base peak corresponding to the A-ring portion by the remarkable cleavage across the 7,8 double bond.[28]

The trans-vicinal coupling constants observed for the A ring of **7** ($J_{1\beta,2\alpha}$ ~ 11.5 Hz) and **9** ($J_{3\beta,4\alpha}$ = 5.5 Hz) can be correlated with the Karplus equation to afford information about their conformational population ratios.[6,29] The pair of cyclohexane chairlike conformations for the A ring of **7** and **9** are schematically represented by **31** and **32.** Simple consideration of classical *A* values for cyclohexanes[30] predicts that **7** and **9** should be strongly biased in favor of conformations **31e** and **32e,** respectively. In the case of **7,** the large trans-vicinal



31e, X = CH_3 (7) **31a**, X = CH_3 (7)
32e, X = OH (9) **32a**, X = OH (9)

splitting suggests that its A ring is locked essentially completely as expected in the diequatorial conformer **31e**. The magnitude of the observed trans-vicinal coupling constant (11.5 Hz) lends credence to the assumption that the upper limit for J_{aa} of 11 Hz used previously in our conformational population ratio calculations is of reasonable magnitude for the vitamin D series.[6,29] By contrast, **9** exists predominantly in the conformer (**32a**) opposite to that predicted (**32e**) on simple steric grounds.[31] We presume that the juxtaposition of the hydroxyls 1,3 diaxial to one another provides a favorable hydrogen-bonding effect that dominates over the unfavorable steric effect. For the related model system *cis*-cyclohexane-1,3-diol,[33] it has recently been found that the ratio of diaxial to diequatorial conformers increases with decreasing substrate concentrations (in chloroform). Moreover, for the analogous 1β-hydroxyvitamin D_3 (the C_1–C_3 bis epimer of **9**), Mazur has found that in a solvent of lower polarity (chloroform) the diaxial form predominates, while in a more polar solvent (acetone) the major conformer is diequatorial.[34] Thus, it seems that factors which favor intramolecular hydrogen bonding (low substrate concentration and less polar solvents) cause the 1,3-diaxial hydroxy conformers to be favored.

The newly synthesized analogues **7** and **8** were evaluated in a preliminary way for their biological activity under in vivo (ICA and BCM) conditions in the chick.[35] In the ICA assay, the time required for onset of maximum response was 50–70 h and 20 h for **7** and **8**, respectively. This is the same relationship as exists for the onset time required for **4** and **3** in the ICA[36] assay and is believed to reflect a necessity for 25-hydroxylation of 1α-OHD_3 (**4**) prior to its interaction with target tissues. It is interesting though that with the pair of 3β-OH steroids (**4** and **3**) this difference is only 8–12 h. For **7** and **8**, the difference is 30–50 h. It is also interesting that both **7** and **8** had significant activity in the BCM assay, which elevates serum calcium levels. We have previously reported[12] that the absence of the 3β-hydroxyl group (**5** and **6**) greatly reduced the BCM response relative to the ICA response. The third new analogue **9** was found to exhibit significant ICA response as well as BCM activity. The biological activity both in vivo and in vitro of these and other related vitamin D analogues will be reported in detail elsewhere.

Experimental Section

General. Ultraviolet (UV) spectra (95% ethanol) were recorded on a Beckman DBGT spectrophotometer, nuclear magnetic resonance (NMR) spectra (deuteriochloroform with tetramethylsilane, τ 10.00) were obtained on a Varian 60-MHz spectrometer unless otherwise indicated, and mass spectra (MS) were recorded on a Hitachi Perkin-Elmer RMU-6D (at 80 eV) or Finnigan 1015C (at 70 eV) mass spectrometer. Microanalyses were performed by C. F. Geiger (Ontario, Calif.) and Elek Microanalytical Labs (Torrance, Calif.). Melting points were measured on a Thomas-Hoover capillary apparatus and are uncorrected. Dry tetrahydrofuran (THF) and dry ether refer to solvents which were distilled from lithium aluminum hydride immediately prior to use. Lbpe refers to 30–60 °C low-boiling petroleum ether. For chromatography, alumina refers to Woelm neutral activity III and silica gel refers to Baker Analyzed reagent. For thin-layer chromatography (TLC), Merck silica gel G was used.

3α-Methyl-1α-hydroxycholest-5-ene (11a) and Its Acetate (11b). Methyllithium (58 mL, 1.7 M in hexane) was added dropwise to a suspension of cuprous iodide (9.36 g, 0.049 mol) in dry THF (0 °C, nitrogen atmosphere, magnetic stirring). After 15 min, the clear solution was cooled (−78 °C), and then the tosylate **10b** (2.75 g, 0.0494 mol) in dry THF (200 mL) was added dropwise to the stirred cuprate solution. After maintaining the mixture at −78 °C for 2 h and then overnight at room temperature, cold aqueous ammonium chloride (saturated) was added to quench the reaction. The product was filtered and taken up in chloroform; the filtrate was extracted several times with chloroform. The combined organic extracts were washed (water), dried (sodium sulfate), and then stripped to afford crude **11a**. Purification by chromatography (alumina, lbpe/20% ether–lbpe) followed by crystallization (methanol) afforded **11a** as colorless needles: 1.59 g, 80%; mp 111–112 °C; NMR (300 MHz) τ 4.53 (H_6, m), 6.29 ($H_{1\beta}$, br, $W \sim 8$ Hz), 8.99 (C_{19} CH_3, s), 9.09 (C_{21} CH_3, d, $J \sim 6.8$ Hz), 9.12 (C_3 CH_3, d, $J \sim 7.0$ Hz), 9.13 ($C_{26,27}$ 2 CH_3, d, $J \sim 6.8$ Hz), 9.26 (C_{18} CH_3, s). Anal. ($C_{28}H_{48}O$) C, H.

The acetate **11b** (acetic anhydride, pyridine, 80 °C, 18 h; ~100%) was obtained as needles (methanol) with mp 70–71 °C. Anal. ($C_{30}H_{50}O_2$) C, H.

3α-Methylcholest-5-en-1-one (12a). The alcohol **11a** (334 mg, 0.83 mol) in acetone (30 mL) was treated with Jones' reagent (0.3 mL).[37] The mixture was diluted with water and extracted with ether, and the ether was backwashed with water and dried (sodium sulfate). Removal of solvent afforded a solid which on crystallization (methanol) afforded the product: 250 mg, 76%; mp 90–91 °C; NMR (300 MHz) τ 4.51 (H_6, m), 8.77 (C_{19} CH_3, s), 9.07 (C_{21} CH_3, d, $J \sim 6.5$ Hz), 9.09 (C_3 CH_3, d, $J \sim 7$ Hz), 9.13 ($C_{26,27}$ 2 CH_3, d, $J \sim 6.8$ Hz), 9.32 (C_{18} CH_3, s). Anal. ($C_{28}H_{46}O$) C, H.

The keto benzoate **13** (0.625 g, 1.24 mmol, in 25 mL of dry THF), prepared as described below, was reacted at 10–15 °C with lithium dimethylcuprate (from cuprous iodide, 2.36 g, 12.4 mmol; dry THF, 25 mL; methyllithium, 1.7 M, 14.6 mL) as described above for the preparation of **11a**. Conventional workup as before followed by chromatography (silica gel, lbpe–benzene) and crystallization (methanol) afforded **12a** (420 mg, 85%; mp 91–92 °C), identical (TLC, NMR, IR) to that prepared by oxidation of **11a**.

The dienone **14** (see below; 65 mg, 0.17 mmol, in 2 mL of dry THF) was treated with a lithium dimethylcuprate solution (cuprous iodide, 325 mg, 1.70 mmol; dry THF, 2 mL; methyllithium, 1.8 M, 1.9 mL) by the procedure described for **13**. Workup and chromatography afforded 33.2 mg (49%) of NMR-pure material, which on crystallization (methanol) afforded **12a**, identical (TLC, NMR, IR, melting point) to the substance prepared from **11a** or **13**.

1α-Hydroxycholesteryl 3β-Benzoate (10d). Benzoyl chloride (1.2 mL) was added to an ice-cooled solution of **10a** (2.2 g, 5.5 mmol) in dry pyridine (50 mL). After 15–20 min, the mixture was worked up (ether–water) and removal of the solvent afforded 2.5 g of crude monoester. Chromatography (silica gel, 2% acetone–benzene) and crystallization (methanol–chloroform) afforded pure **10d** (2.0 g, 72%) with double mp 173–174 °C, 191–192 °C; NMR τ 4.7 ($H_{3\alpha}$, br m), 6.07 ($H_{1\beta}$, m, $W \sim 8$ Hz). Anal. ($C_{34}H_{50}O_3$) C, H.

3β-Benzoyloxycholest-5-en-1-one (13). The alcohol **10d** (1.44 g, 2.84 mmol) in acetone (180 mL) was treated with Jones' reagent[37] (1.2 mL). After 10 min, the mixture was diluted with water, and the product was filtered, washed (water), and dried. Crystallization (methanol–chloroform) afforded 1.40 g (98%) of **13** as fine lustrous needles, mp 172–173 °C; NMR τ 1.9–2.6 (C_6H_5, m), 4.32 (H_6, m), 4.8 ($H_{3\alpha}$, m), 8.70 (C_{19} CH_3, s), 9.08 (C_{21} CH_3, d, $J \sim 5.5$ Hz), 9.13 ($C_{26,27}$ 2 CH_3, d, $J \sim 6$ Hz), 9.31 (C_{18} CH_3, s). Anal. ($C_{34}H_{48}O_3$) C, H.

Cholesta-2,5-dien-1-one (14). A solution of **13** (0.50 g, 0.99 mmol) in dry ether (15 mL) was treated with 1,5-diazabicyclo[4.3.0]non-5-ene (0.24 g, 2.0 mmol) for 1.5 h with stirring at room temperature. Excess 10% hydrochloric acid was added, and the mixture was extracted with ether. The ether extract was back-washed (10% aqueous sodium bicarbonate, water), dried (sodium sulfate), filtered, and then concentrated. The residue (pure **14** by NMR) afforded 102 mg (37%) [mp 100–100.5 °C (lit.[13] mp 98.5–100 °C)] of **14** after chromatography and crystallization (methanol–chloroform). Its NMR spectrum was in accord with the literature report.[13]

Wolff–Kishner Reduction of 12a to 3α-Methylcholest-5-ene (15). A mixture of ketone **12a** (55 mg, 0.14 mmol), diethylene glycol (7 mL), KOH (150 mg), hydrazine (1 mL), and water (2 drops) was heated at 110–120 °C (1.5 h) and then at 220 °C (4 h). The cooled solution was poured into water, acidified, and then extracted with chloroform. The chloroform extract was backwashed (water), dried (sodium sulfate), and concentrated. The resulting residue was passed through a silica gel column (lbpe) to afford 18.5 mg (35%) of crystalline **15** (mp 97–98 °C; mixed melting point with the independently prepared sample described below, 97–98 °C). TLC (10% $AgNO_3$-impregnated silica gel) revealed the absence of the 3β-methyl epimer **16**. The spectral properties (300-MHz NMR, MS) of **15** obtained in this experiment were identical with those of the sample prepared by

the alternate route described below.

3α- and 3β-Methyl-6β-hydroxy-5α-cholestane (19 and 18). Unsaturated alcohol 17[19] (264 mg, 0.659 mmol) was hydrogenated over 10% Pd–C (ethanol). TLC revealed the presence of only two products of which the less polar component predominated. Repeated chromatography (30 g of silica gel, lbpe/30% ether–lbpe) afforded the less polar (major) 3β-methyl isomer **18** (120 mg isolated pure, 45%) and the more polar (minor) 3α-methyl isomer **19** (15 mg isolated pure, 6%). In another experiment, **17** (140 mg, 0.349 mmol) in ethanol was hydrogenated over 5% Rh–C. TLC revealed that now the more polar component predominated. On repeated chromatography as above, the more polar **19** was obtained as the major product (53.2 mg, 38%). Crystallization (methanol) of the more polar **19** afforded short colorless needles, homogeneous by TLC, mp 108–109 °C (lit.[19] mp 108–110 °C). Crystallization (aqueous acetone) of the less polar **18** gave a crystalline powder, also homogeneous and distinctly different from epimer **19** by TLC, mp 93–94 °C (lit.[19] mp 88–92 °C).

Dehydration of 18 to 3β-Methylcholest-5-ene (16). A mixture of **18** (51.6 mg), pyridine (3.1 mL), and phosphorus oxychloride (0.5 mL) was allowed to stand overnight. Quenching (ice water) and conventional working-up (ether, water) afforded a residue which on crystallization (ethanol) afforded pure **16**, mp 83–84 °C (lit.[22] 87 °C); NMR (300 MHz) τ 4.72 (H_6, $W \sim 9$ Hz), 9.02 (C_{19} CH_3, s), 9.08 (C_{21} CH_3, d, $J \sim 5$ Hz), 9.13 ($C_{26,27}$ 2 CH_3, d, $J \sim 6$ Hz), 9.32 (C_{18} CH_3, s); MS (80 eV) *m/e* (rel intensity) 384 (M, base), 369 (60), 271 (23), 229 (28).

A mixture of **16** and the 3α isomer **15** described immediately below exhibited mp 69–71 °C. TLC (10% $AgNO_3$-impregnated silica gel G, but not silica gel G alone) effectively distinguished between the 3β (**16**, R_f 0.56) and 3α epimers (**15**, R_f 0.65).

Dehydration of 19 to 3α-Methylcholest-5-ene (15). Using the same procedure as above, the steroid **19** (28.4 mg), pyridine (1.7 mL), and phosphorus oxychloride (0.3 mL) were reacted and worked up. Crystallization (methanol) afforded pure **15**, mp 97–98 °C; NMR (300 MHz) τ 4.77 (H_6, $W \sim 11$ Hz), 8.99 (C_{19} CH_3, s), 9.07 (C_{21} CH_3, d, $J \sim 5$ Hz), 9.13 ($C_{26,27}$ 2 CH_3, d, $J \sim 6$ Hz), 9.31 (C_{18} CH_3, s); MS (80 eV) *m/e* (rel intensity), 384 (M, base), 369 (58), 271 (52), 229 (55). Anal. ($C_{28}H_{48}$) C, H.

3α-Methylcholesta-5,7-dien-1-one (20a) and 3α-Methylcholesta-5,7-dien-1α-ol (21a). To a refluxing solution of ketone **12a** (1.19 g, 2.99 mmol) in 1:1 benzene–hexane (220 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (DBDMH; 435 mg, 1.52 mmol) at once. After a 15-min reflux period, the mixture was ice-cooled and filtered, and the precipitate was thoroughly washed with cold hexane. The combined filtrate and washings were stripped (vacuum, room temperature), and the residue was dissolved in xylene (25 mL). The xylene solution of bromide was added dropwise to refluxing *s*-collidine (60 mL) under nitrogen. After 30 min, the cooled mixture was dissolved in ether, and the ether was washed with dilute aqueous HCl (until *s*-collidine was absent), aqueous $NaHCO_3$, and water. After drying (sodium sulfate) and concentrating (high vacuum), the crude residue was chromatographed (silica gel, lbpe and 8% ether–lbpe) to afford material enriched in dienone **20a** (contaminated by the $\Delta^{4,6}$ isomer). The crude **20a** was stirred overnight (room temperature, nitrogen) with sodium borohydride (450 mg) in methanol (150 mL). After conventional workup (ether, water), the crude material was triply chromatographed (silica gel, lbpe/20% ether–lbpe), at which point TLC (silica gel and 10% $AgNO_3$-impregnated silica gel) and UV (λ_{max} 280-nm material is free from λ_{max} 240-nm material) revealed that the product (341 mg) was homogeneous. Crystallization (methanol) afforded 265 mg (22%) of material with mp 118–119 °C (shiny flakes); UV λ_{max} 262 nm sh (ϵ 6010), 270 (9050), 281 (10 200), 293 (6880); NMR (300 MHz) τ 4.35 and 4.63 ($H_{6,7}$, AB q, $J_{AB} \sim 5.5$ Hz; B, finely structured), 6.29 ($H_{1\beta}$, br, $W \sim 8$ Hz), 8.94 (C_3 CH_3, d, $J \sim 7.0$ Hz), 9.03 (C_{19} CH_3, s), 9.07 (C_{21} CH_3, d, $J \sim 6.5$ Hz), 9.14 ($C_{26,27}$ 2 CH_3, d, $J \sim 6.8$ Hz), 9.39 (C_{18} CH_3, s). Anal. ($C_{28}H_{46}O$) C, H.

3α-Methyl-1α,25-dihydroxycholest-5-ene (11c). Lithium dimethylcuprate (CuI, 1.94 g; methyllithium, 21 mL, 1.7 M; dry THF, 24 mL) and tosylate **10c**[10] (0.583 g, 1.02 mmol; 24 mL of dry THF) were reacted and then worked up as described above for **10b.** Dry column chromatography (silica gel, 10% acetone–benzene) of the reaction residue afforded TLC-homogeneous **11c** (388 mg, 92%), which on crystallization (acetone–hexane) afforded small colorless needles with mp 159–160 °C; NMR τ 4.47 (H_6, m), 6.25 ($H_{1\beta}$, m, $W \sim 7$ Hz), 8.79 ($C_{26,27}$ 2 CH_3, s), 8.96 (C_{19} CH_3, s), 9.0 ($C_{3,21}$ 2 CH_3, m), 9.30 (C_{18} CH_3, s). Anal. ($C_{28}H_{48}O_2$·hemihydrate) C, H (a completely satisfactory microanalysis for $C_{28}H_{48}O_2$ could not be obtained despite repeated trials).

3α-Methyl-25-hydroxycholest-5-en-1-one (12b). The diol **11c** (390 mg, 0.96 mmol) in acetone (25 mL) was oxidized (Jones' reagent,[37] 0.40 mL) according to the procedure described above for the conversion of **11a** to **12a.** Dry column chromatography (silica gel, 10% acetone–benzene) afforded TLC-pure **12b** (298 mg, 76%). Crystallization (hexane) afforded material with mp 128–129 °C; NMR τ 4.53 (H_6, m), 8.78 ($C_{19,26,27}$ 3 CH_3, s), 9.06 (C_{21} CH_3, d, $J \sim 5.5$ Hz), 9.10 (C_3 CH_3, d, $J \sim 6.5$ Hz), 9.30 (C_{18} CH_3, s). Anal. ($C_{28}H_{46}O_2$) C, H.

3α-Methyl-25-hydroxycholesta-5,7-dien-1-one (20b) and 3α-Methyl-1α,25-dihydroxycholesta-5,7-diene (21b). The transformation **18b** (225 mg, 1.47 mmol) → **20b** → **21b** was carried out exactly as described above for the sequence **12a** → **20a** → **21a,** except no attempt was made to partially purify **20b**. The resulting crude residue of **21b** (contaminated by the $\Delta^{4,6}$ isomer) was chromatographed twice (dry column of 10% $AgNO_3$-impregnated silica gel, 1:1 isopropyl ether–ether). The yield of TLC homogeneous crystalline **21b** (hexane, mp 165–166 °C) was 30 mg (13% based on **12b**); NMR τ 4.32 and 4.58 ($H_{6,7}$, AB q; A, d, $J \sim 6.0$ Hz; B, m), 6.28 ($H_{1\beta}$, m, $W \sim 8$ Hz), 8.78 ($C_{26,27}$ 2 CH_3, s), 9.01 (C_{19} CH_3, s) ~9.0 ($C_{3,21}$ 2 CH_3, m), 9.37 (C_{18} CH_3, s); UV λ_{max} 260 nm sh (ϵ 7250), 272 (9670), 282 (10 1000), 294 (6250); MS (70 eV) *m/e* (rel intensity) 414 (M, 3), 396 (M − H_2O, 2), 378 (M − $2H_2O$, 0.5), 59 (C_3H_7O, base).

3-Deoxy-3α-methyl-1α-hydroxyvitamin D_3 (7). The provitamin **21a** (146.5 mg) was irradiated (8.0 min) in six equal batches (~25 mg of steroid/100 mL of ether, ice cooling with nitrogen purging) as previously described.[38] The combined photolysis residue was chromatographed (silica gel) using a linear gradient between lbpe and 20% ether–lbpe. Fractions enriched in λ_{max} 258 nm, λ_{min} 232 nm material were pooled, concentrated, and then heated (isooctane, 75 ° C, 2.3 h, nitrogen) to equilibrate previtamin (λ_{max} 258 nm) with the vitamin (λ_{max} 263 nm, λ_{min} 227 nm). The residue obtained after removal of the solvent was chromatographed over silica gel (linear gradient between 5% ether–lbpe and 20% ether–lbpe) to afford the readily separable vitamin (22.6 mg, 15%) as a white foam. The material was completely homogeneous to several TLC systems: MS (80 eV) *m/e* (rel intensity; at *m/e* >130, >7%, and at *m/e* <130, >10%) 398 (M, 7), 380 (M − H_2O, 8), 190 (8), 175 (7), 173 (11), 172 (7), 171 (8), 161 (8), 159 (11), 157 (12), 151 (26), 150 (base, A-ring portion by $C_{7,8}$ cleavage), 149 (37), 147 (12), 145 (12), 143 (7), 138 (14), 135 (22), 133 (18), 133 (11), 131 (10), 119 (12), 109 (10), 107 (13), 105 (15), 95 (13), 93 (11), 91 (14); NMR (300 MHz) τ 3.72 and 3.94 ($H_{6,7}$, AB q, $J_{AB} \sim 11.5$ Hz), 4.64 (H_{19}, dd, $J \sim 2.5$, 2.5 Hz), 5.02 (H_{19E}, dd, $J \sim 2.5$, 2.5 Hz), 5.92 ($H_{1\beta}$, d with fine splittings, $J \sim 11.5$ Hz), 7.18 ($H_{9\beta}$, d, $J \sim 13$ Hz), 7.72 (1 H, d, $J \sim 12.5$ Hz), 7.87 (1 H, d, $J \sim 11.5$ Hz), 9.03 (C_3 CH_3, d, $J \sim$ Hz), 9.07 (C_{21} CH_3, d, $J \sim 6$ Hz), 9.13 ($C_{26,27}$ 2 CH_3, d, $J \sim 7$ Hz), 9.45 (C_{18} CH_3, s); UV λ_{max} 262 nm, λ_{min} 227 nm.

3-Deoxy-3α-methyl-1α,25-dihydroxyvitamin D_3 (8). The provitamin **21b** (14 mg) in 100 mL of ether (ice cooling, nitrogen) was irradiated (9.0 min) as described in the preceding section. The resulting residue was chromatographed twice (dry silica gel column, ether and then 1:1 isopropyl ether–ether) to afford material enriched in previtamin (λ_{max} 260 nm, λ_{min} 232 nm). The latter was heated as in the previous section, and the resulting residue was chromatographed twice (dry silica gel, 1:1 isopropyl ether–ether). The vitamin **8** was obtained as a foamy residue (1.6 mg, 11% by UV assuming ϵ_{262} 18 300) which proved to be completely homogeneous to several TLC systems: MS (70 eV) *m/e* (rel intensity; ≥7% for *m/e* 130–200 and ≥45% for *m/e* <130) 414 (M, 0.7), 396 (M − H_2O, 0.8), 378 (M − 2 H_2O, 0.4), 190 (8), 189 (10), 187 (7), 175 (12), 172 (13), 172 (8), 171 (8), 169 (8), 161 (16), 159 (16), 157 (11), 155 (11), 151 (35), 150 (100, A-ring portion by $C_{7,8}$ cleavage), 149 (35), 148 (8), 147 (17), 145 (20), 143 (9), 141 (11), 138 (14), 137 (11), 135 (25), 134 (14), 133 (45), 132 (8), 131 (22), 95 (59), 91 (45), 81 (74), 69 (49), 67 (48), 59 (C_3H_7O, 58); UV λ_{max} 262 nm, λ_{min} 227 nm.

1α,3β-Diacetoxycholest-5-ene (22a). A mixture of **10a** (9.9 g), acetic anhydride (45 mL, freshly distilled), pyridine (45 mL, freshly distilled), and *N,N*-dimethylaminopyridine (6.7 g) was stirred (nitrogen atmosphere, ambient temperature) for 24 h. After conventional workup followed by filtration through a pad of alumina (Woelm Activity III, 1:1 ether–lbpe), the resulting diacetate was obtained sufficiently pure for subsequent steps. Crystallization from ether afforded material (88%) with mp 98–99 °C (lit.[9] liquid).

1α,3β-Diacetoxycholest-5-en-7-one (22b). Chromium trioxide (15 g dried over P_2O_5 for 24 h) was added under nitrogen with ice cooling and stirring to a solution of pyridine (25.5 mL, freshly distilled) in dichloromethane (350 mL, freshly distilled).[39] After 5 min, the ice bath was removed, stirring was continued for 10 min, and diacetate **22a** (5.5 g, 11.3 mmol) in dichloromethane (10 mL, purified) was added in one portion. After 23 h of stirring at room temperature, the reaction solution was decanted and the tarry residue washed with dichloromethane. The combined dichloromethane solution was concentrated under vacuum to afford a residue which was extracted

with ether and then filtered. The filtrate was washed with 5% aqueous HCl and saturated aqueous $NaHCO_3$ and then dried ($MgSO_4$). After filtration and concentration, the residue along with a residue from an analogous 5.3-g (**22a**) scale reaction was combined and chromatographed (silica gel, 65 g; 10–25% ether–lbpe) to afford, after crystallization (ether–lbpe), 6.6 g of **22b** (59%), mp 125–127 °C; NMR τ 4.13 (H_6, $W \sim 3$ Hz), 4.7–5.2 ($H_{1\beta}$, $H_{3\alpha}$), 7.94 (2 OCH_3, s), 8.71 (C_{19} CH_3, s), 9.32 (C_{18} CH_3, s); IR ν_{max} 1730, 1667 cm^{-1}; UV λ_{max} 237 nm (ϵ 12 600). Anal. ($C_{31}H_{48}O_5$) C, H. Starting material (0.6 g) was also recovered.

1α-Acetoxycholesta-3,5-dien-7-one (23). A solution of **22b** (2.5 g, 5 mmol) and *p*-toluenesulfonic acid monohydrate (4 g, 21 mmol) in *p*-dioxane (800 mL, freshly distilled from sodium) was refluxed under nitrogen for 14.5 h. Workup (chloroform, aqueous $NaHCO_3$; dried with Na_2SO_4) and crystallization (isopropyl ether) afforded 1.9 g (86%) of **23**, mp 160 °C; NMR τ 3.82 (H_3, H_4, m), 4.22 (H_6, br s), 4.85 ($H_{1\beta}$, br t, $J \sim 3$ Hz), 7.98 (OCH_3, s), 8.82 (C_{19} CH_3, s), 9.28 (C_{18} CH_3, s); IR ν_{max} 1780, 1680, 1650 cm^{-1}; UV λ_{max} 280 nm (ϵ 24 600). Anal. ($C_{29}H_{44}O_3$) C, H.

1α-Acetoxy-3α-methyl- (24a) and 1α-Acetoxy-3β-methylcholest-5-en-7-one (24b) from 23. To an almost colorless solution of dimethyl sulfide–cuprous bromide complex (1.5 g, 7.3 mmol) in dimethyl sulfide (10 mL, freshly distilled, argon) and ether (10 mL, freshly distilled under nitrogen from $LiAlH_4$) was added (syringe, stirring, room temperature) methyllithium (9 mL, 1.45 M).[40] The addition of methyllithium was stopped when the yellow precipitate dissolved. To a stirred solution of **23** (250 mg, 0.55 mmol) in ether (5 mL, distilled from $LiAlH_4$) was added 3 mL (0.7 mmol) of the above lithium dimethylcuprate solution (all under nitrogen).[25] After 1 h, the reaction mixture was poured into an aqueous ammonia–ammonium chloride solution. Workup (ether–water) afforded 264 mg of the kinetic product (the Δ^4 isomer; NMR, UV), which was dissolved in dry acetone (10 mL). After cooling (ice) and adding 5 mL of 5% hydrogen chloride–acetone, the mixture was stirred for 75 min (nitrogen). Conventional workup (ether, $NaHCO_3$, water; Na_2SO_4) and filtration (silica gel, 5% ether–lbpe) of the resulting residue afforded 236 mg (~91%) of a reasonably pure **24a–24b** mixture. Chromatography (silica gel, 20 g; lbpe–15% ether/lbpe) afforded **24b** (17 mg, 7%) and **24a** (203 mg, 80%). The minor isomer **24b** possessed the following: mp 142–143 °C; NMR (300 MHz) τ 4.20 (H_6, br s, $W \sim 4$ Hz), 4.94 ($H_{1\beta}$, m, $W \sim 9$ Hz), 7.97 (OAc, s), 8.79 (C_{19} CH_3, s), 9.02 (C_3 CH_3, d, $J \sim 6.2$ Hz), 9.09 (C_{21} CH_3, d, $J \sim 6.5$ Hz), 9.13 ($C_{26,27}$ 2 CH_3, d, $J \sim 6.5$ Hz), 9.33 (C_{18} CH_3, s); IR ($CHCl_3$) ν_{max} 1724, 1667 cm^{-1}; UV λ_{max} 241 nm (ϵ 12 000); MS (20 eV) *m/e* (rel intensity) 457 (M + 1, 3), 456 (M, 5), 415 (18), 414 (12), 397 (34), 396 (66), 383 (M − HOAc, 7), 382 (24), 381 (base), 344 (36), 283 (13), 243 (23), 242 (21), 241 (28), 227 (18), 215 (14), 207 (18), 206 (12), 201 (19), 191 (12), 190 (68), 189 (64), 188 (66), 178 (16), 177 (24), 176 (19), 175 (44), 174 (11), 173 (25), 121 (10).

Major isomer **24a** possessed the following: mp 106–107 °C (after crystallization from 95% CH_3CH_2OH, 174 mg, 64%); NMR (300 MHz) τ 4.18 (H_6, br s, $W \sim 5$ Hz), 4.97 ($H_{1\beta}$, m, $W \sim 8$ Hz), 7.98 (OAc, s), 8.75 (C_{19} CH_3, s), 8.98 (C_3 CH_3, d, $J \sim 7.0$ Hz), 9.09 (C_{21} CH_3, d, $J \sim 6.5$ Hz), 9.13 ($C_{26,27}$ 2 CH_3, d, $J \sim 6.5$ Hz), 9.33 (C_{18} CH_3, s); IR ($CHCl_3$) ν_{max} 1730, 1664 cm^{-1}; UV λ_{max} 241 nm (ϵ 12 300). Anal. ($C_{30}H_{48}O_3$) C, H.

The isomers **24a** (major) and **24b** (minor) were clearly distinguishable by silica gel TLC (15% ether–lbpe) or 10% silver nitrate–silica gel TLC (30% ether–lbpe). The major isomer **24a** was identical (300-MHz NMR, TLC) to the material produced by chromium trioxide oxidation of **11b** (next experiment).

1α-Acetoxy-3α-methylcholest-5-en-7-one (24a) from 11b. The oxidation was carried out as described above for the conversion of **22a** to **22b** under the following conditions: **11b** (150 mg, 0.35 mmol), chromium trioxide (525 mg, 5.25 mmol), pyridine (0.84 ml, 10.5 mmol), and dichloromethane (8 mL) at room temperature for 16 h. After workup and chromatography (silica gel, 18 g; lbpe to 5% ether–lbpe), 40 mg of residual **24a** was obtained. The 300-MHz NMR spectrum of this material was identical with that of **24a** obtained from **23** above and this material was found to be distinctly different from **24b** by both 300-MHz NMR and the TLC systems described in the preceding section.

The *p*-Toluenesulfonylhydrazone (25) of 24a. A solution of 3α-methylenone **24a** (50 mg, 0.11 mmol) and *p*-toluenesulfonylhydrazine (110 mg, 0.62 mmol) in methanol (3 mL, purified) was refluxed (nitrogen atmosphere, stirring) for 10 h. The residue, after removing the methanol, was chromatographed (alumina, 20 g; dichloromethane) to afford an essentially quantitative yield of tosylhydrazone **25** (TLC homogeneous), useful for the next step: mp 89–94 °C; NMR τ 2.10 (2 H, Ar, d, $J \sim 8.5$ Hz), 2.70)2 H, Ar, d, $J \sim 8.5$ Hz), 3.63 (H_6, m, $W \sim$ 6 Hz), 5.05 ($H_{1\beta}$, m, $W \sim 10$ Hz), 7.55 ($ArCH_3$, s), 8.05 (OAc, s), 8.78 (C_{19} CH_3, s), 9.1 ($C_{21,26,27}$ 3 CH_3, m), 9.37 (C_{18} CH_3, s).

1α-Acetoxy- (21c) and 1α-Hydroxy-3α-methylcholesta-5,7-diene (21a) from 25. Lithium hydride (100 mg, 12.5 mmol) was added to a solution of tosylhydrazone **25** (50 mg) in benzene (3 mL, freshly distilled nitrogen). The mixture was refluxed under nitrogen for 7.5 h. After conventional workup (ether, 5% sulfuric acid, aqueous $NaHCO_3$, water; Na_2SO_4; filter; concentrate), the residue (44 mg) was filtered through a pad of silica gel (10 g, 30% ether–lbpe). The product (36 mg, syrup) exhibited the following properties: UV (ether) λ_{max} 267 nm sh, 274, 285, 297; NMR τ 4.33 and 4.57 (AB q, $J \sim 6$ Hz), 5.05 ($H_{1\beta}$, m), 7.97 (OAc, s), 8.9–9.2 ($C_{3,19,21,26,27}$ 5 CH_3, m), 9.38 (C_{18} CH_3, s).

To an ice-cooled solution of provitamin acetate **21c** (36 mg, 0.08 mmol) in ether (10 mL, distilled from $LiAlH_4$) under nitrogen was added $LiAlH_4$ (65 mg, 1.6 mmol). The mixture was refluxed for 30 min. The ice-cooled mixture was quenched with ice pellets, and conventional workup with ether afforded a residue (~36 mg). Short column chromatography (silica gel, 10 g; 10% ether–lbpe) afforded directly 15 mg (48%) of **21a** with mp 110–112 °C. This sample was identical to that obtained by sodium borohydride reduction of **20a** by direct comparison: silica gel TLC (50% ether–lbpe), 20% silver nitrate–silica gel TLC (benzene), and NMR. Chromatography and crystallization afforded material with mp 118–119 °C (mixed mp 118–119 °C was obtained with the sample prepared from **20a**).

1α,3α-Dihydroxycholest-5-ene (26a) and Its Diacetate 26b. A solution of diethyl azodicarboxylate (2.64 g, 15 mmol) in dry THF (15 mL) was added to a stirred solution of **10a** (3.02 g, 7.5 mmol), 97–100% formic acid (0.57 mL, 15 mmol), and triphenylphosphine (3.93 g, 15 mmol) in dry THF (90 mL). After 14 h, 20% methanolic NaOH (20 mL) was added, and the mixture was refluxed for several hours. The mixture was cooled, diluted with water, and then thoroughly extracted with ether. The ether extract was washed (water, 10% HCl, and several times again with water), dried, and concentrated to afford a residue which was chromatographed (alumina, 30% to 60% lbpe–ether). Crystallization (methanol) gave diol **26a** (2.45 g, 76%) with mp 205–208 °C; for NMR and MS data see the earlier communication.[1a]

Diol **26a** (2.45 g, 5.9 mmol), acetic anhydride (9 mL), dry pyridine (9 mL), and *N,N*-dimethylaminopyridine (1.8 g) were reacted (room temperature, 12 h) and then worked up conventionally. Chromatography (alumina, lbpe to 40% lbpe–ether) and crystallization (methanol) afforded the diacetate **26b** (2.70 g, 94%) with mp 123–125 °C; for NMR data see the earlie communication.[1a] Anal. ($C_{31}H_{50}O_4$) C, H.

1α,3α-Dihydroxycholesta-5,7-diene (27b). Bromination and then dehydrobromination were carried by the procedure described above for the conversion of **12a** to **20a:** diacetate **26b** (1.00 g, 2.05 mmol), DBDMH (0.292 g, 1.14 mmol), 1:1 benzene–hexane (40 mL), and s-collidine (30 mL). The resulting crude residue, after workup and solvent removal, was dissolved in 5% KOH–methanol (50 mL) and stirred (nitrogen) for 12 h. After conventional workup, the crude diol was chromatographed (10% $AgNO_3$-impregnated silica gel, ether), and fractions enriched in λ_{max} 280-nm (excluding 240-nm material) material were pooled and concentrated. Crystallization (methanol) afforded **27b** (151 mg, 15%) with mp 182–183 °C; for NMR, UV, and MS data see the earlier communication.[1a] Anal. ($C_{27}H_{44}O_2$) C, H.

1α-Hydroxy-3-epivitamin D_3 (9). The provitamin **27b** (12.5 mg in 100 mL of ether) was irradiated (9.0 min) as described above for the preparation of **7**. The photolysates from several such irradiations were pooled and concentrated. The residue was deposited on silica gel and then subjected to chromatography (dry column of silica gel, ether). The previtamin fractions (λ_{max} 260 nm, λ_{min} 232 nm) were pooled, concentrated, and heated (isooctane, N_2, 3 h). Chromatography (dry silica gel column, ether) afforded TLC-homogeneous (silica gel or 10% $AgNO_3$-impregnated silica gel) 1α-hydroxy-3-epivitamin (**9**) in ~5% yield as an amorphous foam: NMR (300 MHz, ~0.05 M) τ 3.58 and 4.02 ($H_{6,7}$, AB q, $J_{AB} \sim 11.4$ Hz), 4.73 (H_{19Z}, m), 5.03 (H_{19E}, m), 5.72 ($H_{1\beta}$, m), 5.97 ($H_{3\beta}$, m), 7.18 ($H_{9\beta}$, d, $J \sim 13$ Hz), 7.46 ($H_{4\beta}$, d, $J \sim 13.0$ Hz), 7.59 ($H_{4\alpha}$, dd, $J \sim 13.0$, 5.5 Hz), 9.08 (C_{21} CH_3, d, $J \sim 6.2$ Hz), 9.13 ($C_{26,27}$ 2 CH_3, d, $J \sim 6.6$ Hz), 9.46 (C_{18} CH_3, s); UV λ_{max} 263 nm, λ_{min} 227; MS (80 eV) *m/e* (rel intensity) 400 (M, 12), 382 (M − H_2O, 58), 364 (M − 2 H_2O, 37), 277 (66), 152 (base, A-ring part by $C_{7,8}$ cleavage), 135 (79), 134 (base − H_2O, 79), 133 (71).

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Six New Bisbenzylisoquinoline Alkaloids from *Thalictrum rugosum*[1]

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The alkaloids thaligosidine (1), thaligosinine (11), thaligosine (14), thalirugine (19), thaliruginine (29), and thalirugidine (32) were isolated from the phenolic alkaloid fraction of *Thalictrum rugosum* Ait. roots. Their structures were advanced on the basis of spectral and chemical evidence.

The genus *Thalictrum* (family Ranunculaceae) has yielded well over 100 alkaloids biogenetically derivable from benzylisoquinoline precursors.[2] As part of a continuing study of alkaloids from *Thalictrum*, we report herein the isolation and structure determination of six new phenolic bisbenzyltetrahydroisoquinoline alkaloids from the roots of *Thalictrum rugosum* Ait. (*T. glaucum* Desf.). This source has already afforded over 20 alkaloids, of which seven have been characterized as bisbenzylisoquinolines.[3]

The residue obtained by extraction of the powdered roots

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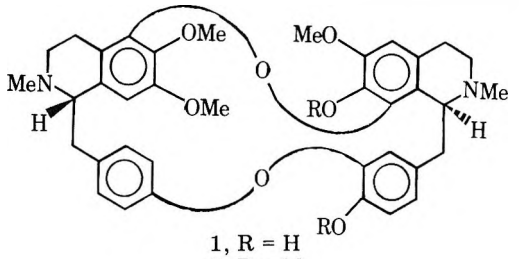
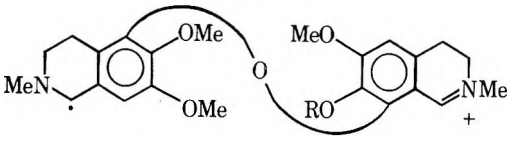
of *T. rugosum* was divided into the phenolic and nonphenolic tertiary alkaloid fractions by the usual solvent partition procedure, and the phenolic tertiary bases were chromatographed on silica gel and fractions thereof further purified to give the reported alkaloids.

Thaligosidine (**1**), obtained as colorless crystals, mp 175–177 °C, was assigned the composition $C_{37}H_{40}N_2O_7$ by high-resolution mass spectrometry, and the ^1H NMR spectrum clearly showed the presence of two *N*-methyls and three *O*-methyls along with nine aromatic protons. Two D_2O-exchangeable protons were assigned to two phenolic groups (vide infra). The UV spectrum exhibited a bathochromic shift in alkali. The IR spectrum showed hydroxyl absorption. The relatively intense molecular ion peak was suggestive of a bisbenzylisoquinoline structure with two diphenyl ethers,[4] and the peak at *m/e* 412 for fragment **2** supported a head to head arrangement as well as the placement of one phenolic group in an isoquinoline ring. Additional fragment peaks assigned to ions **3** and **4** supported the corresponding partial structures.

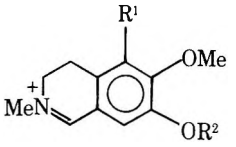
Methylation of thaligosidine (**1**) with diazomethane gave a methylated derivative **5** that showed two additional methoxy



1, R = H
5, R = Me
6, R = Et



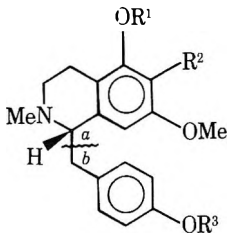
2, R = H
7, R = Et



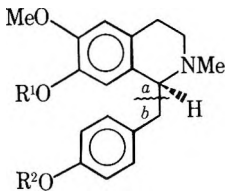
3, R^1 = H; R^2 = Me
4, R^1 = R^2 = H
8, R^1 = H; R^2 = Et
20, R^1 = OH; R^2 = Me
23, R^1 = OEt; R^2 = Me

peaks in the ^1H NMR spectrum and was identical with thalidasine (*S,S* configuration), previously isolated from this plant.[5] This conversion established the carbon skeleton, oxygenation pattern, and stereochemistry for thaligosidine (**1**). The location of the phenolic groups was determined from studies on *O,O*-diethylthaligosidine (**6**). The mass spectral peaks at *m/e* 440 and 220 for fragments **7** and **8**, respectively, confirmed the location of one phenolic group in an isoquinoline unit, and sodium–ammonia cleavage of **6** produced (*S*)-*N*-methyl-*O,O*-diethylcoclaurine (**9**)[6] and (*S*)-5-hydroxyarmepavine (**10**).[5] The nonphenolic product established the positions of the two phenolic groups.

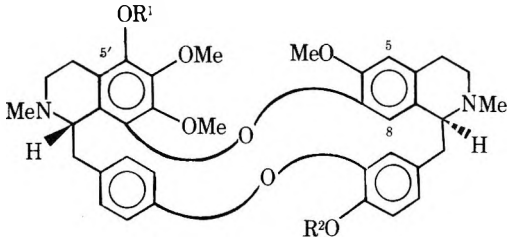
Thaligosinine (**11**), as colorless crystals, mp 233–234.5 °C (dec), with composition $C_{38}H_{42}N_2O_7$ from high-resolution mass measurement showed in the ^1H NMR spectrum two *N*-methyls, four *O*-methyls, and nine aromatic protons. A phenolic hydroxyl was supported by absorption in the IR and NMR spectra (in the latter, D_2O exchangeable), and by ob-



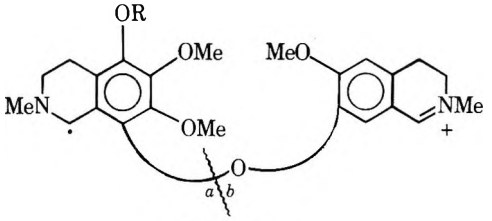
10, R^1 = R^3 = H; R^2 = OMe
18, R^1 = Et; R^2 = OMe; R^3 = H
35, R^1 = Et; R^2 = OMe, R^3 = Me
36, R^1 = Et; R^2 = H; R^3 = Me



9, R^1 = R^2 = Et
17, R^1 = H; R^2 = Me
24, R^1 = Et; R^2 = Me
31, R^1 = R^2 = Me



11, R^1 = Me; R^2 = H
12, R^1 = R^2 = Me
14, R^1 = H; R^2 = Me
16, R^1 = Et; R^2 = Me



13, R = Me
15, R = H

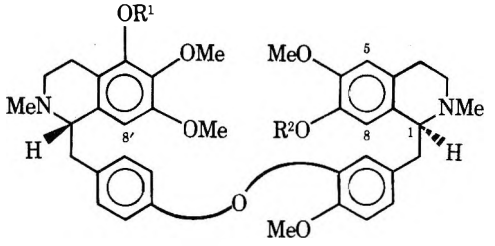
servation of a bathochromic shift in the UV spectrum with alkali. The *O*-methyl derivative was identical with thalrugosaminine (**12**) (*S,S* configuration) and established for thaligosinine the complete structure except for the phenolic hydroxyl position. Since the MS of thaligosinine (**11**) contains a peak at *m/e* 426 corresponding to fragment **13** and other peaks consistent with **13**, the phenolic hydroxyl must be with the benzylic ring.

Thaligosine (**14**), mp 143–145 °C, was found to have the same elemental composition as thaligosinine (**11**) and the NMR spectrum appeared similar; the major difference was in the location of one of the methoxyls. On treatment with diazomethane, thaligosine (**14**) was converted to thalrugosaminine (**12**), making thaligosine (**14**) a position isomer of thaligosinine (**11**). The phenolic group must be located in the tetraoxygenated isoquinoline ring, since the MS spectrum of **14** contains peaks at *m/e* 412, 222, and 192 corresponding to fragments **15**, **15a** + H and **15b** + H, respectively. *O*-Ethylthaligosine (**16**) on sodium–ammonia cleavage afforded two phenolic products **17** and **18**. The former is identical with a cleavage product from thalrugosaminine (**12**).[3a] The latter is new, for which the physical data (NMR, MS) support a structure in which the isoquinoline ring bears an ethoxy and two methoxy groups, and the benzylic ring contains a para phenolic hydroxyl. This compound is identical to one of the degradation products from thalirugine (**19**) for which location of the ethylated phenol was established (vide infra). Thaligosine (**14**) therefore has the phenolic group at the 5′-position and configuration *S,S*.

Thalirugine (**19**) was isolated as an amorphous solid and assigned a dimeric benzylisoquinoline structure on the basis of the number of protons in the NMR spectrum. The mass spectrum showed only very weak peaks above *m/e* 400 but the elemental analyses were consistent with the formula

$C_{38}H_{44}N_2O_7$ for which an apparent molecular ion at *m/e* 640 of 0.01% intensity was present. Such weak molecular peaks are observed for single diphenyl ether linked dimeric alkaloids.[4] The NMR spectrum contained peaks for two *N*-methyls, four *O*-methyls, ten aromatic protons, and two phenolic groups. Positive phosphomolybdic acid[7] and Gibbs'[8] tests supported a para unsubstituted phenol. Partial structures for the two isoquinoline portions in which one contains a phenolic and two methoxyl groups and the other a phenolic and one methoxyl were supported by ions in the mass spectrum at *m/e* 220 and 192 for fragments **20** and **4** (or their equivalent), respectively.

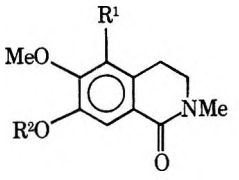
Methylation of thalirugine (**19**) with diazomethane gave a dimethyl derivative **21**, which substantiated the presence of



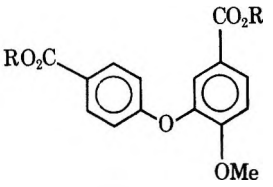
19, $R^1 = R^2 = H$
21, $R^1 = R^2 = Me$
22, $R^1 = R^2 = Et$
29, $R^1 = H$; $R^2 = Me$
30, $R^1 = Et$; $R^2 = Me$

two phenolic hydroxyls and their location in the isoquinoline rings, as did the diethyl derivative **22**. For the latter compound the intense mass spectral peaks at *m/e* 250 and 220 correspond to fragment ions **23** and **8**, respectively. Sodium in ammonia cleavage of *O,O*-diethylthalirugine (**22**) yielded a nonphenolic base **24** that was identical with a cleavage product from *O*-ethylthalrugosidine;[5] thus, one of the phenolic groups in thalirugine (**19**) is at position 7, and the configuration at C-1 *S*. The phenolic cleavage product was found to be identical with product **18** from *O*-ethylthaligosine (**16**); therefore, the other asymmetric center of thalirugine (**19**) is also *S*. The two cleavage products identified the nature of the oxygenation pattern for the individual benzylisoquinoline units of thalirugine (**19**). In addition, the phenolic group in the isoquinoline ring of **18** must be placed at position 5 if thalirugine is to give a positive Gibbs' test. It follows that thaligosine (**14**) must bear the phenolic hydroxyl at 5′.

Permanganate oxidation of *O,O*-diethylthalirugine (**22**) afforded three products, two isoquinolones **25**[9,10] and **26** and



25, $R^1 = H$; $R^2 = Et$
26, $R^1 = OEt$; $R^2 = Me$

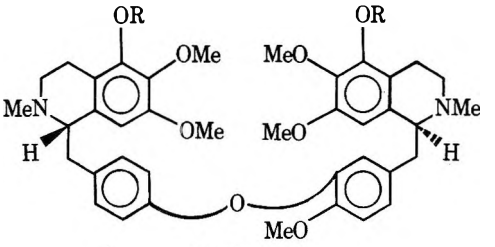


27, R = H
28, R = Me

diphenyl ether dicarboxylic acid **27**, each identified by direct comparison with known samples. 2-Methyl-5-ethoxy-6,7-dimethoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline (**26**) was prepared by oxidation of the diethyl ether product of **10**, a sodium–ammonia cleavage product from thalidasine (**5**).[11] The isoquinolones confirmed the phenol locations in the isoquinoline rings, and the diphenyl ether, also characterized as the diester **28**, established the point of attachment for the monomeric units of thalirugine (**19**).

Thaliruginine (**29**) was obtained as an amorphous solid, $[\alpha]_D$ +104°, and exhibited spectral characteristics of a bisbenzylisoquinoline alkaloid with one diphenyl ether structure (weak molecular ion in MS). The NMR spectrum showed peaks for two *N*-methyls, five *O*-methyls, and ten aromatic protons. Treatment of thaliruginine (**29**) with diazomethane formed a monomethyl derivative **21** identical with the methylated product from thalirugine (**19**); thus, thaliruginine (**29**) is one of two *O*-methylthalirugines, and its MS with a peak at *m/e* 222 (**20**) supported a phenolic group in the trioxygenated isoquinoline ring. The positive Gibbs' test would place the phenolic group at position 5′. Confirmation of this assignment was made by the isolation of benzyl isoquinoline **18** on sodium–ammonium cleavage of *O*-ethylthaliruginine (**30**). The other cleavage product was (*S*)-*O*-methylarmepavine (**31**).

Thalirugidine (**32**), the third monoether-linked bisalkaloid, was assigned formula $C_{39}H_{46}N_2O_8$ on the basis of MS and elemental analyses. The NMR spectrum contained peaks for two *N*-methyls, five *O*-methyls, and nine aromatic protons, two of which were located at upfield positions, characteristic of H-8 and H-8′ protons. Two D_2O-exchangeable protons were from phenols and were supported by the preparation of di-*O*-methyl **33** and di-*O*-ethyl **34** derivatives. The MS of

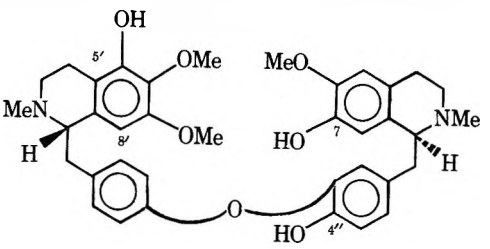


32, R = H
33, R = Me
34, R = Et

thalirugidine (**32**) and its derivatives, all with weak M^+ peaks, were in agreement with the location of a phenolic hydroxyl on each of the two trioxygenated isoquinoline rings. For example, peaks are present at *m/e* 222 for fragment **20** and *m/e* 250 for **23** of thalirugidine (**32**) and diethyl ether **34**, respectively.

Sodium–ammonia reductive cleavage of **34** gave (*S*)-5-ethoxy-4′,6,7-trimethoxy-*N*-methyltetrahydroisoquinoline (**35**) as the nonphenolic product and (*S*)-5-ethoxy-4′-hydroxy-6,7-dimethoxy-*N*-methyltetrahydroisoquinoline (**18**) as the phenolic product. The configuration was assigned on the basis of positive CD maxima at 282 and 230 nm for cleavage products **18** and **35**. Methylation converted **18** to **35**. Permanganate oxidation of *O,O*-diethylthalirugidine (**34**) formed 2-methoxy-4′,5-dicarboxy diphenyl ether (**27**) (identified as the dimethyl ester **28**) and provided the evidence for the location of the ether linkage. In addition, the isoquinolone **26** was also isolated. The CD spectrum of thalirugidine (**32**), with two positive maxima at 280 and 230 nm, is consistent with the *S,S* stereochemistry.

Five of the six new alkaloids, in this report, are derivable biogenetically from a hypothetical monoether-linked bisalkaloid **37** (northalirugine) formed by phenol coupling of (*S*)-northalifendlerine and (*S*)-*N*-methylcoclaurine. Intramolecular phenol coupling of **37** between the 5′-OH and the 8 position would yield thaligosidine (**1**), which on methylation



37

of both phenolic groups forms thalidasine (5). With phenol coupling between the 7-OH and the 8′ position, the precursor of thaligosinine (11) and thaligosine (14) would result. Only methylation, respectively, of the 5′-OH and the 4″-OH is required to the final products. Complete methylation gives thalrugosaminine (12). The remaining two alkaloids, thalirugine (19) and thaliruginine (29), are simple mono- and dimethylated products of the hypothetical precursor 37. The sixth alkaloid, thalirugidine (32), is a monomethylated product of another hypothetical precursor formed from two (*S*)-northalifendlerines.

Experimental Section

Melting points are uncorrected. NMR spectra were determined in stated solvents with Me_4Si as an internal standard using Varian A-60A or Bruker HX-90E instruments and with chemical shifts (δ) reported in ppm and coupling constants (J) in Hz. IR and UV spectra were taken in $CHCl_3$ on a Beckman IR 4230 and in MeOH on a Cary 15 instrument, respectively. Mass spectra were obtained on an AEI MS-9 or DuPont 21-491 instrument by direct inlet probe at 70 eV. Optical rotations were measured on a Perkin-Elmer 241 photoelectric polarimeter and CD spectra in MeOH on a Durrum-Jasco ORD/UV-5 spectropolarimeter with Sproul Scientific SS-20 modification. TLC was performed on silica gel G (E. Merck) and column chromatography on silica gel PF254 (Brinkmann-EM) or alumina (Woelm) with stated solvents. Detection on TLC was with Dragendorff's spray reagent. Microanalyses were by Scandinavian Microanalytical Laboratory, Herlev, Denmark. Roots of *T. rugosum* were collected from plants grown in the College of Pharmacy Medicinal Plant Garden. A voucher specimen is on file.

Extraction of *T. rugosum* Roots and Initial Partitioning. Ground roots (17.7 kg) were percolated to exhaustion with ethanol, and the extract was evaporated to dryness at reduced pressure and 40 °C, leaving 1.5 kg of residue. Suspension of the residue in 18 L of 2% aqueous citric acid and filtering gave a filtrate that was extracted with an equal volume of $CHCl_3$ and then brought to pH 9.0 with NH_4OH. The basic solution was extracted successively with Et_2O (35 L) and $CHCl_3$ (18 L), and the Et_2O fraction was extracted with 12 L of 5% NaOH. Evaporation of the Et_2O left 75 g of nonphenolic tertiary alkaloids, while from the $CHCl_3$ extract 11.6 g of alkaloidal residue remained. The NaOH solution was treated with solid NH_4Cl and the cloudy suspension was extracted with 30 L of Et_2O from which 39.2 g of phenolic tertiary alkaloids was obtained.

Chromatography of the Phenolic Tertiary Alkaloids. The crude phenolic tertiary alkaloid fraction (30 g) was separated on a column of silica gel (0.9 kg), collecting 0.5-L fractions for analysis. The eluting solvents were $CHCl_3$ (5 L) and the following mixtures of MeOH in $CHCl_3$: 2.5% (10 L), 5% (12 L), 7.5% (8 L), 10% (6 L), 15% (3 L), 20% (6 L), 40% (4 L), and 50% (4 L). Final column washes were made with 4 L of MeOH and 2 L of 5% HOAc in MeOH. The eluted fractions gave the alkaloids that follow.

Thaligosidine (1). The residue (1.1 g) from fractions 28–31 was rechromatographed on 35 g of silica gel. The 1% MeOH in $CHCl_3$ eluates gave 230 mg of a residue that was crystallized from benzene to yield 180 mg of colorless crystalline thaligosidine (1): mp 175–177 °C; R_f 0.9 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.5); $[\alpha]_D^{20}$ −45° (*c* 0.26, MeOH); CD $[\theta]_{287}$ −19 000, $[\theta]_{268}$ +6700, $[\theta]_{242}$ +5490 and $[\theta]_{224}$ −31 800; UV λ_{max} 275 (log ϵ 3.72), 283 nm (3.72), and in 0.01 N NaOH 275 (3.75), 284 (3.76), and 310 nm (shld) (3.22); IR ($CHCl_3$) 3540 cm^{-1} (OH); NMR δ ($CDCl_3$) 2.25 and 2.66 (s, 2 NMe), 3.49, 3.75 and 3.86 (s, 3 OMe), 6.2–7.7 (m, 9 ArH), and 5.6 ppm (br, 2 OH, D_2O exchangeable), with benzene adduct showing peaks at δ ($CDCl_3$) 2.42 and 2.66 (s, 2 NMe), 3.43, 3.76, 3.85 (s, 3 OMe), 6.3–7.7 (m, 9 ArH), and 5.88 ppm (br, 2 OH); MS *m/e* 624.2849 (40%, M^+, $C_{37}H_{40}N_2O_7$ requires 624.2835), 412 (7, **2**), 411 (20, **2** − H), 206 (23, double ions of 412 and **3**), and 192 (100, **4**).

Anal. Calcd for $C_{37}H_{40}N_2O_7 \cdot {}^3/_2H_2O$: C, 68.24; H, 6.18; N, 4.30. Found: C, 68.50; H, 6.48; N, 3.81.

***O*-Methylation of Thaligosidine (1).** To 35 mg of thaligosidine (1) in 2.5 mL of MeOH was added ethereal diazomethane prepared from 1 g of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide. After 4 days, the residue remaining after evaporation of solvent was chromatographed on neutral alumina with PhH–$CHCl_3$ (1:1) to give 25 mg of a pale-yellow amorphous base showing identical properties (IR, UV, specific rotation, CD, NMR, and TLC) with authentic thalidasine (5) previously isolated form *T. rugosum*.[5]

***O,O*-Diethylthaligosidine (6).** To 140 mg of thaligosidine (1) in 10 mL of MeOH was added ethereal diazoethane generated from 2 g of *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine. After 5 days the reaction residue was chromatographed on neutral alumina with benzene as solvent. The crystalline residue on recrystallization from MeOH gave colorless needles: mp 198–200 °C; R_f 0.93 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.5); NMR δ ($CDCl_3$) 0.74 and 1.43 (2 t, J = 7, 2 OCH_2CH_3), 4.14 (q, J = 7, OCH_2CH_3) with another methylene quartet of ethoxy hidden in the methylene region, 2.24 and 2.62 (s, 2 NMe), 3.52, 3.74, and 3.87 (s, 3 OMe), and 6.2–7.6 (m, 9 ArH); MS (CI, isobutane) *m/e* 681 (100%, MH^+, $C_{41}H_{49}N_2O_7$ requires 681), EI *m/e* 680 (100%, M^+), 651 (11, M − Et), 440 (7, **7**), 439 (22, **7** − H), 220 (37, **8**), 206 (4, **3**) and 190 (10, **8** − EtH).

Anal. Calcd for $C_{41}H_{48}N_2O_7$: C, 72.33; H, 7.11; N, 4.12. Found: C, 71.94; H, 7.15; N, 4.09.

Na/NH_3 Cleavage of *O,O*-Diethylthaligosidine (6). To 20 mL of liquid NH_3 containing 150 mg of Na at below −50 °C was added dropwise in 0.5 h 8 mL of tetrahydrofuran solution containing 70 mg of **6**. The reaction was maintained for 2 h. The NH_3 was allowed to evaporate and the unreacted Na was decomposed with excess MeOH. The mixture was concentrated in vacuo to 2 mL, taken up in 250 mL of Et_2O, and extracted with 125 mL of 1 N NaOH to separate the products into phenolic and nonphenolic fractions.

From the washed (H_2O) and dried (Na_2SO_4) Et_2O extract was obtained 30 mg of an oil on evaporation that showed one spot, R_f 0.80, on TLC with PhH–Me_2CO–NH_4OH (20:20:0.6). Column chromatography on 2 g of neutral alumina with 100 mL of PhH–$CHCl_3$ (1:1) and 150 mL of $CHCl_3$ as eluents yielded 24 mg of **9** as an amorphous solid: NMR δ ($CDCl_3$) 1.31 and 1.38 (2 t, J = 7, 2 OCH_2CH_3), 3.76 and 3.98 (2 q, J = 7, 2 OCH_2CH_3), 2.51 (s, NMe), 3.82 (s, OMe), 6.09 (s, H-8), 6.55 (s, H-5), and 6.77 and 6.98 (AA′BB′ q, J_{AB} = 8.5, 4 ArH); MS (CI, isobutane) *m/e* 356 (75%, MH^+, $C_{22}H_{29}NO_3$ requires 355), 220 (100, a) and 135 (5, b); CD $[\theta]_{290}$ + 9100, $[\theta]_{272}$ −1700, and $[\theta]_{234}$ +47 000. This compound showed identical TLC behavior, UV, IR, and NMR spectra with that of the corresponding cleavage product prepared from *O,O*-diethylobamegine,[6] but the CD spectrum was antipodal ($[\theta]_{290}$ −9300, $[\theta]_{272}$ +1900, and $[\theta]_{234}$ −38 000).

The NaOH solution was treated with NH_4Cl to pH 8–9 and extracted with Et_2O. The washed (H_2O) and dried (Na_2SO_4) Et_2O solution on evaporation gave 19 mg of a residue that showed two spots on TLC, R_f 0.6 (major) and 0.7, with PhH–Me_2CO–NH_4OH (20:20:0.6). Chromatography on silica gel (2 g) with $CHCl_3$, 2% and 4% MeOH in $CHCl_3$, yielded 12 mg of **10**, identical (TLC, UV, IR, NMR, MS, and CD) with the cleavage product from *O*-ethylthalrugosidine.[5]

Thaligosinine (11). The column fractions 28–31 that on rechromatography afforded thaligosidine (1) gave on elution with 2% MeOH in $CHCl_3$ 526 mg of an early fraction that crystallized from Et_2O to give white crystals of thalrugosine, mp 206–207 °C, already reported from this source.[5] The latter 2% MeOH in $CHCl_3$ effluents yielded 35 mg of a white crystalline solid that crystallized from Et_2O to give thaligosinine (**11**): mp 233–234.5 °C (dec); $[\alpha]_D^{21}$ −58.5° (*c* 0.316, MeOH); CD $[\theta]_{275}$ −13 000, $[\theta]_{242}$ −48 000, $[\theta]_{230}$ +100 000; UV λ_{max} 282 nm (log ϵ 3.90) and in 0.01 N NaOH 284 (4.11) and 307 nm (shld) (3.53); IR ($CHCl_3$) 3540 cm^{-1}; NMR δ ($CDCl_3$, 90 MHz) 2.51 and 2.56 (2 s, 2 NMe), 3.04, 3.40, 3.80, and 3.84 (4 s, 4 OMe), 6.36 (s, H-8), 6.47 (s, H-5), 6.5–7.5 (m, 7 ArH), and ~5.0 (br, OH, D_2O exchangeable); MS 638.3005 (100%, M^+, $C_{38}H_{42}N_2O_7$ requires 638.2992), 426 (15, **13**), 425 (37, **13** − H), 411 (34, **13** − Me), 236 (2, **13a**), 213 (97, double ion of **13**), 192 (31, **13b** + H), 191 (6, **13b**), and 190 (9, **13b** − H).

Methylation of Thaligosinine (11) to Thalrugosaminine (12). A 25-mg sample of **11** in 3 mL of MeOH was treated with excess ethereal diazomethane for 3 days. The product was chromatographed on 2 g of neutral alumina with PhH–$CHCl_3$ (1:1) to give 23 mg of a pale-yellow solid. Its TLC mobility and UV, IR, NMR, and CD spectra were identical with those of thalrugosaminine (12) earlier reported from this plant.[3a]

Thaligosine (14). The residue (1 g) from column fractions 32–34 was rechromatographed on 50 g of silica gel with $CHCl_3$ and 1, 2, 3, and 4% MeOH in $CHCl_3$. The 2 and 3% MeOH in $CHCl_3$ effluents gave a residue that from Et_2O gave 210 mg of thaligosine (**14**) as colorless crystals: mp 143–145 °C; R_f 0.33 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.8); $[\alpha]_D$ −109° (*c* 0.17, MeOH); CD $[\theta]_{287}$ +3200, $[\theta]_{272}$ −1200, $[\theta]_{240}$ −7980, $[\theta]_{225}$ +16 700; UV λ_{max} 282 nm (log ϵ 3.86) and in 0.01 N NaOH 282 (3.83) and 305 nm (shld) (3.64); IR ($CHCl_3$) 3520 cm^{-1} (OH); NMR δ ($CDCl_3$) 2.52 and 2.56 (2 s, 2 NMe), 3.08, 3.39, 3.78, and 3.95 (4 s, 4 OMe), 6.38 (s, H-8), 6.46 (s, H-5), 6.6–7.4 (m, 7 ArH) and 4.7 (br, OH, D_2O exchangeable); MS *m/e* 638 (89%, M^+, $C_{38}H_{42}N_2O_7$ requires 638), 637 (27, M − H), 623 (4, M − Me), 412 (25, 15), 411 (92, **15** − H), 222 (14, **15a** + H), 206 (100, double ion of **15**) and 192 (30, **15b** + H).

Anal. Calcd for $C_{38}H_{42}N_2O_7 \cdot H_2O$: C, 69.49; H, 6.75; N, 4.27. Found: C, 69.35; H, 6.60; N, 4.17.

***O*-Methylation of Thaligosine (14).** A 30-mg sample of **14** in 5 mL of MeOH was treated with excess ethereal diazomethane for 4 days. The product was chromatographed on 1.5 g of neutral alumina with 100 mL of chloroform as eluent and the homogeneous [TLC, R_f 0.5 with PhH–Me_2CO–NH_4OH (20:20:0.8)] material (23 mg) was identical (UV, IR, MS, NMR, and CD) with thalrugosaminine (**12**).[3a]

***O*-Ethylthaligosine (16).** A 120-mg sample of thaligosine (**14**) in 5 mL of MeOH was treated with ethereal diazoethane prepared from 1.5 g of *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine. After 3 days the solvent was evaporated and the residue chromatographed on 6 g of neutral alumina with PhH–$CHCl_3$ (1:1) and $CHCl_3$ as eluents. The ethyl ether **16** as a homogeneous solid (110 mg) with R_f 0.47 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.6) was eluted with the latter solvent and showed: NMR δ ($CDCl_3$) 1.38 (t, J = 7, OCH_2CH_3), ~4.2 (q, J = 7, OCH_2CH_3, partially obscured), 2.50 and 2.55 (2 s, 2 NMe), 3.08, 3.38, 3.78, and 3.92 (4 s, 4 OMe), 6.39 (s, H-8), 6.45 (s, H-5), and 6.6–7.5 (m, 7 ArH); MS *m/e* 666.3316 (100%, M^+, $C_{40}H_{46}N_2O_7$ requires 666.3305).

Anal. Calcd for $C_{40}H_{46}N_2O_7 \cdot 0.5H_2O$: C, 71.09; H, 7.01; N, 4.15. Found: C, 71.45; H, 7.03; N, 4.14.

Na/NH_3 Cleavage of *O*-Ethylthaligosine (16). The ethyl ether **16** (105 mg) was dissolved in 6 mL of tetrahydrofuran and reduced with Na in NH_3 as described for **6**. The reaction mixture was separated into phenolic and nonphenolic fractions. Only unreacted starting material (5 mg) was obtained from the nonphenolic fraction. The phenolic fraction (57 mg) showed two major components on TLC, R_f 0.58 and 0.36 with PhH–Me_2CO–NH_4OH (20:20:0.6), and was separated on 3 g of silica gel.

The 1% MeOH in $CHCl_3$ eluent gave 13 mg of **17** as a yellow solid, identical (UV, IR, NMR, and CD) with one of the cleavage products from thalrugosaminine (**12**).[3a]

The 2% MeOH in $CHCl_3$ eluent gave 20 mg of **18** which crystallized from MeOH: mp 113–114 °C; $[\alpha]_D^{21}$ +103 (c 0.24, MeOH); CD $[\theta]_{284}$ +7300, $[\theta]_{230}$ +56 800; UV λ_{max} 283 nm (log ϵ 3.61); IR ($CHCl_3$) 3595 cm^{-1}; NMR δ ($CDCl_3$) 1.34 (t, J = 7, OCH_2CH_3), 4.05 (q, J = 7, OCH_2CH_3), 2.50 (s, NMe), 3.54 and 3.82 (2 s, 2 OMe), 5.87 (s, H-8), 6.62 and 6.88 (AA'BB' q, J_{AB} = 9, benzylic ring H), and 6.45 (br, OH, lost in D_2O); MS *m/e* 357.1946 (0.5%, M^+, $C_{21}H_{27}NO_4$ requires 357.1940, CI (isobutane) *m/e* 358 (10, MH^+), 250 (100, a), 107 (2, b).

Thalirugine (19). The residue (1.9 g) from fractions 38–44 was rechromatographed on 200 g of neutral alumina with $CHCl_3$ as eluent. The residue precipitated from Et_2O to give thalirugine (**19**) as a white amorphous solid: R_f 0.52 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.8); $[\alpha]_D^{20}$ +92° (c 0.25, MeOH); CD $[\theta]_{282}$ +6400, $[\theta]_{248}$ −3100, and $[\theta]_{226}$ +78 000; UV λ_{max} 280 nm (log ϵ 3.81) and in 0.01 N NaOH 280 (3.86), 285 (3.87), and 310 nm (shld) (3.45); IR ($CHCl_3$) 3520 cm^{-1} (OH); NMR ($CDCl_3$) δ 2.43 and 2.49 (2 s, 2 NMe), 3.58 and 3.83 (2 s, 2 OMe), 3.78 (s, 2 OMe), 5.73 (s, H-8'), 6.38 (s, H-8), 6.47 (s, H-5), 6.6–7.2 (m, 7 ArH), and 5.50 (br, OH, D_2O exchangeable); MS *m/e* 640 (0.01%, M^+), 222 (100, **20**), 207 (35, **20** − Me), and 192 (83, **4**). Positive tests were obtained with phosphomolybdic acid[7] and Gibbs' reagents.[8]

Anal. Calcd for $C_{38}H_{44}N_2O_7 \cdot 0.5H_2O$: C, 70.24; H, 6.98; N, 4.31. Found: C, 70.11; H, 6.96; N, 4.27.

***O*-Methylation of Thalirugine (19) to 21.** A 35-mg sample of **19** in 3 mL of MeOH was treated with excess ethereal diazomethane for 3 days. The residue after evaporation of solvent was chromatographed on 2 g of neutral alumina with $CHCl_3$ to yield derivative **21** as a pale yellow amorphous solid: R_f 0.75 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.8); $[\alpha]_D^{21}$ +105° (c 0.21, MeOH); CD $[\theta]_{282}$ +14 700 $[\theta]_{228}$ +76 600; NMR ($CDCl_3$) δ 2.48 and 2.51 (2 s, 2 NMe), 3.58, 3.63, 3.79, and 3.82 (4 s, 4 OMe), and 3.84 (s, 2 OMe), 5.93 (s, H-8'), 6.13 (s, H-8), 6.53 (s, H-5), and 6.6–7.2 (m, 7 ArH); MS *m/e* 668 (0.3%, M^+, $C_{40}H_{48}N_2O_7$ requires 668), 236 (100, $C_{13}H_{18}NO_3$, trimethoxylated isoquinoline fragment), and 206 (91, **3**).

***O,O*-Diethylthalirugine (22).** A 200-mg sample of **19** in 5 mL of MeOH was treated with excess diazoethane generated from 2 g of *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine. After 5 days the reaction residue after solvent evaporation was chromatographed on 10 g of neutral alumina with 100 mL each of PhH, PhH–$CHCl_3$ (1:1), and $CHCl_3$ as eluents. A yield of 120 mg of a pale-yellow amorphous solid of diethyl ether **22** was obtained: R_f 0.85 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.6); NMR ($CDCl_3$) δ 1.34 (t, J = 7, 2 OCH_2CH_3), 3.82 and 4.05 (2 q, J = 7, 2 OCH_2CH_3), 2.47 and 2.49 (2 s, 2 NMe), 3.57, 3.81 (2 s, 2 OMe), and 3.78 (s, 2 OMe), 5.91 (s, H-8'), 6.16 (s, H-8), 6.51 (s, H-5), and 6.6–7.1 (m, 7 ArH); MS EI *m/e* 696 (0.3%, M^+, $C_{42}H_{52}N_2O_7$ requires 696), 476 (0.4, M − **8**), 446 (1, M − **23**), 250 (45, **23**), 220 (63, 8), and 192 (100, 8 − CH_2CH_2), with CI (isobutane) *m/e* 697 (14, MH^+), 250 (85, **23**) and 220 (100, 8).

Anal. Calcd for $C_{42}H_{52}N_2O_7 \cdot 2H_2O$: C, 68.83; H, 7.70; N, 3.82. Found: C, 68.98; H, 7.15; N, 3.95.

Na/NH_3 Cleavage of *O,O*-Diethylthalirugine (22). A 115-mg sample of **22** in 10 mL of tetrahydrofuran was added dropwise over 1 h to 25 mL of NH_3 containing Na. After an additional 2 h of reaction the products were separated into the phenolic and nonphenolic components by partitioning between Et_2O and 1 N NaOH.

From the ether fraction, 75 mg of a pale-yellow oil, R_f 0.85 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.6), was obtained. Chromatography on 4 g of silica gel with $CHCl_3$ and 1% MeOH in $CHCl_3$ gave the nonphenolic base **24** (47 mg), identical (UV, IR, NMR, MS, and CD) with a cleavage product from *O*-ethylthalrugosidine.[5]

The Naoh extract after treatment with solid NH_4Cl and Et_2O extraction gave the phenolic base fraction (35 mg). Chromatography on silica gel with 2 and 3% MeOH in $CHCl_3$ gave from the latter eluates 23 mg of product **18** that crystallized from MeOH, mp 114 °C, with R_f 0.6 on TLC using the same solvent as for **24**. This substance was identical (mmp, UV, IR, NMR, MS, and CD) with a cleavage product from *O*-ethylthaligosine (**16**).

$KMnO_4$ Oxidation of *O,O*-Diethylthalirugine (22). A 315-mg sample of **22** dissolved in 50 mL of Me_2CO was treated with 600 mg of $KMnO_4$ added portionwise in 1 h while stirring. After an additional 3 h of stirring the excess reagent was decomposed with MeOH, and the MnO_2 was removed by filtration. The filtrate was concentrated, mixed with 25 mL of H_2O, acidified with 5% HCl, and exhaustively extracted with $CHCl_3$. The residue (210 mg) from the washed (H_2O) and dried (Na_2SO_4) $CHCl_3$ extract was chromatographed on 10 g of silica gel with 50 mL of PhH and 100 mL each of PhH–$CHCl_3$ (1:1), $CHCl_3$, and 2.5, 5, and 10% MeOH in $CHCl_3$.

The PhH–$CHCl_3$ (1:1) eluates gave first, after crystallization from MeOH, 36 mg of yellow needles of isoquinolone **25**: mp 120–121 °C; R_f 0.72 on TLC with PhH–Me_2CO (1:1); UV, IR, NMR, and MS identical with those of a synthetic sample[9] of 6-methoxy-7-ethoxy-*N*-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline.[10]

The later PhH–$CHCl_3$ (1:1) eluates gave 30 mg of isoquinolone **26** as a pale-yellow oil: R_f 0.66 on TLC with the same solvent as used for **25**; UV λ_{max} 296 (log ϵ 3.48), 270 (shld) (3.88), 260 (3.96), 253 (shld) (3.92), and 216 nm (4.52); IR ($CHCl_3$) 1645 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.35 (t, J = 7, OCH_2CH_3), 4.06 (q, J = 7, OCH_2CH_3), 2.92 and 3.51 (2 A_2B_2 t, J = 6, CH_2CH_2), 3.12 (s, NMe), 3.90 (s, 2 OMe), and 7.44 (s, H-8); MS *m/e* 265.1320 (100%, M^+, $C_{14}H_{19}NO_4$ requires 265.1314), 250 (3, M − Me), 236 (9, M − Et), 222 (33, M − CH_2NMe), and 194 (35, 222 − CO). This compound was identical (TLC, UV, IR, NMR, and MS) with 5-ethoxy-6,7-dimethoxy-*N*-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline produced by $KMnO_4$ oxidation of the *O*-ethylated cleavage product **10** from authentic thalidasine (**5**).[11]

From the 5 and 10% MeOH in $CHCl_3$ fractions, 100 mg of a white solid was obtained that exhibited the same TLC characteristics as 2-methoxy-4',5-dicarboxy diphenyl ether (**27**) prepared from the corresponding dialdehyde[12] by Ag_2O oxidation. Treatment of both samples with diazomethane afforded diester **28**, mp 79–80 °C, with identical TLC mobility, IR and NMR spectra, and an undepressed mmp.

Preparation of *O,O*-Diethyl 10 and $KMnO_4$ Oxidation. Diphenol **10** (120 mg) obtained by Na/NH_3 cleavage[11] of thalidasine (**5**, 300 mg) in 5 mL of MeOH was treated with excess ethereal diazoethane. After 12 days the solvent was evaporated and the residue chromatographed on 5 g of neutral alumina with PhH (200 mL) and PhH–$CHCl_3$ (4:1, 100 mL). From the latter eluate, 80 mg of the diethyl ether of **10** as a yellow heavy oil was obtained: R_f 0.86 on TLC with PhH–Me_2CO–NH_4OH (10:10:0.1); UV λ_{max} 278 nm (log ϵ 3.77) and unchanged by acid or base; NMR ($CDCl_3$) δ 1.34 and 1.38 (2 t, J = 7, 2 OCH_2CH_3), 3.98 and 4.05 (2 q, J = 7, 2 OCH_2CH_3), 2.50 (s, NMe), 3.57 and 3.82 (2 s, 2 OMe), 5.91 (s, H-8), and 6.77 and 6.97 (AA'BB' q, J_{AB} = 9, 4 ArH); MS *m/e* 385 (0.2%, M^+), 250 (100, **23**), 221 (1, **23** − Et), 220 (8, **23** −Et-H) and 135 (2, M − **23**).

A 70-mg sample of *O,O*-diethyl-**10** was dissolved in 25 mL of Me_2CO, and 150 mg of $KMnO_4$ was added during 1 h while stirring. After reacting an additional 3 h the excess reagent was destroyed by 10 mL of MeOH. The mixture was filtered and the filtrate concentrated to 3 mL. Addition of 10 mL of H_2O and acidification with 0.1 N HCl produced a white precipitate that was removed by filtration. The filtrate was extracted with 150 mL of $CHCl_3$, and the extract after washing (H_2O) and drying (Na_2SO_4) left, on evaporation, 40 mg of a pale-yellow oil. It was chromatographed on 2 g of neutral alumina with PhH (50 mL). The 30 mg of heavy oil was identified by spectral evidence to be isoquinolone **26**, identical (TLC, UV, IR, NMR, and MS) with the corresponding oxidation products from *O,O*-diethylthalirugine (**22**) and *O,O*-diethylthalirugidine (**34**).

Thaliruginine (29). From the same column separation that gave thaligosine (**14**), the 3 and 4% MeOH in $CHCl_3$ eluates gave 260 mg of thaliruginine (**29**) as a white amorphous solid: R_f 0.65 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.8); $[\alpha]_D^{20}$ +104° (*c* 0.16, MeOH); CD $[\theta]_{287}$ +14 500, $[\theta]_{252}$ −2100, $[\theta]_{230}$ +93 000; UV λ_{max} 281 nm (log ϵ 3.90) and in 0.01 N NaOH 281 (3.97) and 309 nm (shld) (3.09); IR ($CHCl_3$) 3520 cm^{-1} (OH); NMR ($CDCl_3$) δ 2.48 and 2.50 (2 s, 2 NMe), 3.57, 3.61, 3.78, 3.80 and 3.83 (5 s, 5 OMe), 5.71 (s, H-8), 6.11 (s, H-8′), 6.53 (s, H-5′), 6.6–7.2 (m, 7 ArH), and 5.4 (br, OH, D_2O exchangeable); MS *m/e* 654 (0.8%, M^+), 222 (68, **20**), 206 (100, **3**), and 192 (26, **3** − Me). Thaliruginine gave positive tests with phosphomolybdic acid[7] and Gibbs' reagent.[8]

Anal. Calcd for $C_{39}H_{46}N_2O_7 \cdot H_2O$: C, 69.62; H, 7.19. Found: C, 69.32; H, 6.86.

O-Methylation of Thaliruginine (29) to 21. A 40-mg sample of **29** in 5 mL of MeOH was treated with excess ethereal diazomethane for 3 days to give 35 mg of derivative **21**, identical (TLC, UV, IR, NMR, and CD) with the methylated product of thalirugine (**19**).

O-Ethylthaliruginine (30). A 100-mg sample of **29** in 5 mL of MeOH was treated with excess ethereal diazoethane. The product was chromatographed on 5 g of silica gel PF 254 using 100 mL each of $CHCl_3$ and 1% MeOH in $CHCl_3$ as eluents to yield 80 mg of **30** as an amorphous pale-yellow solid: R_f 0.8 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.8); NMR ($CDCl_3$) δ 1.34 (t, J = 7, OCH_2CH_3), 4.05 (q, J = 7, OCH_2CH_3), 2.48 and 2.50 (2 s, 2 NMe), 3.58, 3.62, 3.78, 3.80, and 3.82 (5 s, 5 OMe), 5.92 (s, H-8′), 6.13 (s, H-8), 6.58 (s, H-5), and 6.6–7.2 (m, 7 ArH); MS *m/e* 682 (0.2%, M^+, $C_{41}H_{50}N_2O_7$ requires 682), 250 (95, **23**), and 206 (100, **3**).

Na/NH_3 Cleavage of *O*-Ethylthaliruginine (30). A 60-mg sample in 5 mL of tetrahydrofuran was reacted with Na/NH_3, and the products were worked up as described for compound **22**. From the nonphenolic fraction, 11 mg of (*S*)-*O*-methylarmepavine (**31**) was obtained and identified by direct comparison (TLC, UV, IR, NMR, and CD) with an authentic sample. The phenolic fraction gave 10 mg of crystalline 18 which was identified by comparison (mmp, TLC, UV, IR, NMR, and CD) with an authentic sample.

Thalirugidine (32). The residue (360 mg) from column fraction 37 was rechromatographed on 16 g of silica gel with $CHCl_3$ and 2, 4, 8, and 10% MeOH in $CHCl_3$ as eluents. From the 2% MeOH in $CHCl_3$ eluate, 55 mg of thalirugidine (**32**) was obtained as a white amorphous solid: R_f 0.60 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.8); $[\alpha]_D^{20}$ +112° (c 0.19, MeOH); CD $[\theta]_{280}$ +7200, $[\theta]_{230}$ +98 500; UV λ_{max} 278 nm (log ϵ 3.82) and in 0.01 N NaOH 281 nm (3.94); IR ($CHCl_3$) 3530 cm^{-1}; NMR ($CDCl_3$) δ 2.48 and 2.51 (2 s, 2 NMe), 3.61, 3.63, 3.85 (3 s, 3 OMe) and 3.81 (s, 2 OMe), 5.76 and 5.79 (2 s, H-8 and H-8′), 6.6–7.2 (m, 7 ArH), and 5.1 (br, 2 OH, D_2O exchangeable); MS *m/e* 670 (1.4%, M^+), 222 (100, **20**), 221 (3, **20** − H), 220 (3, **20** − 2H), 207 (3, **20** − Me), 206 (8, **20** − Me − H), 192 (8, 220 − CO), and 178 (2, 206 − CO).

Anal. Calcd for $C_{39}H_{46}N_2O_8$: C, 69.83; H, 6.91; N, 4.18. Found: C, 69.78; H, 7.18; N, 4.15.

***O,O*-Dimethylthalirugidine (33).** Thalirugidine (**32**, 20 mg) in 2 mL of MeOH was treated with excess diazomethane for 3 days to give 15 mg of a pale-yellow amorphous solid; R_f 0.83 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.8); $[\alpha]_D^{20}$ +53° (*c* 0.21, MeOH); CD $[\theta]_{285}$ +8700, $[\theta]_{230}$ +42 000; UV λ_{max} 278 nm (log ϵ 3.96); NMR ($CDCl_3$) δ 2.47 and 2.50 (2 s, 2 NMe), 3.59, 3.61, 3.79 (3 s, 3 OMe) and 3.83 (s, 4 OMe), 5.93 and 5.98 (2 s, H-8 and H-8′), and 6.6–7.2 (m, 7 ArH); MS *m/e* (M^+ not observed), 236 (100, isoquinoline fragments).

***O,O*-Diethylthalirugidine (34).** A 130-mg sample of **32** in 5 mL of MeOH was treated with diazoethane for 5 days. The reaction residue was chromatographed on 6 g of silica gel using 1% MeOH in $CHCl_3$ as eluent, to give 120 mg of the diethyl ether **34** as an amorphous solid: $[\alpha]_D^{20}$ +44° (c 0.17, MeOH); CD $[\theta]_{282}$ +5700, $[\theta]_{230}$ +30 500; NMR ($CDCl_3$) δ 1.33 (t, J = 7, 2 CH_2CH_3), 4.03 (q, J = 7, 2 CH_2CH_3), 2.45 and 2.47 (2 s, 2 NMe), 3.58, 3.60, 3.77 (3 s, 3 OMe), 3.81 (s, 2 OMe), 5.92 and 5.96 (2 s, H-8 and H-8′), and 6.6–7.2 (m, 7 ArH); MS *m/e* 726 (0.5%, M^+, $C_{43}H_{54}N_2O_8$ requires 726), 250 (100, **23**), 235 (8, **23** − Me), 234 (7, **23** − Me − H), 221 (4, **23** − Et), 220 (17, **23** − Et − H), 206 (11, 234 − CO), and 192 (7, 220 − CO).

Na/NH_3 Cleavage of *O,O*-Diethylthalirugidine (34). The diethyl ether **34** (105 mg) in 10 mL of tetrahydrofuran was reductively cleaved with 150 mg of Na in ammonia, and the products were divided into phenolic and nonphenolic bases. The nonphenolic fraction (50 mg) as a yellow oil showed two spots, R_f 0.86 (major) and 0.91, on TLC with PhH–Me_2CO–NH_4OH (20:20:0.8). Chromatography on 2.5 g of silica gel PF 254 with 50 mL of PhH–$CHCl_3$ (1:1) and 100 mL of $CHCl_3$ gave 18 mg of **35**, the major base, as a colorless oil. It showed TLC mobility and UV, IR, NMR, and CD spectra identical with the corresponding cleavage product from thalidezine[13] or isothalidezine.[14] The minor product **36**, obtained as a yellow oil (8 mg), showed identical TLC characteristics and UV, IR, and NMR spectra as those for a cleavage by-product from thalidezine.[13]

The phenolic fraction (38 mg) contained one component, R_f 0.36 on TLC with system used for the nonphenolics. Chromatography on 2 g of silica gel PF 254 with 100 mL each of 1 and 2% MeOH in $CHCl_3$ afforded a crystalline residue (26 mg) that was recrystallized from MeOH to give colorless rosettes of **18**, mp 113–114 °C, identical (TLC, UV, IR, NMR, and CD) with a sample from *O*-ethylthaligosine (**16**).

Methylation of **18** with diazomethane gave **35**.

$KMnO_4$ Oxidation of *O,O*-Diethylthalirugidine (34). Compound **34** (50 mg) in 10 mL of Me_2CO was treated with 150 mg of $KMnO_4$. After stirring for 3 h, the workup as reported for the oxidation of **22** yielded 8 mg of isoquinolone **26** and the diphenyl ether diacid **27**. Both were compared directly (the latter as the dimethyl ester **28**) with known samples by TLC and UV, IR, and NMR spectra. Compound **28** also showed no depression of the mmp.

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Registry No.—**1**, 64252-82-0; **6**, 64252-83-1; **9**, 3423-12-9; **10**, 16623-60-2; **10** diethyl ether, 64235-37-6; **11**, 64235-38-7; **14**, 22226-72-8; **16**, 64235-39-8; **18**, 64235-40-1; **19**, 64235-41-2; **21**, 64215-90-3; **22**, 64215-91-4; **25**, 2651-56-1; **26**, 64215-92-5; **28**, 5566-15-4; **29**, 64215-93-6; **30**, 64215-94-7; **32**, 64215-95-8; **33**, 64215-96-9; **34**, 64215-97-0; **35**, 64281-58-9; **36**, 64281-59-0.

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New Cytotoxic Neolignans from *Aniba megaphylla* Mez.[1,2]

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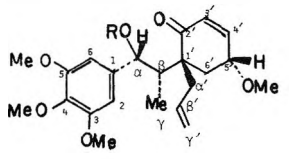
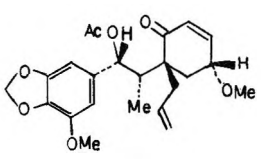
The isolation and elucidation of the structure and stereochemistry of megaphone (**1**), a new cytotoxic neolignan from *Aniba megaphylla* Mez., are reported. Chemical and spectral evidence supported structure **1** for megaphone, and a direct x-ray crystallographic analysis confirmed the structure and established the stereochemistry. Two additional new cytotoxic neolignans, megaphone acetate (**2**) and megaphyllone acetate (**3**), were isolated and their structures deduced in light of the structure of **1**. The lack of activity of these neolignans as inhibitors of mitosis in sea urchin eggs is discussed in terms of structural features.

An alcoholic extract of *Aniba megaphylla* Mez. (Lauraceae)[5] was found to demonstrate inhibitory activity in vitro against cells derived from human carcinoma of the nasopharynx (*KB*).[6] Systematic fractionation of the active ethanol extract (Chart I) guided by KB activity led to the isolation of three new cytotoxic neolignans, megaphone (**1**), megaphone acetate (**2**), and megaphyllone acetate (**3**).



1, R = H
2, R = $COCH_3$



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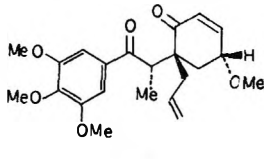
Chromatography of fraction H over silica gel gave a fraction which crystallized from chloroform–ether to afford megaphone (**1**). On the basis of high-resolution mass spectrometry and confirmation by elemental analysis, megaphone was assigned the molecular formula $C_{22}H_{30}O_6$. The NMR spectrum exhibited signals at δ 3.88 (6 H), 3.83 (3 H), and 3.46 (3 H), representing three aromatic and one aliphatic methoxyl groups and suggesting that megaphone was either a lignan or neolignan. The NMR spectrum also showed a singlet at δ 6.66 (2 H) and a doublet at δ 4.64 (1 H) which, when considered with the hydroxyl stretching band at 3600 cm^{-1} in the infrared (IR) spectrum, indicated a benzyl alcohol moiety with the aromatic ring symmetrically substituted. In order to confirm this partial structure, megaphone was oxidized using Jones reagent to give dione **4**, $C_{22}H_{28}O_6$. The two-proton singlet was



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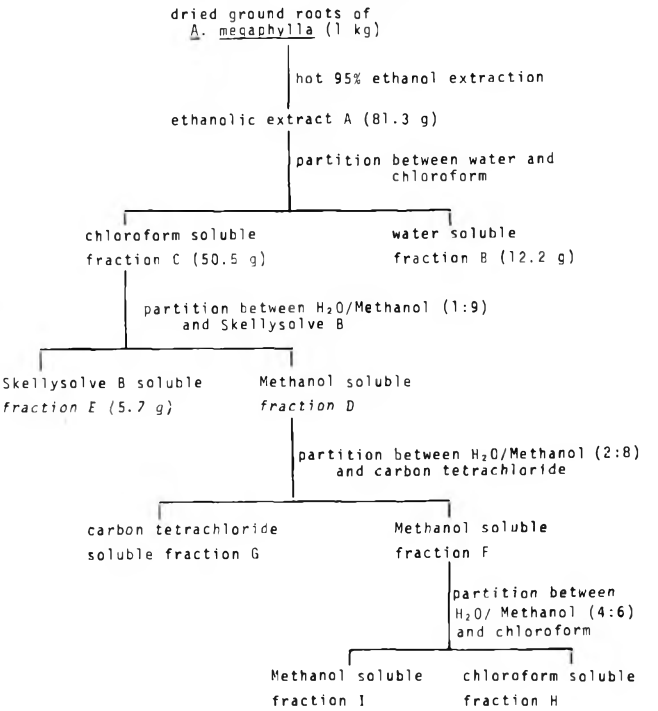
shifted downfield in the NMR spectrum of **4**, and, in the IR spectrum, the hydroxyl band disappeared and a new carbonyl band appeared at 1590 cm^{-1}, thus confirming the presence of an aryl ketone.

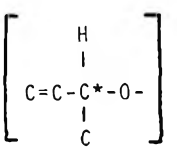
The IR spectrum of **1** showed the presence of an α,β-unsaturated carbonyl moiety (1670 cm^{-1}), and the NMR spectrum exhibited a doublet at δ 7.00 (1 H, J = 10.5 Hz) and a doublet of doublets centered at δ 6.02 (1 H, J = 10.5, 2.2 Hz) which could be assigned to the α and β protons, respectively, in a cis-α,β-unsaturated carbonyl system. Oxidation of **1** to afford **4** gave little change in either the IR or the NMR signals assigned to this moiety, indicating that the α,β-unsaturated carbonyl portion of the molecule was unaffected.

Further inspection of the NMR spectrum of **1** revealed the presence of an allyl group [δ 5.83 (1 H, m), 5.30 (1 H, br), 5.19 (1 H, br)] and a secondary methyl group [δ 0.77 (3 H, d, J = 7.1 Hz)]. In the NMR spectrum of **4**, the doublet for the secondary methyl group shifted to δ 1.18, indicating that it was in close proximity to the benzylic alcohol. Additionally, in the NMR spectrum of **4**, the signal for the proton on the carbon α to the secondary methyl group appeared as a quartet at δ 4.04 (1 H, J = 7.5 Hz), indicating that this carbon was attached to two quaternary carbons.

Chart I. Fractionation of the Cytotoxic Extract from *Aniba megaphylla* Mez.



The data thus accounted for all but one site of unsaturation, suggesting that there was an additional ring which included the α,β-unsaturated ketone. The ^{13}C NMR spectrum of megaphone confirmed the presence of all the above moieties, and the presence of six quaternary carbons was indicated—four in the aromatic moiety, one in the carbonyl group, and one in the cyclohexenone ring. Consequently, the cyclohexenone ring must also contain one methylene carbon. In addition, signals were observed for two carbons with general structure A. One signal was ascribed to the benzylic carbon



A

0022-3263/78/1943-0586$01.00/0

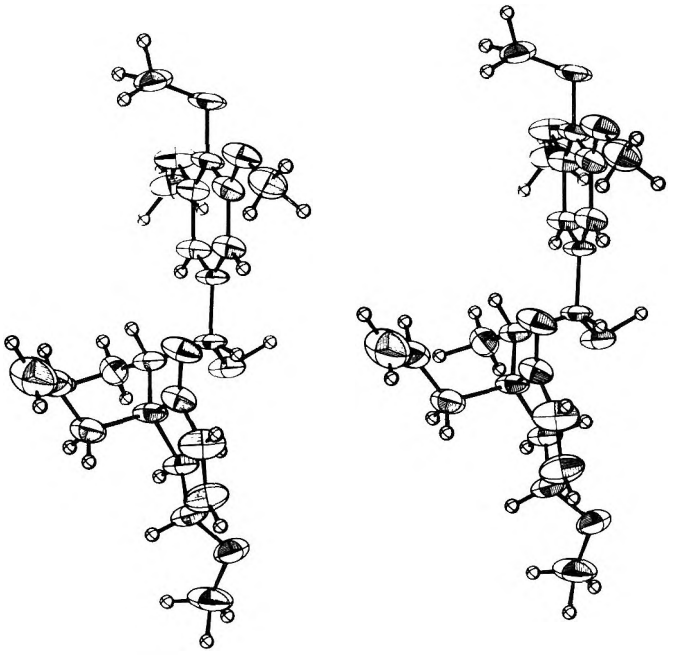
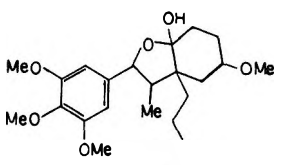


Figure 1. Stereoscopic view (ORTEP) of the molecular conformation.

and the other to the carbon in the cyclohexenone ring attached to the methoxyl group.

Oxidized megaphone (**4**) showed a one-proton doublet of doublets at δ 2.90 (J = 10.5, 12.5 Hz) which could be assigned to one of the methylene protons in the cyclohexenone ring. Irradiation of this signal partially collapsed the multiplet at δ 4.30 (MeO–CH), and irradiation of the multiplet at δ 4.30 partially collapsed the doublet of doublets, thus confirming that the methylene group was in close proximity to the MeO–CH moiety.

Hydrogenation of megaphone (**1**) in EtOH gave an oil which analyzed for $C_{22}H_{34}O_6$ (by high-resolution mass spectrometry) and showed hydroxyl bands in the IR spectrum [3600 (s) and 3425 cm^{-1} (br)] but no carbonyl group. Attempts to oxidize the product with Jones reagent were unsuccessful, suggesting that the secondary alcohol was no longer present. Therefore, a hemiketal structure, **5**, was proposed for the product of the hydrogenation reaction. The NMR data were also consistent with such a structure.



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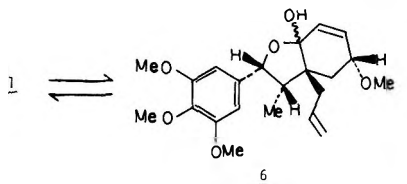
Careful reexamination of the NMR spectrum of megaphone (**1**) revealed "spurious" signals, e.g., δ 0.60 (d, J = 7.5 Hz), 3.37 (s), and 6.48 (s). These signals could be accounted for by the presence of an equilibrium mixture of megaphone and its hemiketal, **6**, in solution. The relative intensity of the signals ascribed to **1** and **6** were found to vary with both solvent and



6

temperature. In $CDCl_3$ at 23 °C the ratio of **1** to **6** was found to be 100:12, whereas in pyridine-d_5 at 23 °C the ratio was 85:100. The temperature dependence was shown by the ratio in pyridine-d_5 at 46 and at 83 °C which was 100:95 and 100:54, respectively.

Table I. Atomic Parameters for the Nonhydrogen Atoms[a]

Atom	x/a	y/b	z/c	B
C(1)	7706 (8)	1283 (7)	5130 (8)	3.4
C(2)	8802 (9)	819 (8)	4937 (8)	3.8
C(3)	10168 (8)	1067 (7)	5887 (8)	3.5
C(4)	10105 (9)	1798 (7)	6915 (8)	3.7
C(5)	8684 (10)	2225 (7)	7130 (8)	3.9
C(6)	7338 (9)	1993 (8)	6191 (8)	3.7
C(7)	11672 (10)	−229 (10)	4940 (10)	5.6
C(8)	12248 (12)	2991 (9)	7447 (11)	6.6
C(9)	7345 (11)	3269 (9)	8473 (9)	5.2
C(α)	5897 (8)	1123 (7)	4084 (8)	3.4
C(β)	5845 (8)	1956 (7)	2904 (8)	3.5
C(γ)	6608 (10)	1472 (9)	1828 (9)	4.4
C(α')	4182 (10)	3272 (8)	1200 (9)	4.6
C(β')	5298 (12)	4225 (9)	1576 (10)	6.0
C(γ')	5062 (17)	5225 (11)	1693 (13)	9.9
C(1′)	4154 (9)	2398 (7)	2366 (8)	3.8
C(2′)	3527 (10)	3028 (7)	3425 (8)	3.6
C(3′)	1879 (11)	3144 (9)	3297 (10)	5.7
C(4′)	867 (10)	2563 (10)	2373 (10)	5.4
C(5′)	1306 (9)	1797 (8)	1429 (9)	4.5
C(6′)	3025 (9)	1425 (7)	1830 (8)	3.8
C(7′)	−179 (14)	389 (9)	54 (12)	6.8
O(3)	11579 (6)	664 (6)	5804 (6)	5.0
O(4)	11450 (7)	2060 (6)	7873 (6)	5.0
O(5)	8770 (7)	2930 (6)	8184 (6)	4.8
O(α)	5772 (6)	0000 (−)[b]	3566 (6)	4.2
O(2′)	4429 (7)	3475 (6)	4384 (5)	4.7
O(5′)	358 (7)	815 (6)	1359 (6)	5.3

[a] Positional parameters for the hydrogen atoms (see supplementary material) are given as fractions of the unit-cell edges ($\times 10^4$) with esd's, in parentheses, on the same scale. Equivalent anisotropic thermal parameters (see supplementary material) are given in Å^2. [b] Held fixed to define the origin.

In both megaphone hemiketal (**6**) and tetrahydromegaphone hemiketal (**5**), the methyl group occurs at high field in the NMR spectrum, i.e., δ 0.60 (J = 7.5 Hz) and 0.62 (J = 7.6 Hz), respectively, thus indicating a cis relationship to the aromatic system, as found in similar neolignans from other *Aniba* species such as porosin.[7,8] The coupling constant of the benzylic proton (δ 5.25, J = 9.7 Hz) in **5** indicated a gauche arrangement to the adjacent proton. Examination of the double doublet at δ 2.90 (one proton of the ring methylene group) showed coupling constants of 12.7 and 10.5 Hz, one of which was the geminal coupling constant. The other, because of its magnitude, must be the result of a 1,2-trans diaxial interaction; hence, the aliphatic methoxyl group was in an equatorial position.

From these data the structure of megaphone could be assigned as **1**. To confirm this structure, and to establish the molecular conformation and absolute stereochemistry, a direct x-ray analysis of **1** was carried out. A stereoscopic view[9] of the molecular structure found is shown in Figure 1, and atomic coordinates are given in Table I. Bond distances and angles and selected torsion angles are given in Figure 2, and additional torsion angles of interest are listed in Table II.

The molecular structure proposed is confirmed as correct. In the crystal the molecule adopts an extended stepped conformation with the bond C(α)–C(β) lying in a plane near normal to the plane of the phenyl ring, the torsion angle C(1)–C(α)–C(β)–C(1′) being −143°. The more favorable, fully staggered, 180° alignment is prevented by the limiting intramolecular contact O(α)–H(6′a) of 2.54 Å which prevents further rotation about C(α)–C(β). The hydroxy group O(α)

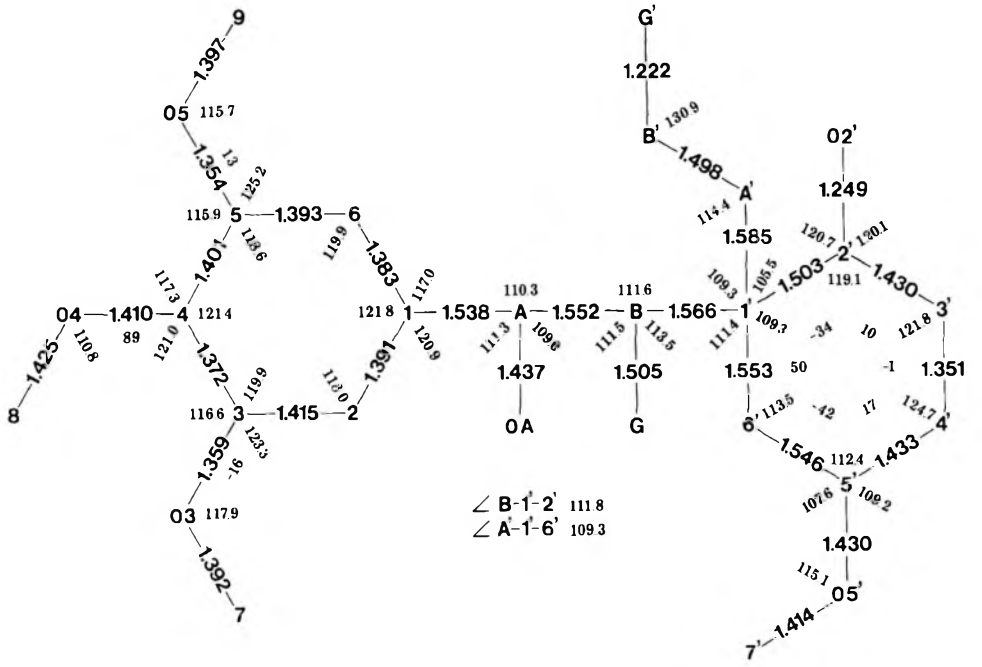


Figure 2. Bond lengths (Å), bond angles (degrees), and selected torsion angles (degrees) in the molecule of megaphone. Estimated standard deviations in bond distances are in the range 0.010–0.016 Å, in bond angles from 0.7 to 1.1°, and in torsion angles ~2°.

Table II. Selected Exocyclic Torsion Angles (Degrees)

C(6)–C(1)–C(α)–C(β)	94	C(α)–C(β)–C(1′)–C(α′)	178
C(6)–C(1)–C(α)–O(α)	−145	C(α)–C(β)–C(1′)–C(2′)	62
C(2)–C(1)–C(α)–C(β)	−80	C(α)–C(β)–C(1′)–C(6′)	−61
C(2)–C(1)–C(α)–O(α)	41	C(γ)–C(β)–C(1′)–C(γ′)	−55
C(1)–C(α)–C(β)–C(γ)	89	C(γ)–C(β)–C(1′)–C(2′)	−171
C(1)–C(α)–C(β)–C(1′)	−143	C(γ)–C(β)–C(1′)–C(6′)	66
C(β)–C(1′)–C(α′)–C(β′)	−55	C(1′)–C(α′)–C(β′)–C(γ′)	−113

is cis to the C(γ) methyl group, one of whose protons, H(γ_b), comes within 2.25 Å of H(α'_b) of the allyl side chain to dictate the slightly less than optimal value of −55° for the torsion angle C(β)–C(1′)–C(α′)–C(β′).

The cyclohexenone ring does not adopt the 1,2-diplanar conformation[10] which would lead to coplanarity of the five atoms, O(2′), C(2′), C(3′), C(4′), and C(5′), but instead adopts a flattened monoplanar (half-chair) conformation defined by the parameters ΔC_2(3′–4′) 7.5°, ΔC_s(3′) 13.1°, and ΔC_s(4′) 22.6°.[11] The four atoms C(2′), C(3′), C(4′), and C(5′) are rigorously coplanar, with the maximum deviation of an atom from their least-squares mean plane[12] being only 0.003 Å. C(6′) is displaced to one side of that plane by 0.41 Å and C(1′) to the other side by 0.22 Å. The 10° endocyclic torsion angle about C(2′)–C(3′) may be traced to the limiting contact O(2′)···H(β) of 2.52 Å. A similar half-chair conformation [ΔC_2(2–3) 3.6°, ΔC_s(3) 15°, and ΔC_s(1) 40.9°] has also been noted in the similarly substituted A ring of 4α-bromo-5α-androst-2-ene-1,17-dione.[13]

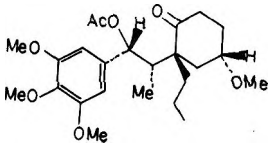
Bond lengths and valence angles in the molecule show expected deviations from ideal values and regular geometry. Steric crowding at C(1′) is reflected in the longer than usual C_{sp^3}–C_{sp^3} bond distances involving that atom, and the steric interactions between the in-plane methyl groups C(7) and C(9) and the ring protons lead to a familiar asymmetry of exocyclic valence angles at C(3) and C(5).[14] The two C–O–CH_3 bond angles for these groups are also significantly larger than that at O(4), again for the same steric reason, and this is also reflected in the differing C–O bond lengths in the three groups, the significant lengthening of C(4)–O(4) by comparison with C(3)–O(3) and C(5)–O(5) being attributable to loss of orbital overlap between O(4) and the phenyl ring. The terminal $CH{=}CH_2$ bond distance in the allylic moiety is much shorter than a normal ethylenic double bond, and the conformation adopted about C(α′)–C(β′), with $\phi = -113°$, has H(γ'_b) and H(α'_a) eclipsed and only 2.45 Å apart, reflected in the larger than usual valence angle at C(β′).

In the trimethoxyphenyl moiety, the two flanking –OCH_3 groups lie approximately in the plane of the phenyl ring, whereas the central –OCH_3 group lies in a plane inclined nearly normal to the ring. The three exocyclic C–O torsion angles are, in sequence from C(3) to C(5), −16, 89, and 13°. This pattern of torsion angles is similar to that observed in reserpine[15] and in mescalin hydrobromide[16] but differs from that characteristic of a variety of trimethoxyphenyl compounds showing activity as inhibitors of mitotic spindle formation.[17] These include certain colchicine derivatives,[18] steganacin and steganangin,[19] and podophyllotoxin[20] whose structures have been determined crystallographically. In these inhibitors, steric factors lead to a significantly nonzero exocyclic C–O torsion angle for one of the flanking –OCH_3 groups, as well as for the central group, with a value near ±90° being associated with greater inhibitory activity[18b] in colchicine derivatives. Margulis[18b] has suggested that the pattern of methoxy group orientation provides specificity in recognition of colchicine derivatives by a component of the microtuble structure by regulating the accessibility of a portion of the benzenoid ring. Both cis and trans arrangements of the two out-of-plane methoxy groups have been observed in inhibitors, and it therefore seems likely that if the potential acceptor of the flanking –OCH_3 site is a hydrogen bond donor it will be coplanar with the phenyl ring and, one may speculate, most probably lies along the direction which would be occupied by an in-plane O–CH_3 bond. This neolignan lacks the 90,90,0° pattern proposed as a requirement, and tests show[21] that neither it nor **2** shows measurable activity as inhibitors of spindle formation in sea urchin eggs.

In the crystal the molecules are linked in chains along the twofold screw axis by hydrogen bond formation between the O(α) hydroxy group of one molecule and the O(2′) carbonyl oxygen of an immediate neighbor (O···O, 2.80 Å). Other intermolecular contacts correspond to normal van der Waals separations.

Chromatography of fraction G over silica gel gave two active

(KB) fractions. The more polar fraction was subjected to extensive preparative TLC leading to megaphone acetate (**2**), $C_{24}H_{32}O_7$. Acetylation of megaphone (**1**) also afforded acetate **2** which was identical with the natural material. Hydrogenation of **2** gave a tetrahydro derivative, **7**. Inspection of the IR



and NMR spectra of both **2** and **7** indicates that there is no hemiketal formation in either case, thus confirming structure **2** for megaphone acetate.

The less polar active fraction from the chromatography of fraction G gave, after further chromatography, megaphyllone acetate (**3**), $C_{23}H_{28}O_7$. **3** differs from megaphone acetate (**2**) only in the replacement of two adjacent methoxyl groups in the aromatic ring with a methylenedioxy moiety. Structure assignment for **3** was based primarily on comparison of its NMR spectrum with that of **2**.

Experimental Section

General. Melting points were determined on a Mettler Model FP2 hot stage and are uncorrected. Ultraviolet absorption spectra were determined on a Beckman Model DK-2A recording spectrophotometer. Infrared spectra were determined on a Perkin-Elmer Model 337 recording spectrophotometer. Nuclear magnetic resonance spectra were determined on a JEOL PS-100 pulsed FT NMR spectrometer interfaced to a Texas Instruments JEOL 980A computer, with tetramethylsilane as an internal standard. Mass spectra were determined on Hitachi Perkin-Elmer Model RMU-6E and AEI Model MS-902 spectrometers. Values of $[\alpha]_D$ were determined on a Perkin-Elmer Model 141 automatic polarimeter. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. All thin-layer chromatography was carried out on silica gel 60 precoated plates, F-254 (E. Merck). Visualization of TLC was effected with short-wave UV and concentrated sulfuric acid–vanillin–ethanol (20:1:3) spray.

Extraction and Preliminary Fractionation. The ground root (1 kg) of *A. megaphylla* was continuously extracted with hot 95% ethanol for 24 h and the ethanol extract concentrated under reduced pressure to a dark brown residue (A, 81.3 g). Fraction A was partitioned between water (2 L) and chloroform (1 L) to give fractions B (12.2 g) and C (50.5 g), respectively. Fraction C was further partitioned between methanol–water (9:1, 0.5 L) and Skellysolve B (0.5 L) to give fractions D and E (5.7 g), respectively. Further partitioning of D with methanol–water (8:2, 1 L) and carbon tetrachloride (300 mL) gave fractions F and G (24.3 g), respectively. Final partitioning of F was carried out with methanol–water (6:4, 1 L) and chloroform (300 mL) to give fraction I (0.4 g) and H (17.4 g), respectively.

Megaphone (1). Fraction H was chromatographed on silica gel 40 (10% water, 1 kg) eluting with ether. Megaphone was crystallized from chloroform–ether: mp 151.5–152.5 °C (273 mg, 0.027%): $[\alpha]^{27}_D$ −23° (*c* 0.15, EtOH); UV λ_{max} (EtOH) 279 nm sh (ε 334), 269 (501); IR (CCl_4) 3600, 3375, 2938, 2830, 1670, 1590, 1505, 1460, 1420, 1330, 1235, 1130, 1012 cm^{-1}; NMR ($CDCl_3$) δ 7.00 (1 H, d, *J* = 10.5 Hz, –CH=C), 6.66 (2 H, s, aromatic), 6.48 (s, aromatic hemiketal), 6.02 (1 H, dd, *J* = 10.3, 2.2 Hz, –CH=C), 5.83 (1 H, m, –CH=C–), 5.30 (1 H, br, CH_2=C), 5.19 (1 H, br, CH_2=C), 5.02 (1 H, s, –OH), 4.64 (1 H, d, *J* = 1.5 Hz, Ar–CH–OH), 4.23 (1 H, m, MeO–CH–), 3.88 (6 H, s, MeO–), 3.83 (3 H, s, MeO–), 3.46 (3 H, s, MeO–), 3.37 (s, MeO, hemiketal–OMe), 2.57–2.19 (4 H, m, $-CH_2CH=CH_2$ and MeO–C′H–CH_2), 1.96 (1 H, br q, *J* = 6.9 Hz, CH_3CH), 0.77 (3 H, d, *J* = 7.1 Hz, Me–), 0.60 (d, *J* = 7.5 Hz, hemiketal–Me); ^{13}C NMR ($CDCl_3$) δ 11.84 (1 C, q, γ-C), 6.21 (hemiketal, q, γ-C), 36.3 (1 C, t, α′-C), 37.7 (1 C, t, 6′-C), 44.8 (1 C, d, β-C), 52.27 (1 C, s, 1′-C), 55.82 (2 C, q, 7,9-C), 56.40 (1 C, q, 8-C), 60.53 (1 C, q, 7′-C), 71.01 (1 C, d, 5′-C), 73.15 (1 C, d, α-C), 102.46 (2 C, d, 2,6-C), 119.11 (1 C, t, γ′-C), 128.67 (1 C, d, β′-C), 132.02 (1 C, d, 3′-C), 135.13 (1 C, s, 1-C), 140.52 (1 C, s, 4-C), 149.94 (1 C, d, 4′-C), 152.51 (2 C, s, 3,5-C), 193.37 (1 C, s, 2′-C); mass spectrum (chemical ionization, methane gas) *m/e* 391.2117 (M^+ + H, calcd for $C_{22}H_{31}O_6$, 391.2120), 373.2008 (calcd for $C_{22}H_{29}O_5$, 373.2015). Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.47. Found: C, 67.66; H, 7.72.

Oxidized Megaphone (4). Megaphone (20 mg) was dissolved in 2 mL of acetone and Jones reagent added dropwise with stirring until the color remained. Water was added and the product was extracted with ether. The ethereal extract was washed with water, dried over anhydrous magnesium sulfate, and then evaporated. The material was subjected to preparative TLC on silica gel eluting twice with ether (R_f 0.55) to give the product as an oil: $[\alpha]^{28}_D$ −32.8° (*c* 0.21, $CHCl_3$); UV λ_{max} (EtOH) 280 nm (ε 8989); IR (CCl_4) 2940, 1677, 1580, 1505, 1465, 1418, 1322, 1132 cm^{-1}; NMR ($CDCl_3$) δ 7.18 (2 H, s, aromatic), 6.93 (1 H, d, *J* = 10.2 Hz, –CH=C), 5.96 (1 H, dd, *J* = 10.0, 2.2 Hz, CH=C), 5.70 (1 H, m, –CH=CH_2), 5.22 (1 H, s, CH_2=C), 5.095 (1 H, s, CH=C), 4.30 (1 H, m, MeO–CH), 4.04 (1 H, q, *J* = 7.5 Hz, CH_3CH), 3.90 (9 H, s, MeO–), 3.46 (3 H, s, MeO–), 2.90 (1 H, dd, *J* = 10.5, 12.5 Hz, $-CCH_2COMe$), 2.51–2.11 (3 H, m, $-CH_2CH=CH_2$ and CCH_2COMe), 1.18 (3 H, d, *J* = 7.6 Hz, –Me); mass spectrum *m/e* 388 (M^+), 224, 195.

Tetrahydromegaphone (5). Megaphone (5 mg) was dissolved in 3 mL of absolute alcohol and 10 mg of 10% Pd/C added. The mixture was stirred under an atmosphere of hydrogen for 0.5 h and then filtered to give, after evaporation of solvent, tetrahydromegaphone (**5**) as an oil: $[\alpha]^{28}_D$ −22.3° (*c* 1.48, $CHCl_3$); UV λ_{max} (EtOH) 270 nm (ε 963), 279 sh (744); IR (CCl_4) 3595, 3420, 2950, 2928, 1585, 1502, 1458, 1415, 1365, 1328, 1232, 1130, 1100, 1012, 965 cm^{-1}; NMR ($CDCl_3$) δ 6.57 (2 H, s, aromatic), 5.25 (1 H, d, *J* = 9.7 Hz, Ar–CHO–), 3.85 (6 H, s, MeO–), 3.83 (3 H, s, MeO–), 3.34 (3 H, s, OMe), 2.78 (1 H, dd, *J* = 9.7, 7.6 Hz, $-CH_2COMe$), 2.09–1.32 (12 H, m), 0.96 (3 H, t, *J* = 7 Hz, Me–), 0.62 (3 H, d, *J* = 7.6 Hz, Me–); mass spectrum *m/e* 394 (M^+), 376, 198, 197, 181, 169, 155, 141, 138, 123.

Megaphone Acetate (2) (Synthetic). Megaphone (10 mg) was dissolved in 5 mL of pyridine and 0.5 mL of acetic anhydride and then heated at 50 °C for 6 h. Evaporation left a material which was submitted to preparative TLC (silica gel, eluted twice with ether) to give 10.1 mg of the acetate 2 as an oil: $[\alpha]^{22}_D$ −2.4° (*c* 0.29, EtOH); UV λ_{max} (EtOH) 269 nm sh (ε 1056), 279 sh (671); IR (CCl_4) 2970, 2930, 2830, 1740, 1665, 1585, 1500, 1450, 1415, 1375, 1325, 1135, 1015, 963, 920 cm^{-1}; NMR ($CDCl_3$) δ 6.91 (1 H, dt, *J* = 10.3, 2 Hz, –CH=), 6.55 (2 H, s, aromatic), 6.00 (1 H, dd, *J* = 10.3, 2.2 Hz, CH=C), 5.68 (1 H, s, ArCH–OAc), 5.46 (1 H, m, –CH=CH_2), 5.06 (1 H, s, CH_2=C), 4.95 (1 H, m, CH_2=C), 4.17 (1 H, m, CCHOMe), 3.88 (6 H, s, OMe), 3.82 (3 H, s, OMe), 3.46 (3 H, s, OMe), 2.63–1.75 (5 H, m), 2.12 (3 H, s, acetate), 0.93 (3 H, d, *J* = 7.4 Hz, –Me); mass spectrum *m/e* 432 (M^+), 266, 224, 197, 169.

Megaphone Acetate (2) (Natural). Fraction I was chromatographed on a column of silica gel 40 (5% H_2O, 1 kg) with ether saturated with water to give an active fraction (6 g) which was subjected to preparative TLC (twice with ether) on silica gel to give megaphone acetate (**2**) (R_f 0.52) as an oil. The material was identical in all respects with the synthetic material: mass spectrum (chemical ionization, methane gas) *m/e* 433.2225 (M^+ + H, calcd for $C_{24}H_{33}O_7$, 433.2226).

Tetrahydromegaphone Acetate (7). Megaphone acetate (**2**, 20 mg) was dissolved in 10 mL of absolute ethanol and stirred under a hydrogen atmosphere in the presence of 20 mg of 10% Pd/C. After 1 h the solvent and catalyst were removed leaving 17 mg of product which was purified by TLC: $[\alpha]^{21}_D$ −35.2° (*c* 0.91, $CHCl_3$); UV λ_{max} (EtOH) 269 nm (ε 872), 278 (654); IR (CCl_4) 2950, 2930, 1738, 1700, 1585, 1503, 1455, 1418, 1325, 1230, 1130, 1104, 1012 cm^{-1}; NMR ($CDCl_3$) δ 6.66 (2 H, s, aromatic), 5.76 (1 H, s, Ar-CH-OAc), 3.89 (6 H, s, MeO–), 3.82 (3 H, s, MeO–), 2.12 (3 H, s, acetate), 0.85 (3 H, d, *J* = 7.4 Hz); mass spectrum *m/e* 436 (M^+), 376, 302, 266, 208, 197, 181, 148, 141.

Megaphyllone Acetate (3). A fraction (1.5 g) eluting just prior to megaphone acetate on chromatography of fraction I was rechromatographed on silica gel 40 (5% water, 1 kg of silica gel) with ether. The active fraction (450 mg) was again chromatographed on silica gel 40 (1 kg) with ethyl acetate–hexane (1:1) and final purification was afforded by preparative TLC on silica gel (EtOAc–hexane) to give megaphyllone acetate (**3**, 214 mg) as an oil: $[\alpha]^{22}_D$ 0°; UV λ_{max} (EtOH) 275 nm (ε 1248), 284 sh (1027); IR (CCl_4) 2925, 1750, 1650, 1635, 1510, 1450, 1430, 1380, 1360, 1320, 1232, 1132, 1093, 961, 920 cm^{-1}; NMR ($CDCl_3$) δ 6.90 (1 H, d, *J* = 10.0 Hz, CH=C), 6.55 (1 H, d, *J* ~ 0.5 Hz, aromatic), 6.50 (1 H, d, *J* ~ 0.5 Hz, aromatic), 5.99 (1 H, dd, *J* = 10.0, 1.9 Hz, CH=C), 5.93 (2 H, s, $-OCH_2O-$), 5.65 (1 H, s, Ar–CH–OAc), 5.45 (1 H, m, –CH=CH_2), 5.06 (1 H, s, CH_2=C), 4.968 (1 H, br, CH_2=C), 4.18 (1 H, m, –CHOMe), 3.93 (3 H, s, –OMe), 3.45 (3 H, s, –OMe), 2.10 (3 H, s, acetate), 2.63–1.74 (5 H, m), 0.91 (3 H, d, *J* = 7.3 Hz, –Me); mass spectrum (chemical ionization, methane gas) *m/e* 417.1928 (M^+ + H, calcd for $C_{23}H_{29}O_7$, 417.1913), 357.1702 (calcd for $C_{21}H_{25}O_5$, 357.1695).

Crystal Data:[22] monoclinic; space group $P2_1$; *a* = 8.757 (3), *b* = 11.942 (3), *c* = 10.177 (3) Å; β = 101.29 (1)°; *U* = 1044 Å^3; *Z* = 2; D_x

= 1.242 g cm^{-3}; $F(000)$ = 420; Cu Kα radiation, λ = 1.5418 Å, μ = 7.4 cm^{-1}.

A single crystal of megaphone (1) suitable for x-ray diffraction study was grown from a solution of chloroform–ether. Unit-cell symmetry was determined from 25° precession photographs taken with Mo Kα radiation. The systematic absences, $0k0$ with k odd, uniquely defined the space group for this optically active material as $P2_1$. Unit-cell dimensions were found by a least-squares fit to the observed values of $\pm 2\theta$ for 20 strong general reflections measured on the diffractometer from a carefully centered crystal.

Intensity Data. A single-crystal plate 0.4 × 0.3 × 0.04 mm was mounted with the c^* axis parallel to the ϕ axis of a Picker full-circle diffractometer controlled by an XDS Sigma 2 computer. A single quadrant of reciprocal space to 2θ = 120° was surveyed with Cu Kα radiation made monochromatic by Bragg reflection from a highly oriented graphite crystal. The θ–2θ scan method was used with a scan range of 2° and a scan speed of 2° min^{-1}. Background intensity was measured for 15 s at both the beginning and end of each scan with both crystal and counter at rest. Scintillation counting was used with pulse-height analysis. Scattered intensity significantly above background [$I > 3\sigma(I)$] was found at 1318 of the 1564 independent locations surveyed. Stability of the experimental conditions was monitored by measurement of the intensities of two reference reflections after every 50 scans. The rms deviation from the mean intensity was in each case <1%. No absorption corrections were made.

Structure Determination and Refinement. The phase problem was solved by routine application of the program MULTAN[23] using the 245 $E(hkl) > 1.41$. Refinement was by the block-diagonal least-squares methods (3 × 3, 6 × 6 blocks) with anisotropic thermal parameters adopted for the nonhydrogen atoms. Hydrogen atoms, other than those of the C(7′) methyl group, were located from three-dimensional difference electron-density maps and their positions optimized by the assumption of standard geometries (C–H, 1.08 Å; H–C–H 109.5°; etc.). Contributions for these atoms in fixed positions and with fixed isotropic B values were included in the least-squares calculations. The function minimized was $\Sigma w(|F_o| - k|F_c|)^2$, with weights assigned in a standard manner.[24] Convergence was assumed with the largest shift to error ratio being 0.14 and the mean ratio being 0.03. The conventional unweighted and weighted residuals were 0.076 and 0.093. Despite the high value of the latter quantity, an analysis of the distribution of weighted differences showed no obvious anomalies. A final difference electron-density map contained no structurally significant information and had no density in excess of 0.26 e/Å^3.

An attempt was made to establish the absolute configuration of the molecule by making use of the anomalous dispersion effect for oxygen. Separate structure-factor calculations including the $\Delta f'$ and $\Delta f''$ terms[25] gave unweighted R values of 0.0759 and 0.0765, the lower residual being associated with the enantiomer described. These values indicate a significant difference between the two enantiomers at the 99% confidence level by the Hamilton R-ratio test,[26] but we have not been able to confirm this indication by consistent measurement of significant differences between Bijvoet pairs of reflections,[27] and so this assignment of absolute configuration should be viewed with caution.

The scattering functions used were taken from ref 28. With the exception of ORTEP and MULTAN, for which use was made of a CDC Cyber 172 computer, all programs used were written in this laboratory for the XCS Sigma 2 computer.

Registry No.—**1**, 64332-37-2; **2**, 64332-38-3; **3**, 64332-39-4; **4**, 64332-40-7; **5**, 64332-41-8; **7**, 64332-42-9.

Supplementary Materials Available: Atomic coordinates used for hydrogen positions, anisotropic thermal parameters for C and O atoms, equations of least-squares mean planes, and selected intramolecular and intermolecular contact distances (6 pages). Ordering information is given on any current masthead page.

References and Notes

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(2) This investigation was supported by grants from the National Cancer Institute (CA-11718 and CA-11760) and the American *Cancer* Society (CH-42M) and by a contract with the Division of Cancer Treatment, N.C.I., National Institutes of Health (NO1-CM-67002).
(3) Deceased Oct 19, 1976.
(4) Present address: U.S. Department of Agriculture, Albany, Calif. 94710.
(5) We thank Dr. Robert E. Perude, Jr., Medicinal Plant Resources Laboratory, U.S. Department of Agriculture, Beltsville, Md., for *A. megaphylla* roots collected in March 1975 in accordance with the program developed by the National Cancer Institute.
(6) The KB activity was assayed under the auspices of the National Cancer Institute. The procedures were those described in *Cancer Chemother. Rep.*, **25**, 1 (1962). **1**, **2**, and **3** showed cytotoxicity against KB cell culture at 1.70, 1.75, and 2.55 μg/mL, respectively.
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Dipolar Micelles. 6. Catalytic Effects of Betaine-Like Micelles on the Hydrolysis of Substituted Phenyl Esters

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The catalytic effects of five betaine-like micelles on the hydrolysis of substituted phenyl esters were measured. The micellaric catalysts are of the general structure $[CH_3(CH_2)_nN^+(CH_3)_2(CH_2)_mCOOH]Br^-$, where $n = 9$, $m = 1$ (I); $n = 15$, $m = 1$ (IA); $n = 9$, $m = 2$ (II); $n = 9$, $m = 3$ (III); and $n = 15$, $m = 3$ (IIIA); compound IV, $n = 0$, $m = 1$, is also included in this study for comparison purposes. The following esters were examined: 2,4-dinitrophenyl acetate (OPNA); 2,4-dinitrophenyl hexanoate (OPNH); 2,4-dinitrophenyl decanoate (OPND); 4-nitrophenyl decanoate (PND); 3-nitrophenyl decanoate (MND); 2,5-dinitrophenyl decanoate (OMND). The catalytic rate constants (k_n) and the nucleophilic catalysis by hydroxide ion (k_{OH}) were determined. From the pH–rate profiles of OPNH in I and in IV, it is observed that in spite of the similarities in the pK_a values of I and IV the catalytic reactivity of the latter is inferior to that of I. Therefore, it is possible to conclude that the catalytic efficiency of I stems from the micelle–substrate intracomplex reaction, which is not the case in IV. The isotope effect of 1.1 determined for OPND in micelle I indicates that catalysis occurs via nucleophilic attack by the carboxylate anion. The plot of log k_{OH} against log k_n in micelle III for esters possessing various leaving groups is nonlinear. Esters having good leaving groups, as in OMND and OPND, fall on a line of slope 1, and the value of the deuterium isotope effect $[k_n(H_2O)/k_n(D_2O)]$ equals 1.15. On the other hand, for esters bearing poor leaving groups, as in MND and PND, the respective values of the slope and the deuterium solvent isotope effect are 2.2 and 1.95. Therefore, it is suggested that in micelle III the catalytic hydrolysis of OMND and OPND follows the nucleophilic route, whereas that of MND and PND approaches the general-base type route.

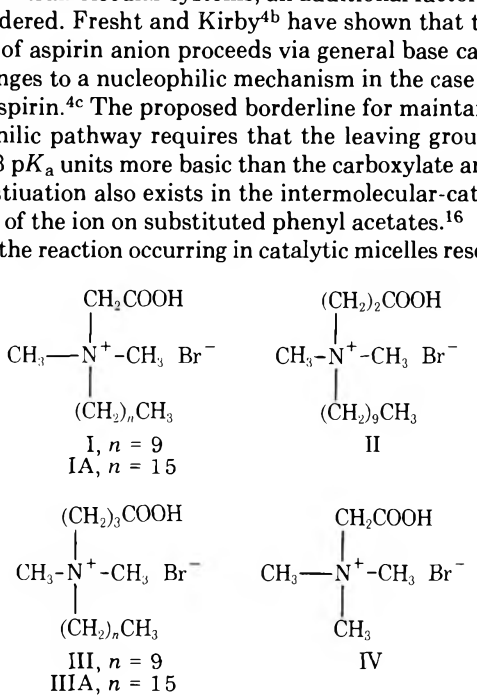
The participation of the carboxyl group in the catalytic route of proteolytic enzymes[1] has prompted many studies on monofunctional intramolecular catalysis as model systems.[2-10] Since at least two or more functional groups are known to participate in the active site of enzymes, chemical models consisting of two catalytic groups were tested.[11-14] As regards the mechanistic route of bimolecular[15] and intramolecular[5] catalysis of the carboxylate anion in phenyl acetate esters, Bruice and Benkavic[8c] concluded that a change in the mechanistic pathway from general base catalysis to nucleophilic catalysis occurs on the conversion of a bimolecular reaction to its intramolecular counterpart. This conclusion was also established in many other monoaryl esters of dicarboxylic acids.

The enhancement of nucleophilic catalysis in intramolecular systems is attributed to the propinquity effect.

With regard to the mechanistic route of the carboxylate anion in intramolecular systems, an additional factor has to be considered. Fresht and Kirby[4b] have shown that the hydrolysis of aspirin anion proceeds via general base catalysis and changes to a nucleophilic mechanism in the case of 3,5-dinitroaspirin.[4c] The proposed borderline for maintaining a nucleophilic pathway requires that the leaving group is at most 2–3 pK_a units more basic than the carboxylate anion. A similar stiuation also exists in the intermolecular-catalyzed reaction of the ion on substituted phenyl acetates.[16]

Since the reaction occurring in catalytic micelles resembles that of a unimolecular process due to the intracomplex formation of substrate–micelle, the participation of the carboxylate group in the hydrolytic pathway might shed light on other parameters affecting either the catalyst or the substrate. Therefore, we designed five types of micelle-forming agents, I, IA, II, III, and IIIA, in an attempt to elucidate microenvironmental and proximity effects in the intramolecular catalysis of these systems.

Catalytic micelles composed of carboxylic head groups might also serve as models for the bifunctional-catalyzed reaction since the internal pK_a value of the acidic species changes with an increasing amount of the dissociated[17] form.



Experimental Section

Reagents. All the micelle-forming agents have been described previously.[18a,b] The esters 2,4-dinitrophenyl acetate (OPNA), 2,4-dinitrophenyl hexanoate (OPNH), 2,4-dinitrophenyl decanoate (OPND), 2,5-dinitrophenyl decanoate (OMND), 4-nitrophenyl decanoate (PND), and 3-nitrophenyl decanoate (MND) were prepared and purified prior to use. The ester 2,4-dinitrophenyl hexanoate was prepared from hexanoyl chloride and 2,4-dinitrophenol in a solution of toluene followed by standard procedure. Anal. Calcd for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 4.96; N, 9.92. Found: C, 51.35; H, 5.10; N, 10.09.

pH Measurements. The pH of the solution used in kinetics studies was measured by a Radiometer Model 26 pH meter with a GK-23226 combined glass electrode. The pH meter was calibrated with two buffer solutions of pH 1.67 and 6.47.

pK_a Measurements. A Radiometer titration assembly was used for the titration cell. Thermostated water at 30 °C was circulated through the jacketed cell. The detergent solution (0.1 M) was titrated with sodium hydroxide, and pK_a values for the various ionization states were found from the plot of $[pH - \log [\alpha/(1-\alpha)]]$ vs. α, where α is the degree of ionization. All pK_a values used in the discussion and in Figure 5 are those of the half-neutralization point ($\alpha = 0.5$).

Kinetic Studies. All kinetic measurements were performed in 0.1 M detergents at an ionic strength of 0.8 M or 2.5 M KCl and at a temperature of 30 or 60 °C on a Gilford 2000 spectrophotometer. Stock solutions of esters were prepared in acetonitrile (0.015 M). The reaction was initiated by the injection of 20 μL of the esters into a preequilibrated solution of micelles. The appearance of absorbance was followed at 328, 285, 350, and 330 nm for 2,4-dinitrophenol, 2,5-dinitrophenol, 4-nitrophenol, and 3-nitrophenol, respectively. The buffers used were valeric acid (0.015 M), succinic acid (0.015 M), and phosphate (0.03 M) in the pH ranges 3.5–5, 5–6, and 6–7.5, re-

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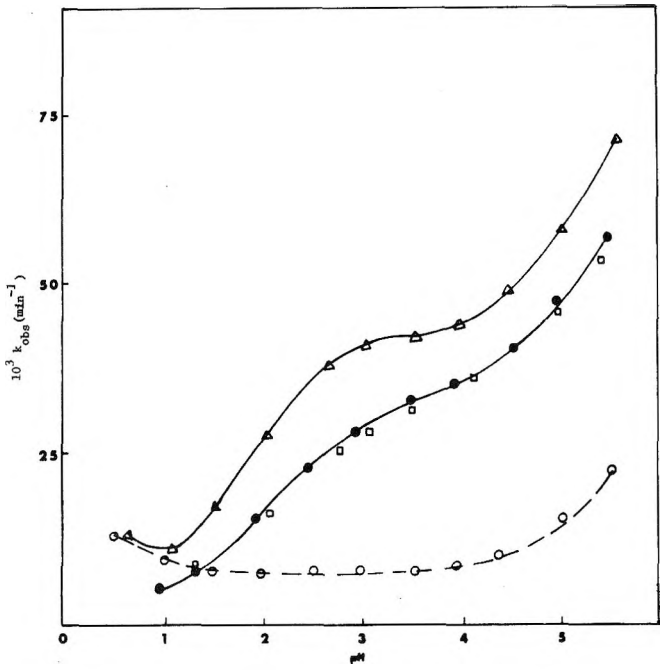

Figure 1. pH vs. k_{obsd} profiles for the hydrolysis of esters OPNA (-△-), OPNH (-●-), and OPND (-□-) in the presence of 0.1 M micelle I and OPNH (--○) in the presence of 0.1 M compound IV at 60 °C, μ = 0.8 M (KCl).

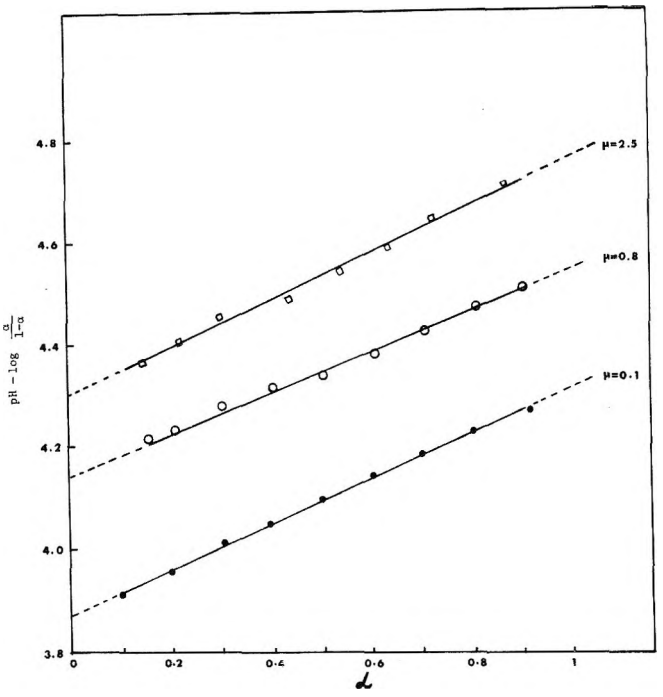

Figure 2. The variation of the intrinsic pK_a [pH − log $[\alpha/(1-\alpha)]$ with the degree of dissociation (α) for 0.1 M micelle III at 30 °C.

Table I. Hydrolytic Rate Constants[a] for 2,4-Dinitrophenyl Esters in 0.1 M Micelle I and in 0.1 M Compound IV

Catalyst; Rate constant	Esters OPNA	OPNH	OPND
I; 10^3k_n, min^{-1}	42	27	27
I; k_{OH}, min^{-1} M^{-1}	20 343	6850	8600
IV; 10^3k_2, min^{-1} M^{-1}	26	10	
IV; 10^3k_0, min^{-1}	10.7	4.5	
IV; k_{OH}, min^{-1}	45 000	28 000	

[a] Determined at 60 °C, μ = 0.8 M (KCl).

spectively. At pH's close to the pK_a of the micelles, the reactions were also carried out without any external buffers. In each case it was found that (a) on extrapolating the rate constants to zero buffer concentration the rate constants were identical with those obtained in the absence of a buffer and (b) the contribution of the buffers at the above-mentioned concentrations to the kinetic rate was not more than 2.5%.

The first-order rate constants of the micellar catalytic reaction were determined from the pH–rate constant profile (see Results and Discussion). The rate constants of the specific-base-catalyzed hydrolysis were determined using a phosphate or carbonate buffer in the pH range 7–8 or 9.5–10.5, respectively. From a linear plot of the first-order rate constant vs. the hydroxide ion concentration, the second-order rate constant (k_{OH}) can be calculated.

Results and Discussion

Figure 1 shows the pH–rate constant profiles for the esters OPNA, OPNH, and OPND in micelle I and for OPNH in IV. The rate constants of the catalytic group in micelle I (k_n) were determined from the plateau region of the pH–rate constant profile plots, where the contribution of the specific-base-catalyzed hydrolysis (k_{OH}) to the overall rate constant is negligible.

With compound IV as a catalyst, a broad low plateau is observed at 0.1 M, which is slightly dependent on the catalyst concentration. The plots of the first-order rate constants vs. the concentration of IV at pH 3.1 allows the second-order rate constant (k_2) and the spontaneous rate (k_0) to be determined.

From Figure 1 and Table I it is apparent that, in the hydrolysis of esters, the carboxylate anion in betaine catalyst IV and betaine-like catalyst micelle I operate by different mechanistic routes. This observation is unexpected since the pK_a values of the carboxylic group in I and IV are similar, and thus the groups should have a similar nucleophilic capacity (I, pK_a 2.20, and IV, pK_a 2.02, at 30 °C, μ = 0.8 M). The difference between the pK_a value of the nucleophile in IV and the leaving group in OPNH is in the range of 2–3 pK_a units, which is the proposed limit to maintain a nucleophilic catalysis. Therefore, in contrast to catalyst IV, it seems that the catalytic efficiency of I originates from the participation of the carboxylate anion in the substrate–micelle intracomplex reaction.

The suppressed nucleophilic reactivity of catalyst IV can be explained on the basis of strong electrostatic stabilization in the ground state as compared to the transition state. This is not the case in micellar intramolecular nucleophilic catalysis. In our previous studies,[18a,b] it was suggested that micelle I resembles an anionic micelle more than a cationic or uncharged micelle because of the strong binding of the negatively charged counterions to the surface. In analogy to other cationic micelles, it is assumed that at the experimental ionic strength of 0.8 M (KCl) 70–80% of the positively charged surface is neutralized.[20,21] The carboxylate anion therefore is less stabilized in the ground state and might react in nucleophilic displacements.

Furthermore, additional factors might also be responsible for the enhanced nucleophilic catalysis in micelle I. (a) Steric effects are assumed to orient both the reaction site and the attacking carboxylate anion to close proximity. The striking similarity in the hydrolytic rate of OPND and OPNH (Figure 1) points to the particular part played by the hydrophobic interactions bearing on the rate of hydrolysis.[18c] (b) From Figure 2 it can be inferred that the intrinsic pK_a value of micelle III increases by 0.3–0.7 unit as the dissociation of the acid is completed. Consequently, the nucleophilic efficiency of the carboxylate anion also increases. This phenomenon consti-

Table II. Rate Constants of OPND in 0.1 M Micelle I, II, and III

Micelle	Registry no.	Temp, °C	μ (KCl), M	pK_a	$10^3 k_n$, min^{-1}	k_{OH}, min^{-1} M^{-1}
I	39995-54-5	30	2.5	2.66	2.5	590
		60	0.8	2.20	27 (24.5)[a]	8600
IA	5466-51-3	60	0.8	2.70	82	
II	26543-24-8	30	2.5	3.76	13	500
III	26851-20-1	30	2.5	4.56	60	480
		60	0.8	4.30	650 (565)[a]	30000
IIIA	64252-74-0	60	0.8	4.53	1000	

[a] Determined in D_2O.

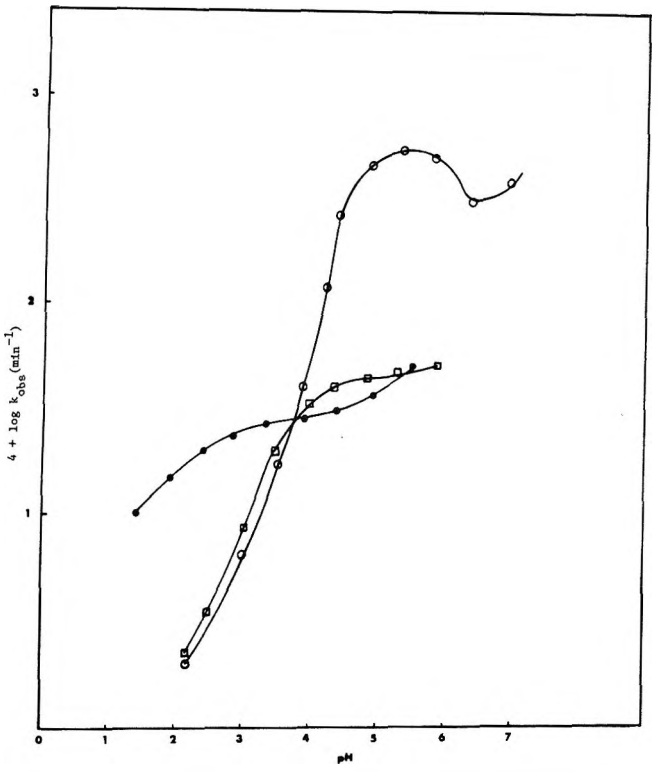

Figure 3. log k_{obsd} vs. pH profile for the hydrolysis of OPND in 0.1 M micelle I (-●-), II (-□-), and III (-○-) at 30 °C, μ = 2.5 M.

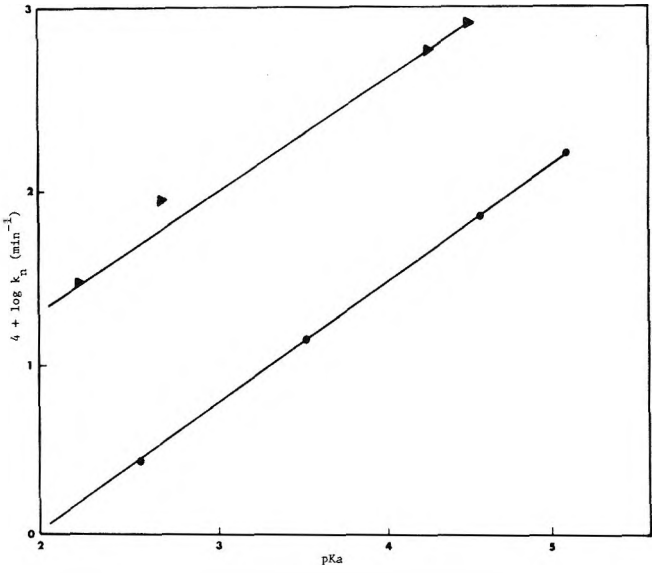

Figure 4. log k_r vs. pK_a of micelles I, II, and III in the hydrolysis of OPND (-●-) at 30 °C, μ = 2.5 M (KCl); (-▲-) at 60 °C, μ = 0.8 M (KCl).

tutes part of a more general microenvironmental effect which is one of the major factors of micellar reactivity.

Supporting evidence for the nucleophilic catalysis route in the hydrolysis of 2,4-dinitrophenyl esters with micelle I as a catalyst is also proven by the deuterium isotope effect. The experimental value of $k_n(H_2O)/k_n(D_2O)$ = 1.1 (Table II), determined for the hydrolysis of OPND, is in accord with this suggestion. Thus, it seems likely that in the presence of a more basic anion, such as in compounds II and III, a nucleophilic mechanism prevails.

Indeed, from the data represented in Table II and in Figure 3 it is apparent that the carboxylate anions of II and III participate in the hydrolysis of OPND, and the enhancing effect is also reflected by the increased pK_a values of the nucleophiles. Moreover, the kinetic isotope effect of 1.15 as observed in micelle III supports this view. Interestingly, it was noted that the reaction of OPND in micelles I, IA, II, III, and IIIA provides a linear Brønsted correlation with the basicity of the carboxylate residue (see Figure 4). The β values of 0.7 and 0.75, obtained from the plots in Figure 3, are in accord with other reported β values for intramolecular nucleophilic reactions of carboxylate anions in substituted phenyl succinates, phenyl glutarates,[15,14a] and phthalate esters[8f] (i.e., β = 0.8–1.14). This latter range of β values was observed also in other systems of nucleophilic reactions, where the leaving group and the attacking nucleophile are of similar basicity.[16,22] It is well-known that a change in the degree of ionization of a micellized head group affects the hydrophilic–lipophilic balance of micelles. Consequently, the question asked is if one can draw a conclusion from the β value attributed to the pK_a of half-neutralization on the reaction pathway. However, in the betaine series it was found that the slope of the linear relationship [pH − log [α/(1 − α)]] vs. α for micelle III at 30 °C, μ = 0.8 M, is very similar to that of micelle I measured under the same conditions. The corresponding values are 0.42 and 0.48. This fact indicates that in the betaine micelles the Brønsted β value is almost independent of the extent of ionization. Thus, we are inclined to accept the possibility that in analogy to nonmicellar systems the β coefficient, as obtained in the betaine-like micelles, is an additional criterion for a nucleophilic route. Moreover, additional results (Figure 5) indicate that as the basicity of the ester leaving group increases the hydrolytic pathway changes to an intramolecular general base catalysis. Inspection of Figure 5 reveals that on plotting log k_n vs. log k_{OH} for OPND, OMND, PND, and MND in micelle III the points are not linearly correlated. The esters possessing good leaving groups (OPND and OMND) fall on a line of slope 1, while the esters PND and MND lie on a line of slope 2.2. That such a phenomenon might reflect a change in reaction mechanism is well-known in analogous systems.[16,23,24] Furthermore, it was experimentally found that the deuterium isotope effect [$k_n(H_2O)/k_n(D_2O)$] of PND in micelle III is 1.95. Thus, it seems likely that, whereas the esters OPND and OMND are hydrolyzed via a nucleophilic mechanism, the

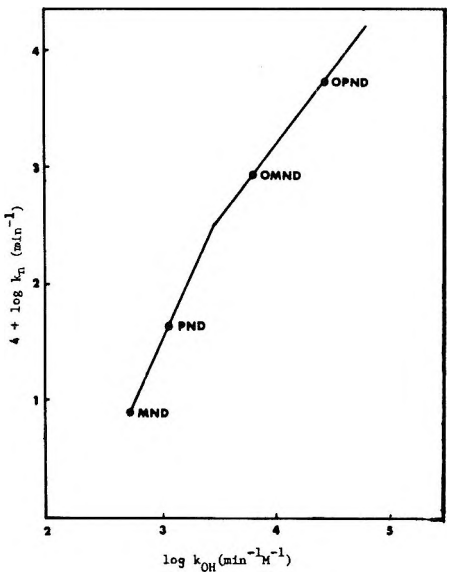

Figure 5. log k_n vs. log k_{OH} for substituted phenyl decanoate esters in 0.1 M micelle III at 60 °C, μ = 0.8 M (KCl).

hydrolytic pathway of PND and MND approaches a general base catalysis.

The latter results are unexpected since it is known that carboxylate anion will react as an intramolecular nucleophile even if the difference in pK_a between the attacking and leaving groups is large (ΔpK_a = 5–6 units). This is in marked contrast to the corresponding intermolecular systems where a ΔpK_a of 2–3 units might change the mechanism to general base catalysis. Since the hydrolysis of PND in the presence of micelle III was interpreted as indicating general base catalysis, it seems likely that the efficiency of the carboxylate anion in a micellar system closely resembles an intermolecular catalysis. (The pK_a of *p*-nitrophenol at 25 °C and that of micelle III at 30 °C is 7.2 and 4.3, respectively.) On the other hand, the above-mentioned results (Figure 1, compounds I and IV) indicate that betaine-like micelle I is a better nucleophile than betaine IV, due to the ability of I to react in an intramicellar pathway. Therefore, it can be assumed that, when compared to an intermolecular reaction, the carboxylate anion in a micellar system is probably a more efficient catalyst, but much less efficient than in other intramolecular reactions.

In order to gain more kinetic information on the catalytic potency of the carboxylate anion in micellar and other intramolecular systems, it is necessary to compare systems bearing both identical leaving groups and carboxylic groups of equal basicity. Because of this limitation, we estimated the rate constant of a model derived from mono-2,5-dinitrophenyl glutarate, where the pK_a value of the free carboxylic group is that of compound III. On using the data of Bruice and Pandit[8b] for the hydrolysis of mono-*p*-bromophenyl glutarate, and considering a Brønsted β coefficient of 1.14 for the leaving groups and 0.8 for the carboxylic nucleophile, it was found that the first-order rate constant of mono-2,5-dinitrophenyl glutarate, possessing a carboxylic group of pK_a = 4.3, is 238 min^{-1} at 30 °C. On the other hand, the pseudo-first-order rate constant of OPNA in 0.1 M acetate is 0.0033 min^{-1}. (The second-order rate constant of OPNA with acetate anion is 0.032–0.034 min^{-1} M^{-1} at 25 °C.[16,25]) These kinetic results conform with the view of an intermediate role of the carboxylate anion in a micellar system. The carboxylate anion in micelle III is 238/0.06 $\simeq$ 4000 times less reactive than the corresponding carboxylate anion in an intramolecular system of glutaric acid monoester, but 0.06/0.0033 $\simeq$ 18 times more reactive than the acetate ion in a bimolecular reaction.

It is noteworthy that, in contrast to other intramolecular systems, the capability of the carboxylate anion in micelles to participate in hydrolytic reactions is restricted. It was experimentally observed that the rate constant of PNA hydrolysis in micelle I is 0.0025 min^{-1} (μ = 0.8 M, 80 °C). The latter value was also found for the hydrolysis of PNA in the absence of catalyst I. However, on replacing micelle I (pK_a = 2.25 at 80 °C, μ = 0.8 M) by micelle IA (pK_1 = 2.45 at 80 °C, μ = 0.8 M), the first-order rate constant increased to a value of 0.0043 min^{-1}. These results indicate that in the case of micelle I a ΔpK_a of 5 units between the leaving group of the ester and the carboxylic group of the micelle is the upper limit for catalysis.

Although carboxylic micelles exhibit a low catalytic potency, the system is of general interest due to its ability to affect reactions in an analogous way to polyelectrolytes and to induce various microenvironmental effects in the vicinity of the reaction site.

Inspection of Table II reveals that the specific base catalysis reaction in the presence of micelles I, II, and III is strongly dependent on the ionic strength of the solution. Whereas at an ionic strength of 0.8 M micelle I inhibits the reaction rate as compared to micelle III, at an ionic strength of 2.5 M the reaction rates in the presence of the three micelles are similar. However, the relative catalytic power of the above micelles is not effected by a change in the ionic strength. This suggests that the carboxylic head groups of micelles I, II, and III reside in similar regions in the vicinity of the surface and are exposed to the same degree of electrostatic interactions. Consequently, the folded conformation seems to be the preferred state of the alkyl head group in micelles II and III.

An interesting phenomenon can be noticed in Figure 3. The pH–rate profile of OPND in micelle III exhibited a bell-shaped curve in the pH range of 4.5–6.5. From potentiometric measurements of polymeric acids and bases, it is known that the intrinsic dissociation constant of the polyion is dependent on its degree of ionization.[17] Similar behavior was observed in micelle III (Figure 2). At first glance it seems that the kinetic bell shape might be derived from a bifunctional catalysis due to the change of the pK_a value at various degrees of ionization, but the small difference of 0.5 unit in ΔpK_a does not support this suggestion. Moreover, in experiments aimed to detect bifunctional catalysis in a mixed micelle system (I + III, 1:1), no evidence for this pathway could be obtained. The possibility that the bell shape is derived from electrostatic effects operating on the specific base catalysis can also be excluded: (a) the contribution of specific base catalysis at a pH range of 4.5–6.5 is very small as compared to the catalytic rate of the carboxylate anion; (b) at higher temperatures, where the rate of the specific base catalysis is increased, the bell shape is less pronounced.

A reasonable explanation for the bell-shaped pH–rate profile can be given on the basis of the reverse reaction in which the phenoxide ion of the leaving group attacks the anhydride formed during the reaction. Therefore, it can be assumed that (a) the diffusion of the leaving group from the Stern layer should be slow, (b) the phenoxide ion should reside in close proximity to the anhydride intermediate, and (c) the pK_a value of the phenoxide ion should be greater than that of the micellar carboxylic group. Indeed, further observations indicate that the reverse reaction is favorable.

On adding 8.5×10^{-4} M 2,4-dinitrophenol to the reaction mixture, which consisted of OPND in micelle III, the first-order rate constant was reduced. Moreover, at pH 6.4 (peak), the rate constant was decreased by 2.2-fold and at pH 5.4 (trough) by 1.3-fold. These results are in accord with the assumed reversibility of the reaction and might account for the bell shape in Figure 3.

A further study is in progress.[21]

Acknowledgment. This work was supported by a grant from the Joint Research Fund of the Hebrew University and Hadassah.

Registry No.—IV, 5938-06-7; OPNA, 4232-27-3; OPNH, 64252-81-9; OPND, 61063-34-1; OMND, 61063-35-2; PND, 1956-09-8; MND, 61063-38-5; hexanoyl chloride, 142-61-0; 2,4-dinitrophenol, 51-28-5.

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Syntheses of Electronegative Substituted Tetrathiafulvalene Derivatives

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Tetracyano-, tetracarbomethoxy-, and tetraphenyltetrathiafulvalene have been prepared from 4,5-disubstituted 1,3-dithiole-2-thiones in the presence of triphenylphosphine and trialkyl and triphenyl phosphites. Acid- and base-catalyzed hydrolyses of tetracyano- and tetracarbomethoxytetrathiafulvalenes led to the formation of new derivatives. A new synthetic route to parent tetrathiafulvalene was established.

The phenomenon of high electrical conductivity[1] in the complex of tetrathiafulvalene (TTF) with tetracyanoquinodimethane (TCNQ) has recently aroused intense interests. Several synthetic methods[2] of TTF derivatives have been reported so far: (i) deprotonation of 1,3-dithiolium ions;[3] (ii) desulfurization of 1,3-dithiole-2-thiones with trivalent phosphorus compounds;[4] (iii) pyrolysis of orthothiooxalates;[5] (iv) reaction of acetylenes with carbon disulfide.[6,4b] As a series of our study[4f,7,8] on the reactions of thiocarbonyl compounds with trialkyl phosphites, we previously reported[4f] the successful synthesis of tetracyanotetrathiafulvalene (**1**) by the reaction of 4,5-dicyano-1,3-dithiole-2-thione (**2**) with triphenyl phosphite. In this paper, we wish to report the application of this synthetic method to the preparation of tetracarbomethoxytetrathiafulvalene (**3**) from 4,5-dicarbomethoxy-1,3-dithiole-2-thione (**4**) and tetraphenyltetrathiafulvalene (**5**) from 4,5-diphenyl-1,3-dithiole-2-thione (**6**). Tetracyano-,[4d-f] tetracarbomethoxy-,[4b,g] and tetraphenyltetrathiafulvalene[3b] have all been previously synthesized. By the acid hydrolyses of **1** and **3**, tetraamidetetrathiafulvalene (**7**) and dicarboxytetrathiafulvalene (**9**) were newly obtained, respectively. The alkaline hydrolysis of **3** led to the formation of tetracarboxytetrathiafulvalene (**8**), which was converted to its anhydride (**10**) and **9**. Pyrolysis of **9** provided a new synthetic route to parent tetrathiafulvalene in good yields.

Results and Discussion

The synthesis of tetracyanotetrathiafulvalene (**1**) by the reactions of 4,5-dicyano-1,3-dithiole-2-thione (**2**) with triphenylphosphine, trialkyl, and triphenyl phosphite was briefly reported in our preceeding communication.[4f] The procedure in detail is described in the Experimental Section of this paper. In the reaction of **2** with triphenylphosphine in benzene under reflux, **1** was obtained only in 6% yield and the betaine

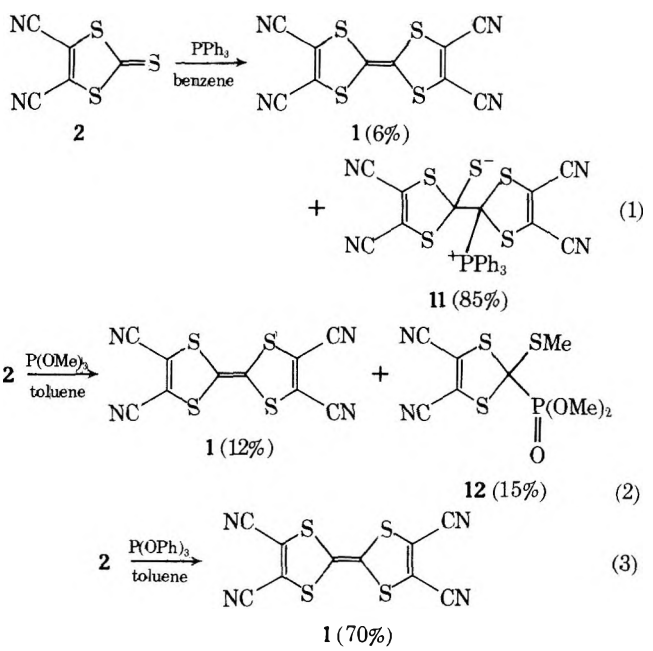

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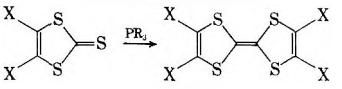
Table I. Desulfurizaton Reaction of Disubstitated 1,3-Dithiole-2-thiones



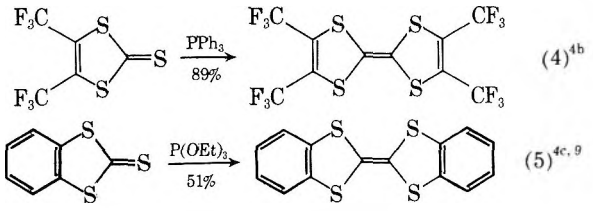
X	R	Product	Yield, %
CN	Ph	1	6
CN	OMe	1	12
CN	OPh	1	71
COOMe	Ph	3	90
COOMe	OMe	3	63
Ph	OMe	5	21

11 as the major product. Heating of 11 in dichlorobenzene afforded 1. The reaction of 2 with trimethyl phosphite gave 1 in 12% yield and the Arbuzov reaction type product which was formed by the methyl rearrangement. When triphenyl phosphite was used in order to inhibit the alkyl rearrangement, 1 was obtained in 70% yield.

Similar desulfurization reaction of 4,5-dicarbomethoxy-1,3-dithiole-2-thione (4) successfully yielded tetracarbomethoxytetrathiafulvalene (3), which was firstly prepared from dimethyl acetylenedicarboxylate and carbon disulfide.[4b] Different from the reaction behavior of 2, the reaction of 4 with triphenylphosphine in toluene under reflux was found to lead the exclusive formation of 3. However, the reaction proceeded too slowly. After 30 h, 60% of 4 was recovered. The reaction of 4 with trimethyl phosphite, which proceeded faster than with triphenylphosphine, gave 3 in 63% yield and several unidentified products. Triphenyl phosphite also reacted with 4 to give 3, but the reaction rate was extremely low. The preparation of 3 in high yield (90%) was achieved by the reaction of 4 with triphenylphosphine in xylene under reflux for 10 h.

Tetraphenyltetrathiafulvalene (5) was also prepared from 4,5-diphenyl-1,3-dithiole-2-thione (6) and trimethyl phosphite in 21% yield, together with several unknown by-products. The results are summarized in Table I.

The synthetic studies of TTF derivatives using trivalent organophosphorus compounds have recently been reported by several groups. Tetrakis(trifluoromethyl)tetrathiafulvalene



(4)[4b]

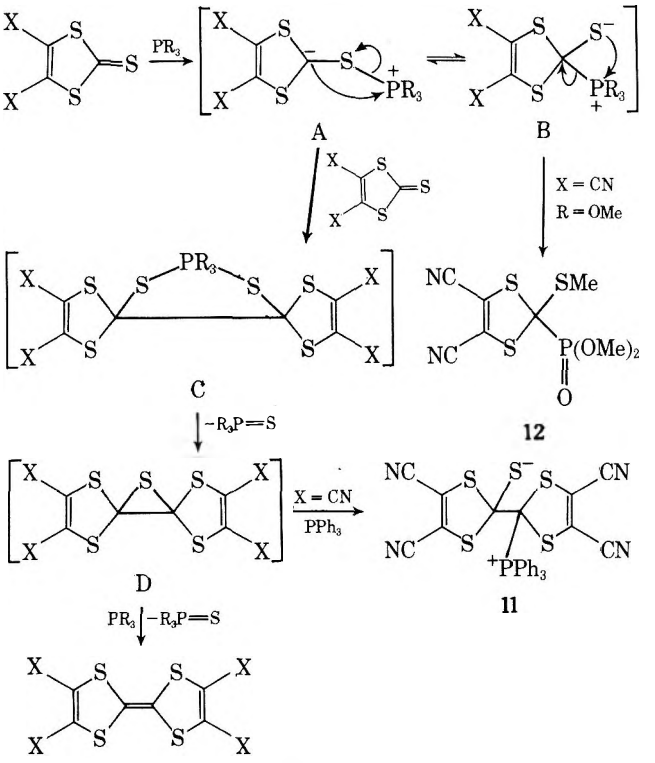
(5)[4c,9]

was prepared by the use of triphenylphosphine[4b] and dibenzotetrathiafulvalene by the use of triethyl phosphite.[4c,9] Desulfurization with trialkyl phosphite has also been reported for tetracyano-[4d-f] and tetracarbomethoxytetrathiafulvalenes.[4g] It is obvious from these results that 1,3-dithiole-2-thiones substituted by electron-withdrawing groups generally undergo desulfurization reaction with triphenylphosphine or trialkyl phosphites.

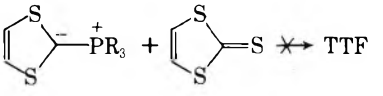
On the other hand, the reactions of 1,3-dithiole-2-thiones substituted by electron-donating groups in the presence of trivalent phosphorus compounds were carried out, but the tetrathiafulvalene derivatives were not obtained. For example, the reaction of dimethyl-1,3-dithiole-2-thione with trimethyl phosphite in toluene at reflux temperature gave a variety of unidentified products but no TTF derivative.

A mechanistic interpretation of the reaction of 2 and 4 with trivalent phosphorus compounds is shown in Scheme I. As seen in Scheme I, initial thiophilic attack of PR_3 at the thio-

Scheme I

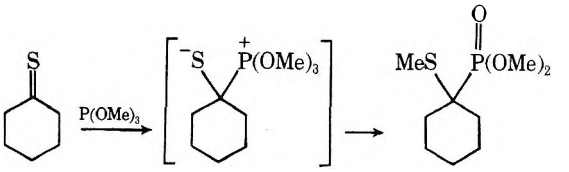


carbonyl sulfur atom of 1,3-dithiole-2-thione would afford ylide A (C^-–S–P^+R_3), which might isomerize to betaine B (S^-–C–P^+R_3). Similar ylide–betaine isomerization was suggested by Ogata et al.[10] in the reaction of thiobenzophenone with trialkyl phosphites. The intermediate A would react with another 1,3-dithiole-2-thione to give the intermediate C followed by the intermediate D and result in the formation of the TTF derivatives. When triphenylphosphine was used in the reaction of 4,5-dicyano-1,3-dithiole-2-thione, triphenylphosphine would attack at the carbon atom of the thiirane ring of D to afford the betaine 11. A similar reaction scheme via the ylide type intermediate A was mentioned by Schrowsky et al.[9] in the reaction of benzo-1,3-dithiole-2-thione with triethyl phosphite. Miles et al.[4e] proposed another mechanism for desulfurization via ylide intermediate E. However, Cava[11] has recently presented the experimental results that in the reaction of ylide E with 1,3-dithiole-2-thione no TTF was obtained. This finding lends more support for our proposed mechanism via the intermediate A.



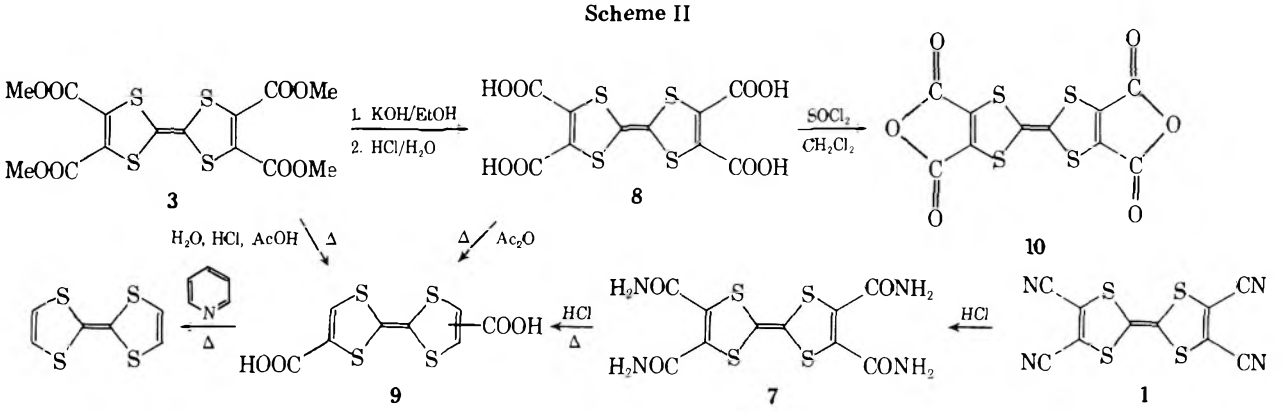
E

The phosphonic acid ester 12 is considered to be obtained from the betaine type intermediate B by the alkyl rearrangement. Such alkyl rearrangement has been reported from this laboratory[7] in the reaction of alicyclic thiones with trialkyl phosphites.



Hydrolysis of 1 in concentrated hydrochloric acid at room temperature afforded light purple crystallines melting at high temperature (>360 °C). The elemental analysis and spectral data were all consistent with the formation of tetraamidetetrathiafulvalene (7). Hydrolysis of 3 gave two different acid

Scheme II



derivatives depending on the reaction condition: tetracarboxytetrathiafulvalene (8)[4g] under basic condition and dicarboxytetrathiafulvalene (9)[12] under acidic condition, respectively. It is noteworthy that 9 was directly synthesized in high yield by refluxing aqueous acetic acid solution of 3 in the presence of hydrochloric acid, since 1,3-dithiole-2-thiones substituted with carboxy groups did not react with trivalent phosphorus compounds to give tetrathiafulvalenes and moreover parent tetrathiafulvalene was directly synthesized from 9 as seen in Scheme II.

On the other hand, refluxing an ethanol solution of 3 with potassium hydroxide followed by acidification afforded light purple tetracarboxytetrathiafulvalene (8). The reaction of 8 with thionyl chloride in methylene chloride gave bis(anhydride)tetrathiafulvalene (10) quantitatively, which was identified by its infrared absorptions at 1850 and 1870 cm^{-1} characteristic for unsaturated five-membered anhydride and its mass spectrum. Attempts to prepare 10 as usual by refluxing of 8 in acetic anhydride resulted in the formation of 9 in good yield, in connection with which the decarboxylation of 8 has been reported not to be attained in basic solvent such as pyridine.[4g]

The parent TTF is well known to be easily air-oxidized, while the TTF derivatives obtained in this work, 1, 3, 7, 8, 9, and 10, are very stable against air oxidation, which is consistent with the calculated results by HMO method that the energy levels of highest occupied molecular orbitals of those derivatives are quite low compared with that of the parent TTF.

Although parent TTF was first prepared by deprotonation of 1,3-dithiolium cation,[3a] the Du Pont group's synthesis[12] is by far the best method for preparing large amounts of TTF, and the procedure of Wudl et al.[3f] is easy to carry out for smaller scale reactions. We tried to prepare TTF by combining our facile preparation of dicarboxytetrathiafulvalene (9) and the decarboxylation of 9 by Hartzler et al.[12] This route to TTF including only three steps (4 → 3 → 9 → TTF) with a total yield of 53% based on 4.[13] Scheme II shows the synthetic route and the relating experimental results.

The colors of 1 (deep purple), 3 (brown), 7 (light purple), 8 (light pruple), 9 (red), and 10 (dark brown) indicate that they have absorption in longer wavelength than parent TTF (yellow orange). The absorption band at the longest wavelength of 1 exhibits a blue shift by changing solvents: λ_{max} 502 nm (benzene), 500 (methylene chloride), 492 (acetonitrile), 493 (DMF), and 480 (methanol), which can be explained in terms of intramolecular charge transfer. The band of 3 also exhibits a similar solvent shift to short wavelength: λ_{max} 461 (*n*-hexane), 462 (benzene), 455 (methylene chloride), 446 (DMF), and 445 (ethanol).

Experimental Section

Melting points were determined using a Büchi melting point apparatus in sealed capillary tubes and are uncorrected. The electronic absorption spectra were measured on a Hitachi ESP-3T recording photometer, the infrared spectra were determined on a Hitachi grating IR spectrophotometer, Model 215, the mass spectra were determined on a Hitachi RMU-6C or RMS-4 mass spectrometer, the ^1H NMR spectra were recorded on a Varian HA-100 spectrometer, and the ^{13}C NMR spectra were recorded on JEOL FX-60. Elemental analyses were carried out at the Elemental Analytical Center of Kyoto University.

4,5-Dicyano-1,3-dithiole-2-thione (2) was prepared as described by Klingsberg,[14] and **4,5-dicarbomethoxy-1,3-dithiole-2-thione (4)** was prepared as described by O'Connor et al.[15] The phosphine and phosphites were commercial materials and were used as received.

Reaction of 2 with Triphenylphosphine. To a boiling solution of 2 (0.200 g) in 15 mL of dry benzene under nitrogen was added a solution of triphenylphosphine (0.450 g) in 10 mL of benzene. After several minutes the orange solid began to precipitate. The resulting solid was filtered, washed with cool benzene, and recrystallized from methylene chloride–ether to give 0.270 g (85%) of orange crystals (11): mp 169–172 °C dec; IR (KBr) 2210, 2170, 1415 cm^{-1}. Anal. Calcd for $C_{28}H_{15}N_4PS_5$: C, 56.17; H, 2.53; N, 9.36. Found: C, 56.27; H, 2.56; N, 9.42.

The filtrate was concentrated and column chromatographed on silica. The red band upon evaporation gave 0.018 g (6%) of dark purple needles after recrystallization from methylene chloride–ether: mp 264–265 °C dec; IR (KBr) 2208, 1535, 1182, 1066 cm^{-1}; *m/e* 304.

Anal. Calcd for $C_{10}N_4S_4$: C, 39.46; N, 18.41; S, 42.14. Found: C, 39.04; N, 18.38; S, 42.37.

Reaction of 2 with Trimethyl Phosphite. A mixture of 1.00 g of 2 and 1.50 g of trimethyl phosphite in 50 mL of toluene was heated under reflux for 6 h under nitrogen. The resulting dark solution was concentrated and chromatographed on silica eluting with benzene. The yellow band upon evaporation gave 0.117 g (15%) of yellow crystals 12: mp 140–141 °C; IR (KBr) 2220, 1547, 1240 (P=O stretching), 1180 (P–O–Me), 1054–1012 cm^{-1} (P–O–R); ^1H NMR ($CDCl_3$) δ 2.75 (s, 3 H, SMe), 3.83 (d, $J_{c\text{-}p}$ = 11.2 Hz, 6 H, P–O–Me). Anal. Calcd for $C_8H_9N_2O_3PS_3$: C, 31.16; H, 2.94; N, 9.09; P, 10.05. Found: C, 31.32; H, 2.70; N, 9.11; P, 10.31.

In this reaction, 1 was obtained in 12% yield.

Reaction of 2 with Triphenyl Phosphite. A mixture of 1.008 g of 2 and 15 mL of triphenyl phosphite in 50 mL of toluene was heated under reflux overnight and concentrated. The dark residue was subjected to chromatography on silica eluting with benzene. The red band upon evaporation gave 0.603 g (71%) of 1.

$\Delta^{2,2'}$-Bis(4,5-dicarbomethoxy-1,3-dithiolidene) (3). A. A mixture of 0.250 g of 4 and 0.416 g of triphenylphosphine in 20 mL of toluene was heated under reflux for 30 h. The red solution was concentrated and chromatographed on silica eluting with chloroform. The initial colorless band contained triphenylphosphine and triphenylphosphine thioxide. The yellow band led to recovery of 0.150 g of 4. The subsequent red band upon evaporation gave 0.082 g (92%) of brown crystals: mp 168–169 °C (lit. 169–170 °C[4b]); IR (KBr) 1745, 1716, 1576, 1290, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.83 (s); *m/e* 436. Anal. Calcd for $C_{14}H_{12}O_8S_4$: C, 38.52; H, 2.77; O, 29.32. Found: C, 38.54; H, 2.94; O, 29.57.

B. A mixture of 0.506 g of 4 and 1.00 g of trimethyl phosphite in 30 mL of toluene was allowed to reflux for 5 h. A dark residue after concentration was chromatographed on silica to give 0.222 g (62%) of 3.

C. A mixture of 0.250 g of 4 and 0.530 g of triphenylphosphine in 10 mL of xylene was heated under reflux for 10 h. A dark residue after evaporation of solvent was chromatographed on silica to give 0.195 g (90%) of 3.

$\Delta^{2,2'}$-Bis(4,5-diphenyl-1,3-diphenyl-1,3-dithiolidene) (5). A

mixture of 286 mg of 4,5-diphenyl-1,3-dithiole-2-thione (**6**), 0.5 mL of trimethyl phosphite, and 10 mL of toluene was heated under reflux under nitrogen for 24 h. The red solution was evaporated and the residue was recrystallized from acetonitrile to give 54 mg (21%) of orange crystals, mp 261.5–263 °C (lit. 262–263 °C).[3b] Spectral data were identical with authentic sample.

$\Delta^{2,2'}$-Bis(4,5-dicarbamide-1,3-dithiolidene) (7). A mixture of 76 mg of finely ground **1** and 10 mL of concentrated hydrochloric acid was allowed to stand for 2 weeks at room temperature under stirring. The solid was filtered and washed with water and with ethanol. After drying 74 mg (79%) of purple solids was obtained: mp > 360 °C; IR (KBr) 3600–2900, 1670, 1390–70 cm^{-1}; UV (DMF) λ_{max} 449 nm (log ϵ 3.31), 319 (4.18); *m/e* 376. Anal. Calcd for $C_{10}H_8N_4O_4S_4$: C, 31.90; H, 2.14; N, 14.88; O, 17.00. Found: C, 31.67; H, 2.29; N, 14.57; O, 17.10.

$\Delta^{2,2'}$-Bis(4,5-dicarboxy-1,3-dithiolidene) (8). A mixture of 0.637 g of **3**, 1.0 g of potassium hydroxide, and 40 mL of ethanol was heated under reflux for 1 h. The resulting orange potassium salts were filtered and dissolved in 15 mL of water. Neutralization with hydrochloric acid yielded purple solids. These were filtered and dried without washing, because of water solubility. Recrystallization from DMF–ether gave 0.590 g (100%) of light purple crystals: mp > 360 °C; IR (KBr) 3600–2700, 1550, 1503, 1360 cm^{-1}; UV (DMF) λ_{max} 477 nm (log ϵ 3.33), 311 (4.17), 302 (4.10). Anal. Calcd for $C_{10}H_4O_8S_4$: C, 39.25; H, 9.41; O, 29.88. Found: C, 39.21; H, 9.56; O, 29.97.

$\Delta^{2,2'}$-Bis(4(5)-carboxy-1,3-dithiolidene) (9). A. 8 (63 mg) was suspended in 5 mL of acetic anhydride and heated under reflux for 0.5 h. Red crystals precipitated and were filtered and dried to give 36 mg (76%) of **9**: mp > 360 °C; IR (KBr) 3400–3200, 1650, 1540, 1425, 1295 cm^{-1}; ^{13}C NMR (DMSO-d_6) δ from TMS 160.0 (C*=O), 132.6 (=C*CO), 128.7 (=C*H), 110.1 (S_2C=CS_2). Anal. Calcd for $C_8H_4O_4S_4$: C, 32.86; H, 1.38; O, 21.89. Found: C, 32.84; H, 1.49; O, 22.08.

B. A mixture of 0.400 g of **3**, 18 mL of water, 18 mL of concentrated hydrochloric acid, and 50 mL of glacial acetic acid was heated under reflux for 3 h. The resulting solids were filtered and dried and yielded 0.250 g (92%) of red crystals **9**.

$\Delta^{2,2'}$-Bis(4,5-dicarboxy anhydride-1,3-dithiolidene) (10). A mixture of 60 mg of **8**, 0.5 mL of thionyl chloride, and 3 mL of methylene chloride was heated under reflux for 1 h. The dark solution was evaporated to give the dark residue, which was crystallized from *n*-hexane to give 53 mg (100%) of **10** as dark brown needles: mp > 360 °C; IR (KBr) 1850, 1780, 1560, 1255 cm^{-1}; *m/e* 344.

Anal. Calcd for $C_{10}O_6S_4$: C, 34.88; O, 27.88. Found: C, 35.01; O, 27.92.

Tetrathiafulvalene, $\Delta^{2,2'}$-Bis(1,3-dithiolidene). A mixture of 141 mg of **9** and 4 mL of pyridine was sealed in a heavy wall glass tube under argon. The tube was heated at 250 °C for 1.5 h. After cooling, the solvent was evaporated. The dark residue was extracted with three 10-mL portions of acetonitrile. The extracts were evaporated and the residue was sublimed at 110 °C (0.3 mmHg) to give 63 mg of orange product (63%). The structure was identified by the ^1H NMR spectra.

Registry No.—**1**, 55052-32-9; **2**, 1005-10-3; **3**, 26314-39-6; **4**, 7396-41-0; **5**, 23780-79-2; **6**, 17534-37-1; **7**, 64414-04-6; **8**, 59269-79-3; **9**, 51751-19-0; **10**, 64414-03-5; **11**, 64414-02-4; **12**, 55513-26-3; triphenylphosphine, 603-35-0; trimethyl phosphite, 121-45-9; triphenyl phosphite, 101-02-0; TTF, 31366-25-3.

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Carbon Acidity. 55. Acidity of 8,8-Dimethyl-8,12b-dihydrobenz[*a*]fluoranthene. Conjugating Effect of a Coplanar Phenyl[1]

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The preparation of the title compound (DDF) is described. Its anion is of the 9-phenylfluorenyl type with the phenyl group constrained to coplanarity with the fluorenyl moiety by the *gem*-dimethyl bridge. The pK_{CsCHA} of DDF, 15.45, is 3.0 pK units more acidic than 9-phenylfluorene. Of the total ΔpK_{CsCHA} of 7.6 units from fluorene itself, about one-third is attributed to polar effects and two-thirds to conjugation.

The phenyl group in 9-phenylfluorenyl anion (PF^-) is known to conjugate only weakly with the fluorene nucleus, undoubtedly because interactions with the 1- and 8-fluorene hydrogens prevent coplanarity. 9-Fluorene substitutents that exert inductive effects only have been shown to give a linear correlation in a plot of the relative acidity (pK_{CsCHA}) in the cesium cyclohexylamide (CsCHA) system against the polar substituent constant σ^*.[2] According to this correlation, the phenyl substituent with $\sigma^* = 0.600$[3] would provide a pK_{CsCHA} of 19.5 for a 9-phenylfluorene (PF) in which the phenyl group exerted a polar effect only.

In an important recent paper, Bordwell and McCollum[4]

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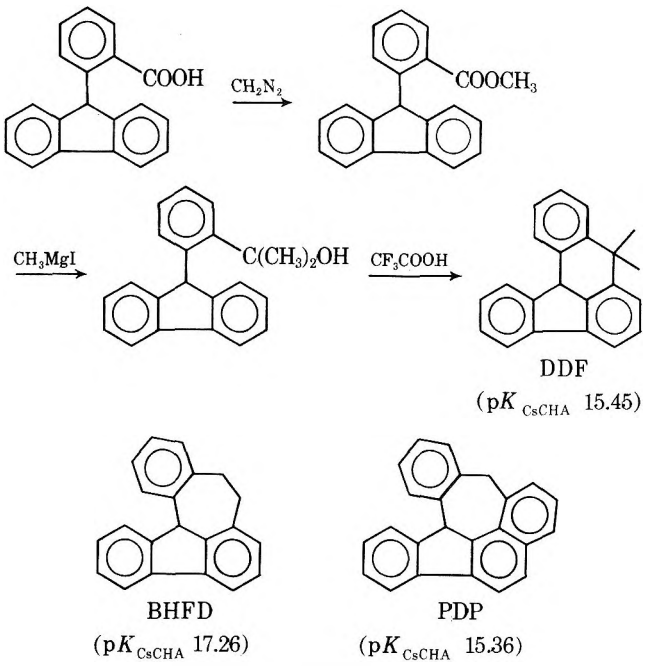
Chart I



have shown that aliphatic alkyl groups alone cannot be used to establish a meaningful $\rho\sigma^*$ or $\rho\sigma_I$ relationship. Their results spectacularly confirm the earlier analysis of Ritchie and Sager[5] that the polar effect of alkyl groups does not differ from that of methyl. We have long been wary of basing polar effect correlations on alkyl groups alone and have generally incorporated the benzyl group in our series. The benzyl group has a well-defined polar substituent constant and should lead to reasonable conclusions regarding the role of polar effects. Hence, the above derivation of the polar effect in 9-phenylfluorene should not be far in error.

In an alternative derivation of this number we recall that the phenyl substituent in the anion derived from 10-phenyl-9,9-dimethyl-9,10-dihydroanthracene (PDDA) is essentially nonconjugating. For example, the *p*-biphenylyl group is only 0.3 pK units more acidifying in this system than the phenyl group itself (Figure 1).[6] This small effect may be compared with the ΔpK of 2.2 reported for toluene and *p*-methylbiphenyl.[7,8] Hence, the pK_{CsCHA} difference of 2.3 between the phenyl compound PDDA and the methyl derivative 9,9,10-trimethyl-9,10-dihydroanthracene, TDA, may be associated with the polar effect difference of an essentially nonconjugating phenyl and a methyl substituent. A similar ΔpK_{CsCHA} of 2.0 is found for phenyl and methyl substituents on dibenzocycloheptadiene (Figure 1) in which phenyl conjugation is still more restricted. If a ΔpK of this magnitude is applied to the pK_{CsCHA} of 22.3 for 9-methylfluorene, we derive a pK of about 20 for the hypothetical PF with a nonconjugating phenyl group. Hence, both independent approaches give comparable values. These values are only 1–1.5 pK units higher than the pK_{CsCHA} of 18.49 associated with PF itself and indicate that the phenyl in this system is only weakly conjugating. Weak conjugation is also indicated by the fact that 9-*p*-biphenylylfluorene is only 0.4 pK units more acidic in aqueous Me_2SO than PF itself.[9] From a more detailed study of phenyl substituent effects on equilibrium acidities of 9-arylfluorenes, Cockerill and Lamper[9] concluded that the phenyl group was seriously twisted and that conjugation effects were only partially transmitted to the 9-fluorenyl position. Bordwell et al.[10] have also recently discussed the variable role of phenyl groups on the equilibrium acidities of carbon acids.

In order to evaluate the effect of a fully coplanar and conjugating phenyl group in the 9-phenylfluorenyl π system, we

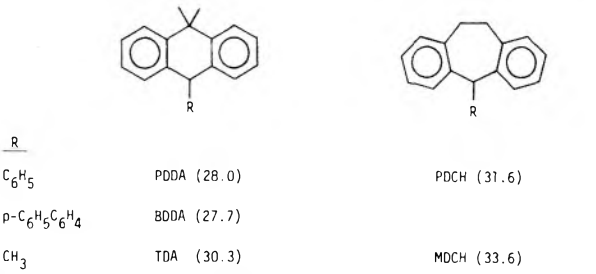


Figure 1. pK_{CsCHA} values for bridged di- and triarylmethanes (ref 6).

prepared the hydrocarbon 8,8-dimethyl-8,12b-dihydrobenz[*a*]fluoranthene (DDF), in which a *gem*-dimethylmethylene group bridges the ortho position of the phenyl and the 1-fluorenyl position of a 9-phenylfluorene. The synthesis was straightforward and is outlined in Chart I. The spectrum of the cesium salt was obtained in CHA and was used to obtain the pK_{CsCHA} of the hydrocarbon by reference with 1,12-(*o*-phenylene)-7,12-dihydropleiadene (PDP), whose pK_{CsCHA} has been determined previously to be 15.36.[11] The value thus obtained for the pK_{CsCHA} of DDF is 15.45 ± 0.13.

In the anion from DDF, models show clearly that the phenyl group is locked into effective coplanarity with the fluorenyl anion. In order to use its pK value to estimate a value for a hypothetical 9-phenylfluorenyl system with a strain-free coplanar phenyl we need to assess the relative contributions of strain effects in DDF, the polar effect of the bridge, and the rotational entropy effect.[6] No accurate assessment of the strain effect is feasible but it is likely to be relatively small, particularly since some of the strain components are common to the hydrocarbon and its anion. Note that DDF can also be viewed as a dihydroanthracene derivative with an *o*-phenylene group bridging the anthracene 1 and 9 positions. It seems most likely that DDF is slightly more acidic than an equivalent hypothetical strain-free system.

The rotational entropy effect results from the circumstance that the phenyl group in 9-phenylfluorene has some rotational mobility which is reduced in the anion. In DDF the bridge freezes such rotational motion in both carbon acid and carbanion. This effect operates to make 9-phenylfluorene less acidic than it would be in the absence of this effect. For a freely rotating phenyl group in the carbon acid the effect has been estimated to be roughly 1 pK unit; the effect is less if the phenyl group has partially restricted rotation in the carbon acid as is probably the case for 9-phenylfluorene. That is, we expect that the rotational entropy effect by itself would suggest a pK_{CsCHA} corresponding to our hypothetical planar 9-phenylfluorenyl anion as several tenths units higher than DDF.

Finally, we consider the polar effect of the alkyl bridge in DDF. From ring-substituent effects on acidities of fluorene[12] and phenyl substituent effects on 9-phenylfluorene,[9] we estimate the effect of the dimethylmethylene bridge to be somewhat less than 1 pK unit; hence, the hypothetical coplanar 9-phenylfluorenyl anion which has no substituents would be lower than DDF by this magnitude. Thus, we find that the strain and rotational entropy effects are expected to cause a pK change in the opposite direction to and of comparable magnitude to the alkyl substituent effect of the bridge.

The foregoing analysis suggests that the pK_{CsCHA} corresponding to a hypothetical strain-free planar 9-phenylfluorenyl anion is about 15.5, or 7.5 units lower than fluorene itself. Compared to the value of 19.5–20 derived above for a 9-phenylfluorenyl system in which the phenyl group exerts only a polar effect, we derive a 4–4.5 pK unit effect for conjunction itself. This result of a 2.5–3 pK unit polar effect and a 4–4.5

pK unit conjugation effect may be compared with our earlier comparison[13] of triphenylmethane and triptycene wherein we concluded that roughly one-third of the greater ion pair acidity of triphenylmethane relative to cyclohexane was due to a polar effect. Note that this 2:1 ratio of conjugation to polar effects is substantially smaller than the ~4:1 ratio estimated by the Bordwell group[10] for 9,10-dihydroanthracene and xanthene in Me_2SO.

An interesting application of the present result involves additional comparison with the pK_{CsCHA} of 17.26 determined previously[11] for 8,9,13b-trihydrotribenzo[a,cd,h]azulene (bishomofluoradene, BHFD). This hydrocarbon is a 9-phenylfluorene with an ethano bridge between the phenyl and the fluorene. Dreiding models indicate that in the carbanion derived from BHFD the phenyl group is locked at an angle of about 30° relative to the fluorenyl plane. The three points now available for 9-phenylfluorenyl systems (0°, 15.5; 30°, 17.3; 90°, 19.5–20) form a smooth curve in which interpolation of the pK_{CsCHA} of real PF corresponds to a twist angle of about 50°. This value is somewhat higher than earlier and cruder estimates.[9,14]

Finally, we point to an interesting comparison with some recent work of the Bordwell group.[10] In Me_2SO, acetone and acetophenone have pK values of about 25 and they showed that a phenyl substituent increases the acidity of each compound by about 7 pK units. These compounds are sufficiently free of steric effects that the phenyl group is expected to conjugate fully. Fluorene has about the same pK value and we have now shown that a fully conjugating phenyl also has about a 7 pK unit acidifying effect. This finding gives added justification to their proposed correlation between the pK of a parent acid and the phenyl group substituent effect, at least for delocalized carbanions. Indeed, this correlation may provide a significant new tool for establishing the localized or delocalized nature of carbanions.

Experimental Section

8,8-Dimethyl-8,12b-dihydrobenz[*a*]fluoranthene (DDF). 9-(*o*-Carboxyphenyl)fluorene[15] was esterified with diazomethane in ether at 0 °C. Alternative methods of esterification failed to give the desired compound.[16] To a Grignard solution prepared by adding 12.5 mL (0.2 mol) of methyl iodide to 4.89 g (0.202 mol) of magnesium in 40 mL of ether held at reflux for 1.5 h was added a solution of 6.05 g (0.020 mol) of 9-(*o*-carbomethoxyphenyl)fluorene in benzene diluted with ether. After 0.5 h, the burgundy red solution turned opaque and the solid magnesium salt of the alcohol precipitated out of the solution. After further reflux for 2 h, the reaction was worked up with saturated ammonium chloride and ether extraction. The dried extract yielded 4.04 g (67%) of *o*-(9-fluorenylphenyl)dimethylcarbinol, mp 160–163 °C (cyclohexane).

Anal.[17] Calcd for $C_{22}H_{20}O$: C, 88.0; H, 6.7. Found: C, 87.9; H, 6.6.

To 70 mL of distilled trifluoroacetic acid was added 0.515 g (1.72 mmol) of the above carbinol. The solution was refluxed for 2 h, cooled to room temperature, and poured into a separatory funnel containing ether and water. The ether layer was washed with dilute potassium carbonate and then water. Evaporation of the dried ether extract gave an oil which was dissolved in a minimum amount of benzene and streaked onto two 20 × 20 cm, 2.0-mm thick fluorescent preparative TLC plates (Brinkman Instruments, Inc.). The plates were developed three times using 5% benzene–hexane. The fastest moving strip was extracted in a Sohxlet extractor with ether. Removal of the ether under reduced pressure left a light yellow oil which crystallized from benzene–ethanol as fine white needles, mp 102–104 °C, 0.289 g (60%).

Anal.[17] Calcd for $C_{22}H_{18}$: C, 93.6; H, 6.4. Found: C, 93.4; H, 6.4.

Other carbonium ion ring-closure attempts failed to give the desired hydrocarbon.[16]

Spectral and Equilibrium Measurements. The apparatus and procedure for spectral and equilibrium measurements at room temperature have been described previously.[18,19] The spectrum of DDF as measured on a Cary 118 spectrophotometer is: λ_{max} (ϵ) 528 (2538), 500 (3062), 470 nm (sh).

The indicator used on the DDF equilibrium runs was 1,12-(*o*-phenylene)-7,12-dihydropleiadene (PDP) which was prepared from material supplied by Professor P. T. Lansbury.[20] Its spectrum has been reported previously.[11] The equilibrium between these cesium salts was measured in five runs[16] with the concentration ranges: DDF, 5–10 × 10^{-4} M and its cesium salt 1–4 × 10^{-4} M; PDP, 1–4 × 10^{-3}M and its cesium salt 4–12 × 10^{-4} M. The equilibrium constant for PDPCs + DDF $\rightleftarrows$ DDFCs + PDP is 0.83 ± 0.25, corresponding to a pK_{CsCHA} for DDF of 15.45 ± 0.13 (stand dev).

Registry No.—DDF, 64611-29-6; 9-(*o*-carboxyphenyl)fluorene, 64611-30-9; diazomethane, 334-88-3; methyl iodide, 74-88-4; 9-(*o*-carbomethoxyphenyl)fluorene, 64611-31-0; *o*-(9-fluorenylphenyl)-dimethylcarbinol, 64611-32-1; trifluoroacetic acid, 76-05-1.

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Solid-State Racemization of 4,4′-Diamino-1,1′-binaphthyl

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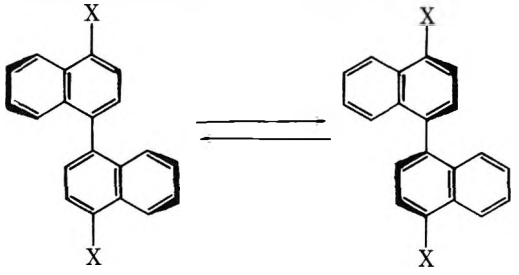
The rates of solid-state racemization of several polycrystalline samples of optically active (*S*)-(+)-4,4′-diamino-1,1′-binaphthyl (i.e., naphthidine) have been determined at 130 and 150 °C. A rapid initial reaction follows an approximate first-order relationship, but the rates are dependent on characteristics of individual samples and are increased by grinding the crystals. Racemization occurs by conversion of a eutectic crystal form to a racemic compound. The phase relationships of this polymorphic system show the racemate (mp 202 °C) to be the stable form up to the transition point of 197 °C and the eutectic form to be stable from 197 °C to its melting point of 204 °C. Reversal of the racemization reaction (at 130–195 °C) is possible simply by small variations in temperature; i.e., racemic naphthidine can be made to resolve into the optically active eutectic form by heating at 203 °C (via a solid → melt → solid transformation) or at 197 °C (via a direct solid → solid transformation). The samples showed a strong bias for production of dextrorotatory naphthidine.

The thermal conversion of racemic into optically active 1,1′-binaphthyl is a solid-state reaction that shows a high degree of stereochemical control.[1] In solution, optically active binaphthyl is spontaneously racemized quite rapidly ($t_{1/2}$ = 15 min at 50 °C), yet the opposite reaction, which produces optically active from racemic compound, may proceed nearly completely in a solid-state transformation at temperatures of 97 to 150 °C. At 150 °C, the interconversion of enantiomers, which occurs by rotation around the interannular bond, is very



X = H, (*R*)-(−)-1,1′-binaphthyl (*S*)-(+)-1,1′-binaphthyl
X = NH_2, (*R*)-(−)-naphthidine (*S*)-(+)-naphthidine

rapid. Nevertheless, the highly stereospecific selection and growth of one enantiomer onto chiral crystals result in the production of predominately one enantiomorphic solid. The optical resolution in the solid state therefore proceeds in a completely reversed direction from the well-known racemization in the liquid phase. A choice in the chirality of product is possible when "seeds" of one enantiomorph,[2] or chiral materials of a variety of types,[3] selectively induce the nucleation of one enantiomer.

In contrast to this solid-state resolution reaction of binaphthyl, it has been briefly reported that 4,4′-diamino-1,1′-binaphthyl (i.e., naphthidine) *loses* optical activity on storage for several months ($t_{1/2}$ ~2 months at room temperature).[4] This difference in the thermal resolution of binaphthyl and the reported racemization of its 4,4′-diamino derivative prompted a more thorough investigation of the solid-state thermal reactions of neat, polycrystalline naphthidine. We report results here which allow an interpretation of the opposite reactivities of the solid states of binaphthyl and naphthidine.

Experimental Section

4,4′-Diamino-1,1′-binaphthyl. Racemic naphthidine was prepared by the method of Cohen and Oesper,[5] except that 28 g of 1-naphthylamine was used with 34 mL of concentrated hydrochloric acid and the mixture was first warmed on a steam bath to give a light purple precipitate of the amine salt. The mixture was then cooled to 0–3 °C before diazotization by the referred method and quantities given. The reduction and rearrangement of 1,1′-azonaphthalene were carried out as described,[5] and the product was crystallized by slow cooling from 3:1 ethanol–pyridine after filtering the hot solution. This naphthidine (7.1 g, 26%) was obtained as well-formed, light brown plates, mp 200–202 °C (lit.[5] mp 198–199 °C).

Naphthidine was further purified by sublimation at 2–3 mm between a bath temperature of 190 °C and an air-cooled cold finger. The crystals obtained were colorless or slightly pink leaf-like plates and were always in the racemic form (see below). The prominent infrared bands of the racemic solid, which distinguished it from the eutectic solid, are at 695, 785, 795, 892, and 1015 cm^{-1}. Other absorptions are at 760 and 837 cm^{-1}, which are both much stronger than corresponding bands from the eutectic solid.

Resolution of Naphthidine. Method A. Racemic naphthidine was resolved by the classical procedure of Theilacker and Hopp[4] using ammonium (+)-α-bromo-D-camphor-π-sulfonate to give the diastereomeric naphthidinesulfonate salt. Specific rotations for various batches were $[\alpha]^{22}_D$ 91–93 ° (lit.[4] $[\alpha]_D$ +99°) in 60% acetone–water after recrystallization from 60% ethanol. To obtain free naphthidine, the salt was suspended in a 10-fold weight of ice-cold ethanol, and dilute ammonium hydroxide was added until the solution was basic and the salt completely dissolved. Ice was then added immediately to the solution, and the free (+)-naphthidine precipitated. The product had $[\alpha]_D$ +43, 40, 41, and 40° in four batches, mp 202–204 °C (lit.[4] $[\alpha]_D$ 42 ± 1° and mp 206–207 °C). These eutectic crystals showed fewer infrared peaks than the racemate and had prominent absorption at 760 (relatively sharp), 827 (relatively weak and broad), and 1010 and 1030 cm^{-1} (both relatively weak).

Method B. "Spontaneous resolution" of previously sublimed racemic samples into eutectic crystals was carried out with ~10-mg samples in evacuated vials at 197–203 °C. (If air was present dark green or black colored material was produced which interfered with polarimetric analysis.) Eutectic crystals were produced over a period of up to 3 days. Preheating of racemic samples at 192–193 °C for up to 5 h decreased the number but increased the size (up to 7 mg) of the eutectic crystals formed at 197 °C. The contents of individual vials were dissolved completely for polarimetric analysis (see text for the results), or individual crystals were dissolved in a minimum of acetone for analysis. The highest rotations from single crystals obtained were $[\alpha]_D$ +49 ± 1° (6.95-mg crystal) and $[\alpha]_D$ −49 ± 1° (3.35-mg crystal).

Kinetic Method. The loss of optical activity in neat, polycrystalline samples of (+)-naphthidine was determined from a set of weighed samples, ~10 mg each, in 2-mL sealed vials completely immersed in a constant-temperature silicone oil bath. At an appropriate time, an individual sample was withdrawn and cooled to room temperature. Each sample was completely dissolved in acetone and transferred to a 2-mL volumetric flask which was diluted to the mark. Optical rotations were obtained at the sodium D line (5890 Å) using a Bendix type 143A automatic polarimeter with a 1-cm length cell calibrated with standard sucrose solutions.

Infrared spectra were obtained from the suspension of solid naphthidine in Nujol mulls on sodium chloride plates. Calorimetric analyses of naphthidine samples (~5 mg) were carried out by using a Perkin-Elmer Model DSC-1B differential-scanning calorimeter at a scanning rate of 10°/min.

Results and Discussion

Rates of Racemization. Several different individual batches of optically active (+)-naphthidine, mp 202–204 °C,

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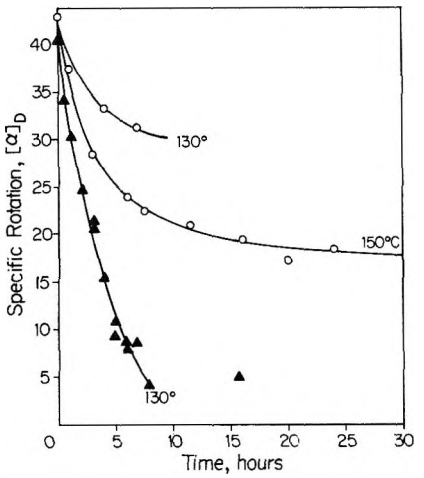

Figure 1. Loss of specific rotations in samples of (+)-naphthidine heated at 130 and 150 °C: ○, preparation 1; ▲, preparation 2.

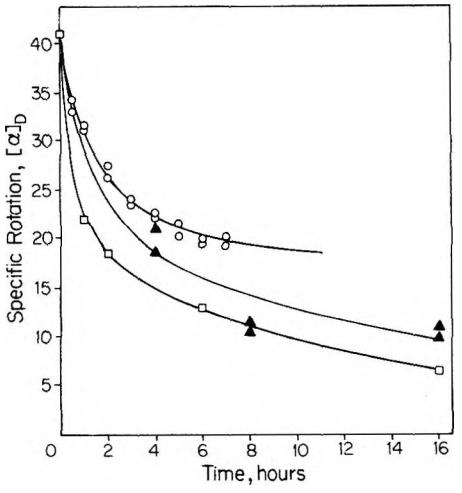

Figure 2. Loss of specific rotations in samples of (+)-naphthidine (preparation 3) heated at 130 °C: ○, initial preparation; ▲, ground samples; □, more highly ground samples.

were heated at constant temperatures of 150 or 130 °C and samples were periodically analyzed to determine loss of optical activity. In each case the initial specific rotations rapidly dropped, but some optical activity persisted for much longer times of heating; e.g., in one sample rotation dropped to 50% in 6 h at 130°, but 30% of the original activity was present after 220 h. Although individual samples from a single preparation racemized in a fairly smooth manner in the initial part of the racemization, a great variation in rate was obtained from different batches. This is shown in Figure 1, which shows the decrease in specific rotation for two different batches of (+)-naphthidine at 130 and 150 °C. Sample 1 racemized slowly at 130 °C, and its rate at 150 °C was still slower than that of another sample (2) at 130 °C.

The wide variation of observed rates for various preparations of (+)-naphthidine points up the great sensitivity of solid-state reaction kinetics to the previous history of the sample.[6] The rapid initial reaction shown in Figure 1 is opposite to the much more commonly observed induction periods followed by rapid acceleration for a solid-state reaction. The polycrystalline state of the sample, in which growth of the racemic product can immediately occur over a relatively large surface area, may be reflected in the observed initial rapid reaction. Consistent with this is that further division of the crystallites of the sample by grinding resulted in more rapid reaction to a greater extent (as shown in Figure 2 for a third preparation of (+)-naphthidine).

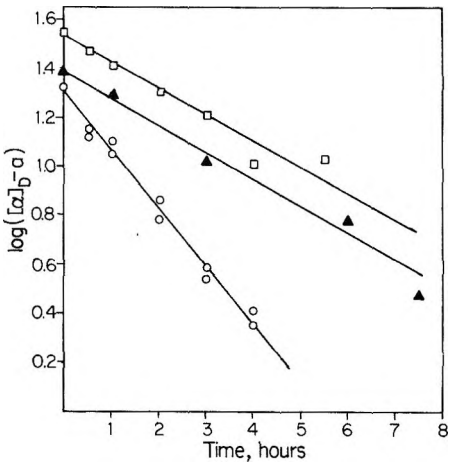

Figure 3. First order plots for racemization of (+)-naphthidine. The specific rotation at the end of the initially fast reaction, α, has been subtracted from the rotation at various times, $[\alpha]_D$: ○, sample 1, α = 18° at 150 °C; ▲, sample 2, α = 5° at 130 °C; □, sample 3, α = 20° at 130 °C.

The racemization rate up to the point where it almost stops (with a slow and erratic reaction thereafter) seems best described as a first-order reaction (see Figure 3). Preparations 2 and 3 gave essentially the same rate constant at 130 °C, even though the loss of optical activity slowed down at different fractions of the reaction. The more finely divided parts of the sample may follow a first-order equation, as is observed for some finely crushed inorganic powders,[7] while the second, slow, and widely variable part of the racemization may arise from differing amounts of larger crystals in the various batches. It should be noted that the incomplete racemization over much longer times of heating was not due to production of any nonracemizable products. Once dissolved, kinetic samples previously heated for long periods of time in the solid state racemized like normal naphthidine in solution. The great sensitivity of the rate and extent of racemization of the sample condition made any kinetic study on available polycrystalline samples less feasible, and they were not pursued further.

Mechanism of Racemization. The observed solid-state racemization might, in principle, arise simply from a conversion of a sample consisting only of enantiomorphic crystals of one configuration into an equal mixture of the two enantiomeric crystals (i.e., the production of a eutectic mixture). The driving force for racemization would then be only the greater entropy of the mixture and would be similar to the driving force for spontaneous racemizations in solutions. However, a free-energy change for ideal mixing in a solution amounts only to 580 cal/mol at 150 °C and would be even smaller in the less complete mixture of larger aggregates (crystallites) of the two enantiomers in a solid-eutectic system. The rigidity of molecules present in a crystallite would tend to kinetically prevent such a small free-energy decrease from coming into operation in a solid-state racemization. The result is that most optically active materials are optically stable indefinitely in the solid state even if a simple process (like the bond rotation in naphthidine) is possible for the racemization in the freer state of a solution. For example, no racemization of a 2,2′-disubstituted biphenyl compound occurred during heating at 100 °C for 55 days, even though, in solution, the half-life is 2 h at this temperature.[8]

A greater driving force for a solid-state conversion is possible if the racemization involves conversion to a structurally different (not just enantiomeric) product, i.e., the production of a racemic compound. Racemic naphthidine and optically active naphthidine do indeed have different crystal structures, as shown by the marked differences in their solid-state in-

frared spectra (especially in the 670–900 and 1000–1060 cm^{-1} regions).

In addition to differences in IR spectra, the transformation of a eutectic to a racemic form of naphthidine may be seen by changes in a (+)-naphthidine sample during differential-scanning calorimetry. A sample previously heated at 130 °C until it was 85% racemized showed endotherms for low-melting naphthidine (196–200 °C) which dominated the previously major endotherm (202–204 °C) shown by fully resolved naphthidine. Correspondingly, the IR spectrum of the heated sample showed development of the bands due to the racemic form. The naphthidine phase system is therefore one in which two polymorphic forms exist, a eutectic form (which may be optically active) and an inactive racemic form. The observed racemization on storage is accounted for in that the racemic form is more stable at room temperature and, from the kinetic data shown in Figures 1 and 2, up to at least 150 °C.

Phase Relationship of Naphthidine Polymorphs. A more thorough understanding of thermal racemization requires knowledge of the phase diagram of the two forms of naphthidine. In such a polymorphic system, two possibilities for relative stabilities exist.[9] Either the racemate is more stable than the eutectic form at all temperatures up to the melting point (a monotropic system) or it is stable up to a certain solid-to-solid transition temperature at which the eutectic solid becomes more stable (a so-called enantiotropic system). The first possibility must be excluded since the DSC results definitely showed that racemic naphthidine has a slightly lower melting point than the optically active eutectic form. A narrow range of temperature therefore exists in which the relative stabilities of the phases are racemate < melt < eutectic solid, and the eutectic solid is therefore stable with respect to the racemic solid, at least within that range. The solid-to-solid transition point for a change of racemic to eutectic forms must lie below 202 °C (the melting point of the racemate); the results of Figure 1 show that it lies above 150 °C. In order to refine this temperature range and determine the transition point, pairs of samples, one racemate and the other eutectic naphthidine, were heated at constant temperatures under vacuum for several hours. Up to 195 °C, the racemic sample remained unchanged (except for a slight yellowing) over a 1-week period, while after 24 h eutectic samples showed development of the IR bands of the racemic form. At 197 °C, however, the situation is reversed; eutectic crystals grow from racemate within 24 h, while a sample of eutectic crystals showed no change in its IR spectrum over 64 h. The temperature of the solid-state transformation of the two crystal forms must therefore be ~195–197 °C, and the phase diagram is correspondingly shown in Figure 4.

The solid states of naphthidine present an enantiotropic system in which each solid form has a range of true stability. The racemate is stable from below room temperature to 197 °C and metastable up to 202 °C, where it converts to melt. The eutectic form is the stable phase over the narrow range from 197 °C to ~204 °C, where an optically pure eutectic sample would melt and racemize. Below 197 °C, optically active naphthidine is metastable with respect to racemate and is thermally converted with accompanying racemization in a direct solid-to-solid-state reaction to the racemic form.

Except for the individual temperatures of transitions, the phase diagram of Figure 4 for naphthidine takes a form identical with that of binaphthyl.[1] The opposite characters of the solid-state reactions (i.e., racemization with naphthidine and resolution with binaphthyl) arise from the different ranges of temperature in which racemic and eutectic phases are stable. Above ~100 °C in a region where the rates of solid-state reactions of these organic solids are rapid enough to be noticeable, the eutectic form of binaphthyl is the stable

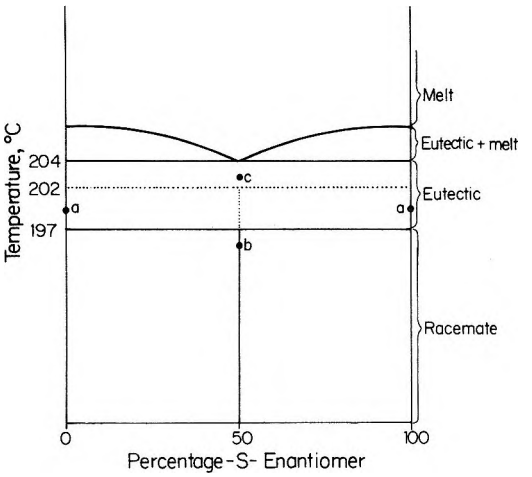

Figure 4. Phase diagram of the naphthidine system. The melting point of the racemic compound is 202 °C, of the eutectic form 204 °C, and the solid-to-solid-state transition temperature is 197 °C.

state; with naphthidine (except for a narrow region of stable eutectic solid at 197–204 °C) the racemic form is the more stable state.

This pair of compounds (X = H and X = NH_2) thus provides an interesting contrast in stereochemical results (resolution vs. racemization) which, nevertheless, both arise from the same basic property, i.e., the highly stereospecific character of solid-state reactions. Clearly the difference lies in the presence or absence of the 4,4′-diamino groups on the binaphthyl system, which serve to shift the ranges of solid-state stabilities. The detailed crystal structure of naphthidine is not known,[10] and, in any case, a crystallographically based explanation of relative stabilities of polymorphic phases does not seem possible as yet.

Control of Racemization vs. Resolution. Although such stereospecific reactions in the organic solid state can therefore not be predicted on the basis of molecular structure, they can be utilized once the phase relationships are known. If, as shown below, seed crystals to promote growth of the other phase are present, the stereospecific character can be reversed simply by a variation of temperature by a few degrees. Eutectic naphthidine is stable and produced at 198 °C (points a on Figure 4) and racemic naphthidine is stable and produced at, say, 195 °C (point b on Figure 4). The existence of a temperature range at which the eutectic solid is the thermodynamically stable state suggests that optically active samples of this eutectic form may be produced by thermal treatment alone. This would be similar to the spontaneous solid-state resolution of binaphthyl.[1,2]

To investigate this possibility, 17 weighed samples of ordinarily prepared racemic naphthidine were heated to just above the melting point (point c on Figure 4). The naphthidine melted rapidly and then slowly crystallized. After ~5 hours at 203 °C, the samples were cooled, dissolved completely, and analyzed to give specific rotations of $[\alpha]_D$ +40, +16, +30, +14, +42, +9, +25, +31, +17, −2, +18, +36, +36, +24, +33, +32, and +30°. The samples had certainly resolved, some to nearly 100% optical purity ($[\alpha]_D$ ±49°). They also showed an interesting bias for production of the dextrorotatory enantiomer. (Had the bias been *absent*, the chance of obtaining the observed 16 dextrorotatory samples out of 17 trys would be only 1 in 7710.)[3] The racemic preparation had apparently picked up adventitious seed of the (+) enantiomer of naphthidine, which is the one predominate in our laboratory since it was previously produced by classical resolution procedures (see Experimental Section). The growth of these seeds present in the naphthidine melt accounts for the strongly biased results.

The presence of such seeds was further indicated when racemic naphthidine was heated to 215–220 °C, which is well above the melting point of both forms of naphthidine. This destroyed all seed crystals, and when the samples were returned to 203 °C no crystallization occurred over long periods of time. With further cooling (to 175 °C) crystallization occurred, but the samples were completely optically inactive and in the racemic form. Naphthidine melt has a great tendency to supercool, and spontaneous nucleation apparently does not occur in the range of temperature above 197 °C, where the optically active eutectic form is stable. Thus, in contrast to the demonstrated[2] spontaneous production of optical activity in binaphthyl, naphthidine cannot be made to resolve in a truly spontaneous way. Only a bias arising from inadvertent seeding may be amplified by growth of the eutectic form at 203 °C.

Some further variations of experiments arising from knowledge of the phase relationships given in Figure 4 are possible. Above 197 °C and below the melting point of 202 °C, samples of racemic naphthidine should undergo a direct solid-to-solid-state resolution reaction. Eleven samples of racemic preparation were heated to 197 °C, where only the eutectic form is stable. At this temperature the racemization observed up to 195 °C is reversed, resolution occurred, and after 65 h the samples showed rotations of $[\alpha]_D$ +13, −5.5, +25, +26, +29, +32, +39, +36, −3.0, +27, and +20°. Again a bias toward the (+) enantiomer is caused by the presence of adventitious seeds of the eutectic form. If such seeds are annealed out by heating samples at 192 °C for over 5 h (or melted out by heating to 215 °C and solidifying at 175 °C) and the samples then held at 197 °C, no production of optically active samples, nor even the growth of any eutectic crystals, was observed. The spontaneous nucleation of the eutectic form apparently does not occur in solid naphthidine. Also, as mentioned above, it does not occur in supercooled naphthidine melt in the 197–204 °C range.

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Registry No.—(*S*)-(+)-Naphthidine, 18531-98-1; (±)-naphthidine, 64282-15-1; (*R*)-(−)-naphthidine, 64235-43-4.

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Synthesis and Epoxidation Kinetics of Some Fused-Ring Cyclopropenes

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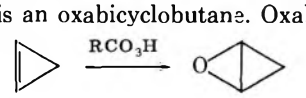
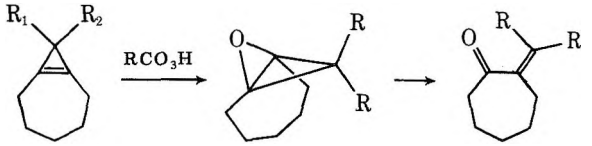
A series of 8,8-disubstituted bicyclo[5.1.0]oct-1(7)-enes was prepared. Measured relative rates of epoxidation were obtained for these allylically substituted fused-ring cyclopropenes. An attempt to fit the partial rate constants of epoxidation to a simple linear free energy dependence revealed a moderate backside interaction of the allylic cyclopropene substituents with the cycloheptane ring.

For many years we[4] have been attempting to delineate the details of cyclopropene epoxidations, since the expected initial product is an oxabicyclobutane. Oxabicyclobutanes

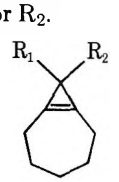


have been postulated as unstable intermediates in many different reactions.[5] They are also interesting theoretical molecules due to a potential antiaromatic interaction of the cyclopropane ring with the neighboring nonbonded electrons on the oxygen atom. Such an interaction mimics the electronic π-type resonance in the yet to be synthesized oxirenes.[6]

Our previous work[4] has studied the epoxidation kinetics and products using simple cyclopropenes. In this work, we sought to epoxidize cyclopropenes that are fused to a seven-membered ring. Not only are the resulting intermediate oxabicyclobutanes unique and novel propellanes,[6b] but we also hoped to establish a quantitative linear free-energy relationship between the epoxidation rate constants and the steric substituent constants of the cyclopropene allylic substituents.



The desired cyclopropenes are compounds **1a–d.** These four compounds form two relevant series. The first series, **1a, 1b,** and **1c,** can be used to probe the steric reaction constant with respect to allylic substituents of different size. The compounds in the second series, **1a, 1b,** and **1d,** all have R_1 = Me with increasing steric bulk for R_2.



1a, R_1 = Me; R_2 = Me
1b, R_1 = Me; R_2 = Et
1c, R_1 = Et; R_2 = Et
1d, R_1 = Me; R_2 = *i*-Pr

Results

All four cyclopropenes were prepared by irradiation of the tosylhydrazone salts of their corresponding ketones, **2a–d.**

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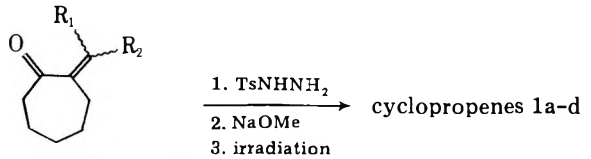
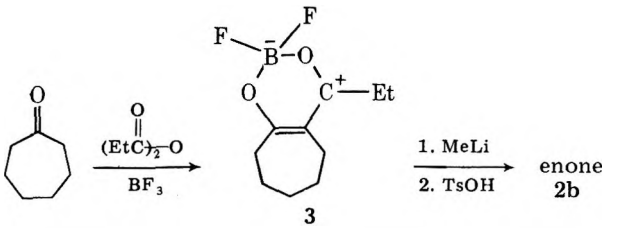


2a, R_1 = Me; R_2 = Me
2b, R_1 = Me; R_2 = Et
2c, R_1 = Et; R_2 = Et
2d, R_1 = Me; R_2 = *i*-Pr

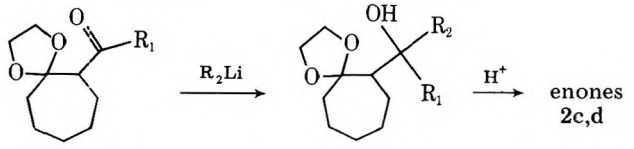
Cyclopropene **1a**[7] and its corresponding enone[8] are known compounds.

The syntheses of the unknown exocyclic enones **2b–d** were relatively straightforward. Enone **2b** was prepared by literature analogies.[9,10] Treatment of cycloheptanone with propionic anhydride–BF_3 forms the stable fluoroborate complex **3**, which on reaction with MeLi and treatment with acid gives enone **2b**.

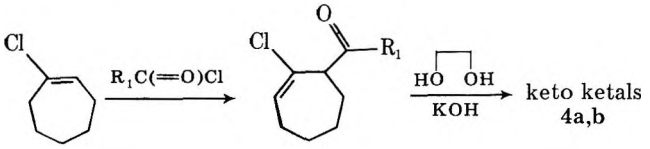


3

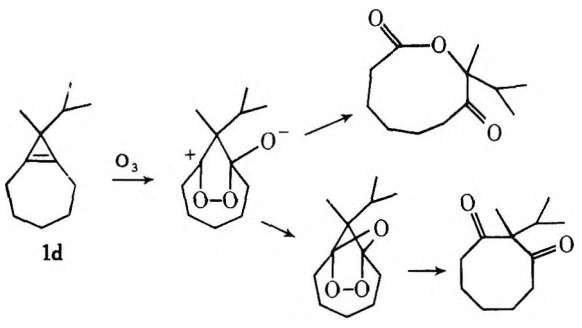
Enones **2c,d** were prepared from their respective keto ketals **4a,b**. The keto ketals were made using literature methods[11] by acylation of cycloheptenyl chloride followed by ketalization with ethylene glycol and base.



4a, R_1 = Et
4b, R_1 = *i*-Pr



The structures of the final cyclopropenes **1a–d** are firm, not only because they possess the proper spectral properties, but also because the syntheses involve unambiguous routes. Furthermore, epoxidation of each cyclopropene gave a quantitative yield of enones **2a–d**. Such enone products have been the only products from cyclopropenes of this type when treated with peracid.[4] The detailed stereochemistry of the enone products will be the subject of a separate paper that relates not to the epoxidation of cyclopropenes, but to the fragmentation of oxabicyclobutanes. As a final structure proof ozonolysis of **1d** gave the expected 2-methyl-2-isopropyl-1,3-cyclooctadione, along with a small amount of a lactone (see Experimental Section) formed by a Baeyer–Villiger type of rearrangement.



1d

Table I. Relative Rate Constants of Epoxidation[a] of Cyclopropenes[b] 1a–d

Compds	Rel k[c]
1a vs. **1b**	1.97 ± 0.05
1b vs. **1c**	2.68 ± 0.13
	2.98 ± 0.14
1d vs. **1c**	1.27 ± 0.02

[a] *m*-Chloroperbenzoic acid in CCl_4 at 0 °C. [b] ~0.01 M. [c] Errors are standard deviations of the calculated relative k's from a single kinetic run.

Table II. Rate Constants of Epoxidation[a] of Cyclopropenes[b] 1a–d

Compd	Registry no.	k,[c] M^{-1} s^{-1}	Rel k[d]	Rel k[e]
1a, Me, Me	17900-97-9	0.90 ± 0.03	(1.00)	(1.00)
1b, Me, Et	64425-32-7	0.29 ± 0.03[f]	0.32[f]	0.51
1c, Et, Et	64425-33-8	0.16 ± 0.02	0.18	0.18
1d, Me, *i*-Pr	64425-34-9	0.18 ± 0.01	0.20	0.23

[a] *m*-Chloroperbenzoic acid in CCl_4 at 0 °C. [b] ~3×10^{-4} M. [c] Errors are standard deviations with two degrees of freedom from independent runs. Tetramethylcyclopropene has $k = 1.1 \times 10^{-2}$ M^{-1} s^{-1} under the same conditions.[4e] [d] From absolute kinetics in this table. [e] From data in Table I. [f] These numbers may be in error, see text.

The epoxidation kinetic studies were done two ways. Since we are primarily interested in relative rate constants, we performed a series of competitive kinetic experiments in which two cyclopropenes compete for the common peracid.[12] By following the disappearance of the two cyclopropenes, relative second-order rate constants can be obtained.

$$\frac{\ln A/A_0}{\ln B/B_0} = \frac{k_A}{k_B}$$

This method is particularly good for relative k's that are approximately equal to one and produces reliable values even if there may be undetected impurities that destroy peracid. Table I lists these results.

We have also measured absolute kinetics in the standard manner by following the titrimetric disappearance of peracid, see Table II. These absolute values may not be as accurate as the relative rate constant data of Table I because any unrecognized biases in the kinetic method lead to biased rate constants. Table II shows that the competitive relative k's are in good agreement with the absolute kinetics for all compounds except **1b**.

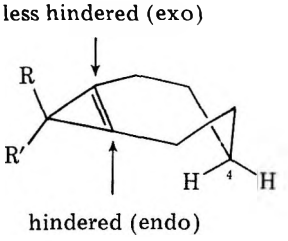
The rate constant for **1b** appears too low in comparison with the other cyclopropenes. There appears to be a reproducible bias in this absolute rate constant. We have chosen to publish this number because, by hindsight, we can find no *chemical* reason to throw out the value. Nevertheless, we have complete confidence in the relative k's that are derived from the data in Table I and will refer to these values in the remaining part of the paper.

Discussion

The inductive effect of the different allylic substituents in the epoxidation of cyclopropenes **1a–d** should be the same because the differences in alkyl substitution occur two carbon atoms removed from the cyclopropene double bond and because σ^* for the differing alkyl substituents are all approximately the same.[13] The rigid position (except for rotational conformers) of the allylic substituents above and below the olefin π system will therefore affect the epoxidation rate constants by primarily a steric effect. Large allylic substituents which cannot rotate out of the way of the entering peracid

should raise the transition-state energy for epoxidation, thereby retarding the rate of epoxidation.

Before a detailed analysis of the relative rate constants is given, it is important to point out an unusual feature of the cyclopropenes. Molecular models of the fused-ring cyclopropenes show that C-3, C-4, and C-5 are not in the plane of the double bond. Atom C-4 is most prominent, which is puckered almost 90° out of the molecular plane. As a result, the endo H on C-4 has a sufficient van der Waals radius that it hinders peracid approach to the endo side of the π system of the

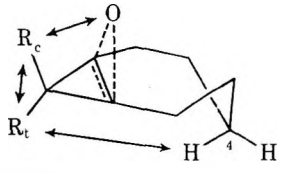


double bond. In fact, models show that the endo side is so hindered that we do not believe that any substantial amount of epoxidation occurs from the endo side.

The endo C-4 hydrogen must absorb at unusually high field in the ^{1}H NMR. Unfortunately, it is only a one-proton absorption which is coupled to five other protons, so that it is not individually seen in the ^{1}H NMR spectrum.

The rate ratio of ~0.5 for **1b/1a** superficially suggests that the ethyl group in **1b** completely blocks epoxidation from the side of the cyclopropene that contains the ethyl group. In conflict with this conclusion is the fact that steric substituent constants, E_s, for Et are only slightly larger than for Me.[14] Even more important is that if the Et completely blocked epoxidation in **1b**, then **1c** with two Et groups should be almost inert to epoxidation from both sides of the double bond. Rather, the rate ratio of **1c/1a** is 0.18, which shows that a simple single linear free-energy relationship cannot be obtained.

An explanation for these rate phenomena can be found by further examination of molecular models. As the allylic substituents are changed, there are three interactions that change in the epoxidation transition state. In addition to potential



interactions between the entering peracid and the cis-substituted cyclopropene allylic substituent, it is evident that there are also potential interactions of the trans cyclopropene allylic substituent with the C-4-endo hydrogen as well as between the two allylic substituents themselves.

These three interactions are not independent. For example, if R_c is Et and R_t is Me, the allylic substituent system forms a butane chain. Peracid–Et interaction is only severe when the butane chain is in a lowest energy anti conformation. Correspondingly, when the butane chain is in a higher energy gauche conformation, the peracid–Et interaction is much reduced. Since these interactions are inversely correlated, there are only approximately two net independent interactions that determine the energy of the epoxidation transition state relative to reactants. Therefore only two observed relative rates are needed to uniquely define the magnitude of these net interactions.

If $\Delta G^{\ddagger}_0$ is the free energy of activation for epoxidation of **1a** from *one side* of the π system, then the rate constant for epoxidation of **1a** from both sides of the π system is

$$k_{1a} = 2\frac{kT}{h}e^{-\Delta G^{\ddagger}_0/RT}$$

For **1c**, there are, as discussed above, two net interactions that raise the free energy of epoxidation above that for **1a**. Let $\Delta\Delta G^{\ddagger}_1$ and $\Delta\Delta G^{\ddagger}_2$ be the two net free-energy increments due to frontside and backside (relative to peracid) interactions. Then

$$k_{1c} = 2\frac{kT}{h}e^{-(\Delta G^{\ddagger}_0+\Delta\Delta G^{\ddagger}_1+\Delta\Delta G^{\ddagger}_2)/RT}$$

For compound **1b**, part of the epoxidation occurs cis to the Me and trans to the Et substituent where the partial rate factor is

$$k_{1b}(\mathrm{Me}) = \frac{kT}{h}e^{-(\Delta G^{\ddagger}_0+\Delta\Delta G^{\ddagger}_2)/RT}$$

Only $\Delta\Delta G^{\ddagger}_2$ is included with $\Delta G^{\ddagger}_0$, since the assumption is that there is only one net independent energy increment of the backside Et group with either the Me or the C-4 ring hydrogen. Similarly, the partial rate constant for epoxidation cis to the Et group in **1b** is

$$k_{1b}(\mathrm{Et}) = \frac{kT}{h}e^{-(\Delta G^{\ddagger}_0+\Delta\Delta G^{\ddagger}_1)/RT}$$

The total expression for k_{1b} is a sum of the partial rate factors

$$k_{1b} = \frac{kT}{h}e^{-(\Delta G^{\ddagger}_0+\Delta\Delta G^{\ddagger}_1)/RT} + \frac{kT}{h}e^{-(\Delta G^{\ddagger}_0+\Delta\Delta G^{\ddagger}_2)/RT}$$

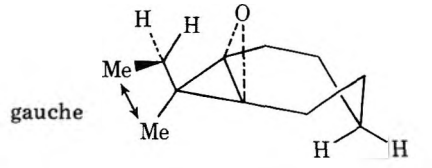
With these assumptions expressions can be written for the relative rate ratios in Table II. Solution of these equations gives

$$k_{1b}/k_{1a} = 0.51 = \tfrac{1}{2}(e^{-\Delta\Delta G^{\ddagger}_1/RT} + e^{-\Delta\Delta G^{\ddagger}_2/RT})$$

$$k_{1c}/k_{1a} = 0.18 = e^{-(\Delta\Delta G^{\ddagger}_1+\Delta\Delta G^{\ddagger}_2)/RT}$$

$\Delta\Delta G^{\ddagger}_1 = 805 \pm 40$ or 126 ± 10 cal/deg mol^{-1} with $\Delta\Delta G^{\ddagger}_2 =$ 126 or 805 cal/deg mol^{-1}, respectively. A distinction between the two solutions cannot be made mathematically, but can be deduced from conformational thermodynamics.

As defined above, $\Delta\Delta G^{\ddagger}_1$ is the frontside free-energy increase when peracid attacks cyclopropene **1b** cis to the Et group. As indicated above, this epoxidation probably occurs with a gauche butane conformation for the two allylic substituents. In the starting cyclopropene, the conformation of



the butane unit is most likely anti with the Et group rotated toward the cyclopropene double bond. The change in free energy of the butane unit between starting material and transition state is then

$$\Delta\Delta G^{\ddagger} = \Delta H^{\ddagger}_{\text{gauche Bu}} - T(R \ln 2)$$

The R ln 2 term is included because there are two degenerate gauche conformations. With an enthalpy of 800 cal/deg mol^{-1} for a gauche butane interaction,[15] $\Delta\Delta G^{\ddagger} = 425$ cal/deg mol^{-1}. This is the minimum possible value for $\Delta\Delta G^{\ddagger}_1$. To this must be added any peracid–Et interaction. As a result, we conclude

that $\Delta\Delta G^{\ddagger}_1$ is the larger value of 805 cal/deg mol^{-1}. The smaller value, $\Delta\Delta G^{\ddagger}_2$ = 126 cal/deg mol^{-1}, corresponds to the net increment interaction of an Et group (compared to Me) with the molecule on the backside when the butane group is in an energy minimum conformation.

The above analysis leads to the reasonable conclusion that the ratio of partial rate factors for **1b** is

$$\frac{k_{1b}(\mathrm{Me})}{k_{1b}(\mathrm{Et})} = e^{-(\Delta\Delta G^{\ddagger}_2 - \Delta\Delta G^{\ddagger}_1)/RT} = \frac{78}{22}$$

Finally, an analysis is needed for why **1d**/**1a** is 0.23. There are various conformational assumptions that can be made about the differences between the Et group in **1b** and the *i*-Pr group in **1d**. Since each assumption is speculation, we prefer to analyze the simplest phenomenological assumption, i.e., that the net effect of the *i*-Pr group in **1d** is some multiple factor, q, of the effect of the Et in **1b**. If so, the partial rate constants for epoxidation of **1d** would be

$$k_{1d}(\mathrm{Me}) = \frac{kT}{h} e^{-(\Delta G^{\ddagger}_0 + q(\Delta\Delta G^{\ddagger}_2))/RT}$$

$$k_{1d}(i\text{-Pr}) = \frac{kT}{h} e^{-(\Delta G^{\ddagger}_0 + q(\Delta\Delta G^{\ddagger}_1))/RT}$$

Then

$$k_{1d}/k_{1a} = 0.23 = \tfrac{1}{2}(e^{-q\Delta\Delta G^{\ddagger}_2/RT} + e^{-q\Delta\Delta G^{\ddagger}_1/RT})$$

Using the previously determined values of $\Delta\Delta G^{\ddagger}_1$ and $\Delta\Delta G^{\ddagger}_2$, q is found to be 3.4 with an estimated standard deviation of ~0.3. Experimentally, this means that the net steric difference between *i*-Pr and Me is about three and a half times as great as the steric difference between Et and Me. This is not at all unreasonable because in standard systems, *i*-Pr has a steric substituent constant, E_s, which is six to nine times greater than Et (E_s for Me = 0).[13,14]

A possible reason why q is 3.4 instead of a larger value as in standard systems is *not* because *i*-Pr presents a smaller steric size, but perhaps because Et presents a larger size than in standard systems. In standard systems, an Et can rotate out of the way of a crowded transition state. In the cyclopropenes **1b,c**, such a movement away from the π double bond only results in a gauche or eclipsing butane-like conformation. In other words, the quaternary allylic cyclopropene center presents sufficient congestion to the regions surrounding the double bond in the epoxidation transition state that substituents of any size have moderately large steric interactions in all conformations.

An alternate explanation for q = 3.4 does not rely on an unusually congested transition state. Rather, Hancock[14b] has recognized that E_s's for Et and *i*-Pr are less negative than their true steric effect would indicate. The reason is because of a hyperconjugative interaction between the α hydrogen C–H bonds of the substituents and the reaction center in the acid-catalyzed hydrolysis of esters. Such hyperconjugation stabilizes the starting ester and causes the hydrolysis to occur slower than the true steric effect of the substituent would indicate. The effect is greatest for Me because of the three α hydrogens and amounts to a change in E_s of ~0.3 per α hydrogen. Relative to Me (E_s = 0), the corrected E_s's for Et and *i*-Pr are −0.38 and −1.08, respectively. In other words, the true steric effect of *i*-Pr is only 2.84 times greater than Et (relative to Me). This value is similar to our calculated q = 3.4 ± 0.3.

Using q = 3.4, the ratio $k_{1d(\mathrm{Me})}/k_{1d}(i\text{-Pr})$ is 99:1, which shows a large selectivity for formation of only one oxabicyclobutane.

Conclusion

Four fused-ring cyclopropenes with varying allylic substituents were epoxidized. Relative rate constant ratios show that contrary to standard systems, the steric effect of an allylic Et group is significantly larger than that of a Me group. The reason for the difference may be because in the standard acid-catalyzed hydrolysis of esters, substituents with α hydrogens retard hydrolysis by a hyperconjugative mechanism, thereby causing E_s to contain not only a steric effect, but also an electronic effect.

Experimental Section

General. Instruments were used as follows: melting point, Fisher-Johns; GC, Perkin-Elmer 900, Varian A-90P, Hewlett-Packard 720; UV, Cary 118; IR, Perkin-Elmer 137 or 467; ^{1}H NMR, JEOLCO C-60HL or MH-100; ^{13}C NMR, JEOLCO PFT-100; MS, Perkin-Elmer RMU-6E or Du Pont 21-490B. Elemental analyses were obtained from Chemalytics, Inc., Tempe, Ariz.

2-(Dithiomethoxymethylene)cycloheptanone. Following Corey's procedure for the six-membered ring homologue,[16] 145.2 mL (0.353 mol) of 2.43 M *n*-butyllithium in hexane was added over 0.5 h to 77.7 g (0.352 mol) of 2,6-di-*tert*-butyl-*p*-cresol (DBPC) in 2 L of anhydrous ether at 0 °C under N_2. The white cloudy mixture was warmed to room temperature and 18.50 g (0.165 mol) of cycloheptanone with 60.7 g (0.800 mol) of carbon disulfide were added over 15 min. The bright yellow reaction mixture was stirred at room temperature for 21 h. Then 62.5 g (0.441 mol) of methyl iodide was added and the mixture was stirred at room temperature for an additional 4.5 h. The reaction was poured into 1.5 L of water. The phases were separated and the water solution was extracted twice with ether. Most of the ether was distilled from the combined ether solutions. The organic solution was then dried with Na_2SO_4, filtered, and concentrated. The yellow liquid was cooled to −20 °C and seeded with DBPC. The yellow solid was isolated and recrystallized from pentane. The filtrates containing product and DBPC were then combined, concentrated, and cooled to −20 °C. This process was repeated until a solution was obtained that contained approximately equal amounts (by ^{1}H NMR) of DBPC and product. The DBPC was then distilled under vacuum, bp 66–92 °C (0.25 mm), yielding a dark yellow liquid in the pot which was the desired product, 18.39 g (51%), purity 80–90% by ^{1}H NMR. This crude product was not purified for the next reaction. A sample for analysis was purified by silica gel chromatography and a pure sample was finally obtained by preparative GC (6 ft, 5% Carbowax 20M on Chromosorb W, 140 °C): IR (neat) 1693 cm^{-1}; ^{1}H NMR (CCl_4) 2.70–2.37 (4 H, m), 2.33 (3 H, s), 2.25 (3 H, s), 1.82–1.71 (6 H, m); UV (hexanes) 223 sh (ϵ 3280), 270 (3430), 297 nm sh (2690); MS (70 eV) *m/e* 216 (M^+, 43), 203 (10), 202 (12), 201 (100), 173 (13), 169 (30), 125 (33), 93 (37), 85 (28).

Anal. Calcd for $C_{10}H_{16}OS_2$: C, 55.51; H, 7.45. Found: C, 55.54; H, 7.16.

2-Isopropylidenecycloheptanone (2a). A black solution of lithium dimethylcuprate was made by the method of Johnson and Duka[17] with 8.87 g (46.6 mmol) of CuI in 29 mL of dry ether. This solution was added over 40 min under N_2 to 4.55 g (21.1 mmol) of crude 2-(dithiomethoxymethylene)cycloheptanone in 25.0 mL of dry ether at −78 °C. The reaction mixture was stirred at −78 °C for 45 min, and then 16 mL of methanol was cautiously added. The solution was warmed to room temperature and water was added. The mixture was filtered, the phases were separated, and the water solution was acidified with concentrated HCl and extracted three times with ether. The combined organic solutions were dried with Na_2SO_4 and concentrated. The yellow liquid was vacuum distilled to give 2.08 g (65%) of a colorless liquid, bp 101–102 °C (11 mm) [lit.[8] 120–124 °C (17 mm)]. An analytical sample was obtained by preparative GC (10 ft, 20% Carbowax 20M on Chromosorb P, 153 °C): IR (neat) 1678, 1619 cm^{-1}; ^{1}H NMR (CCl_4) δ 2.53–2.18 (4 H, m), 1.81 (3 H, s), 1.76 (3 H, s), 1.72–1.43 (6 H, m); UV (hexanes) 238 (ϵ 7290), 323 nm (70); MS (70 eV) *m/e* 152 (M^+, 65), 137 (15), 124 (12), 109 (51), 95 (26), 82 (100), 81 (65), 68 (42), 67 (76).

Preparation of Tosylhydrazones. Following the general procedure of Closs,[7b] 50 mmol of the enone was dissolved in 15 mL of MeOH and warmed to ~45 °C. Then 50 mmol of tosylhydrazide was added with stirring over several minutes, followed by stirring for periods from one-half to several hours. The mixture was cooled to 0 °C for 12 h and filtered, and the product was recrystallized as desired.

2-Isopropylidenecycloheptanone tosylhydrazone: mp 158–161 °C dec (from CH_2Cl_2) (lit.[7b] 171–172 °C); IR (KBr) 3200, 1681, 1583

cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (2 H, d, J = 8 Hz), 7.45 (1 H, br s), 7.20 (2 H, d, J = 8 Hz), 2.38 (3 H, s), 2.34–2.01 (4 H, m), 1.72–1.25 (6 H, m), 1.62 (3 H, s), 1.47 (3 H, s); UV (MeOH) 225 (ε 12 920), 274 nm sh (1610); MS (70 eV) m/e 320 (M^+, 1), 166 (10), 165 (100), 109 (30), 91 (12).

Anal. Calcd for $C_{17}H_{24}N_2O_2S$: C, 63.72; H, 7.55; N, 8.74. Found: C, 63.51; H, 7.55; N, 8.92.

(Z)- and (E)-2-(2-Butylidene)cycloheptanone tosylhydrazone: mp 152–154 °C dec (from MeOH); NMR ($CDCl_3$) δ 0.50–1.30 (3 H, m), 1.62 (3 H, s), 1.30–1.93 (6 H, m), 1.93–2.47 (6 H, m), 2.44 (3 H, s), 7.17–7.51 (3 H, m), 7.67–8.04 (2 H, m); MS (70 eV) m/e 334 (M^+, 4) 179 (100), 151 (94) 135 (75), 121 (91), 107 (50), 93 (75), 91 (75), 79 (69), 77 (44), 67 (44).

2-(3-Pentylidene)cycloheptanone tosylhydrazone: ^1H NMR ($CDCl_3$) δ 7.82 (2 H, d, J = 8.0 Hz), 7.25 (2 H, d, J = 8.0 Hz). 7.25 (1 H, s), 2.40 (3 H, s), 2.38–1.94 (4 H, m), 2.02 (2 H, q, J = 7.5 Hz), 1.75–1.36 (6 H, m), 1.65 (2 H, q, J = 7.5 Hz), 0.96 (3 H, t, J = 7.5 Hz), 0.60 (3 H, t, J = 7.5 Hz).

(E)- and (Z)-2-(3-Methyl-2-butylidene)cycloheptane tosylhydrazone: mp 162–164 °C dec (from CH_2Cl_2); IR (KBr) 3208, 1598 cm^{-1}; H NMR ($CDCl_3$) 7.74 (2 H, d, J = 8 Hz), 7.29 (1 H, br s), 7.27 (2 H, d, J = 8 Hz), 2.36 (3 H, s), 2.32–1.93 (5 H, m), 1.66–1.25 (6 H, m), 1.47 (2.25 H, s), 1.07 (0.75 H, s), 0.88 (1.5 H, d, J = 7 Hz), 0.62 (4.5 H, d, J = 7 Hz); UV (MeOH) 225 (ε 12 960), 274 nm (1370); MS (70 eV) m/e 349 (M + 1, 0.4), 348 (M^+, 0.4), 194 (15), 193 (100), 178 (23), 151 (57), 95 (14), 91 (15).

Anal. Calcd for $C_{19}H_{28}N_2O_2S$: C, 65.48; H, 8.10; N, 8.04. Found: C, 65.25; H, 7.86; N, 8.24.

Preparation of Cyclopropenes 1a–d. Following the general procedure of Durr,[18] N_2 was bubbled through a solution of 15 mmol of tosylhydrazone (pure or mixture) in 350 mL of purified dioxane for 3 h. Next, 60 mmol of NaOMe was added and stirred under N_2 for 6 h. The solution was irradiated through Pyrex with a 450-W Hanovia medium-pressure mercury-arc lamp. Evolved N_2 was collected and measured. Typically, N_2 evolution would cease after ~8 h with ~50% conversion to N_2. The reaction was poured into ether and washed several times with water. The remaining ether solution was washed with 0.6 M $NaHCO_3$ and dried over Na_2SO_4. The solvent was rotoevaporated to give an oil which was purified by preparative GC. The cyclopropenes could not be sent away for analysis because they react slowly with air.

$\Delta^{1,7}$-8,8-Dimethylbicyclo[5.1.0]octene (1a). GC (10 ft, 10% SE-30 on Chromosorb W, nonacid washed, 81 °C) showed three products. I: cyclopropene 1a, area ratio ~50%; retention time 15 min; ^1H NMR (CCl_4) δ 2.54–2.18 (4 H, m), 1.94–1.47 (6 H, m), 1.15 (6 H, s) [lit.[7b] δ 1.15 (6 H, s)]. II: 1-(1-propen-2-yl)cycloheptene, area ratio 20%; retention time 31 min; ^1H NMR (CCl_4) δ 5.97 (1 H, t, J = 7 Hz), 4.94 (1 H, s), 4.80 (1 H, s), 2.49–2.11 (4 H, m), 1.85 (3 H, s), 1.94–1.35 (6 H, m). III: 3-isopropylidenecycloheptene, area ratio ~30%; retention time, 35 min; ^1H NMR (CCl_4) δ 6.30 (1 H, d, J = 10 Hz), 5.83–5.48 (1 H, m), 2.57–1.85 (4 H, m), 1.85–1.48 (4 H, m), 1.73 (6 H, s) [lit.[19] ^1H NMR agrees].

$\Delta^{1,7}$-8-Ethyl-8-methylbicyclo[5.1.0]octene (1b): GC, 10 ft 10% SE-30 on Anakrom ABS, 89 °C, retention time 17 min; IR (CCl_4) 1850, 1710 cm^{-1}; ^1H NMR δ 2.51–2.22 (4 H, m), 2.02–1.35 (8 H, m), 1.11 (3 H, s), 0.67 (3 H, t, J = 7.5 Hz); MS (70 eV) m/e 150 (M^+, 42), 135 (70), 121 (93), 107 (88), 92 (100), 79 (86).

$\Delta^{1,7}$-8,8-Diethylbicyclo[5.1.0]octene (1c): GC, 10 ft, 10% SE-30 on Anakrom ABS, 105 °C; IR (neat) 1846 cm^{-1}; ^1H NMR (CCl_4) δ 2.54–2.09 (4 H, m), 2.09–1.24 (6 H, m), 1.56 (4 H, q, J = 7.5 Hz), 0.64 (6 H, t, J = 7.5 Hz); MS (70 eV) m/e 164 (M^+, 53), 149 (15), 136 (14), 135 (100), 121 (22), 107 (33), 93 (63), 91 (28), 81 (28), 79 (48), 67 (30), 55 (30), 41 (36). In addition, 3-(3-pentylidene)cycloheptene was obtained: IR (neat) 3016 cm^{-1}; ^1H NMR (CCl_4) δ 6.20 (1 H, d, J = 12 Hz), 5.49 (1 H, d of t, J = 12, 5 Hz), 2.53–1.80 (4 H, m), 2.06 (4 H, q, J = 7.5 Hz), 1.80–1.28 (4 H, m), 0.96 (6 H, t, J = 7.5 Hz).

$\Delta^{1,7}$-8-Isopropyl-8-methylbicyclo[5.1.0]octene (1d): GC, 10 ft, 10% SE-30 on Chromosorb W, nonacid washed; IR (CCl_4) 1845, 1382, 1370 cm^{-1}; ^1H NMR (CCl_4) δ 2.74–2.19 (4 H, m), 2.19–1.21 (7 H, m), 1.08 (3 H, s), 0.74 (6 H, d, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ_{Me_4Si} 134.15, 42.35, 40.41, 35.98, 32.22, 30.70, 26.40, 25.12; UV (hexanes) 210 end absorption (ε 1680), 242 nm sh (370).

Boron Difluoride Complex of 2-Propionylcycloheptanone (3). Following the method of Hauser,[9] boron trifluoride gas was bubbled into 133 g (1.78 mol) of propionic acid with mechanical stirring for 20 min. A white semisolid formed. The gas inlet was replaced by a dropping funnel filled with 49.9 g (0.445 mol) of cycloheptanone and 115.7 g (0.890 mol) of propionic anhydride, which was added under N_2 with ice cooling. After 5 h, 1 L of water was added causing the complex to precipitate. The solid was filtered and dried for 48 h in a vacuum drying oven, giving 77.0 g (79.9%) of a yellowish powder. The complex was used without further purification. A sample which was recrystallized from benzene gave the following properties: mp 75–77 °C; IR ($CHCl_3$) 1560, 1500 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (3 H, t, J = 7.5 Hz), 1.5–2.0 (6 H, m), 2.3–2.9 (6 H, m).

Anal. Calcd for $C_{10}H_{15}BF_2O_2$: C, 55.60; H, 6.99. Found: C, 55.69; H, 7.15.

(Z)- and (E)-2-(2-Butylidene)cycloheptanone (2b). Following the analogy of Smith and Spencer,[10] a 188-mL portion (0.334 mol) of 1.77 M MeLi (Alfa, titrated by Gilman's method[20]) was added dropwise to 36.17 g (0.167 mol) of the borate complex **3** in 360 mL of benzene (passed through activity I alumina). After 0.5 h the reaction was quenched with 300 mL of a ~0.1 M aqueous NH_4Cl. A gelatinous precipitate formed that was removed by suction filtration. Approximately 0.5 g of p-toluenesulfonic acid was added and the solution was heated to reflux and water was azeotropically removed with a Dean–Stark trap over a period of several hours. The solution was washed with three 500-mL portions of water and dried over Na_2SO_4 and the solvent was removed on a rotary evaporator, leaving 33.0 g (120%) of yellow oil, which, by VPC analysis, was found to consist of ~40% of the two enones.

The Z and E isomers were separated and collected by VPC using a 6-ft 20% Carbowax 20M column at 110 °C. The isomer with the longer retention time has: IR (CCl_4) 1668, 1605 cm^{-1}; ^1H NMR (CCl_4) δ 1.02 (3 H, t, J = 7.5 Hz), 1.79 (3 H, s) 1.40–1.86 (9 H, m), 1.86–2.57 (6 H, m); ^1H NMR (PhH) δ 1.93 (3 H, s), 0.82 (3 H, t, J = 7 Hz). The isomer with the shorter retention time has: IR (CCl_4), 1668, 1614 cm^{-1}; ^1H NMR (CCl_4) δ 1.00 (3 H, t, J = 7.5 Hz), 1.71 (3 H, s), 1.35–1.89 (6 H, m), 1.90–2.58 (6 H, m); ^1H NMR (PhH) δ 1.47 (3 H, s), 1.07 (3 H, t, J = 7 Hz). A mixture of the two enones gave: MS (70 eV) m/e 166 (M^+, 100), 151 (26), 137 (56), 123 (39), 109 (80), 96 (50), 81 (62).

1-Chlorocycloheptene. The material was made in 53% yield by the procedure of Braude from PCl_5 and cycloheptanone: bp 66–71 °C (19 mm) [lit. 54–58 °C (14 mm)[21]]; IR (neat) 3042, 1647 cm^{-1}; ^1H NMR (CCl_4) δ 5.84 (1 H, t, J = 6.2 Hz), 2.72–2.33 (2 H, m), 2.33–1.88 (2 H, m), 1.88–1.10 (6 H, m). Also, a 20% conversion of 1,1-dichlorocycloheptane was obtained in this reaction: bp 71–74 °C (8 mm); ^1H NMR (CCl_4) δ 2.74–2.34 (4 H, m), 1.96–1.39 (8 H, m).

Isobutyryl Chloride. Following the procedure of Bosshard[22] et al., a 10.20-g (0.116 mol) portion of isobutyric acid (Eastman) with 8 drops of DMF (Mallinckrodt) was added dropwise at room temperature over 1 h with stirring to 15.05 g (0.126 mol) of distilled thionyl chloride (Eastman) in a 50-ml round-bottom flask. The reaction solution was stirred at 40 °C for 4.5 h. The product was distilled at atmospheric pressure through a 15-cm Vigreux column. Conversion: 9.90 g (80%); bp 90.0–91.5 °C [lit.[23] 90–92 °C]; IR (neat) 1865, 1805, 1768, 1391, 1371 cm^{-1}; ^1H NMR (CCl_4) δ 2.91 (1 H, heptet, J = 6.8 Hz), 1.30 (6 H, d, J = 6.8 Hz).

2-Chloro-3-isobutyrylcycloheptene. A 7.36-g portion (69.1 mmol) of isobutyryl chloride was added over 5 min to 11.53 g (86.5 mmol) of $AlCl_3$ (Fisher) in 52 mL of CH_2Cl_2. The mixture was stirred for 15 min and filtered through glass wool into a three-neck flask under N_2. A 9.00-g portion (69 mmol) of 1-chlorocycloheptene was added dropwise over 10 min at −15 °C under N_2. The reaction mixture was stirred at −20 °C for an additional 10 min and then slowly warmed to +10 °C over 1.5 h. The reaction was quenched by cautiously pouring it into 100 mL of a 3.2 M aqueous HCl with 75 mL of ice. The water layer was extracted twice with CH_2Cl_2. The combined organic solutions were washed once with water and dried with Na_2SO_4. Distillation gave: 6.55 g (47%); bp 74–77 °C (0.64 mm); IR (neat) 3039, 1713, 1646, 1388, 1371 cm^{-1}; ^1H NMR (CCl_4) δ 6.06 (1 H, t, J = 6.5 Hz), 3.75–3.50 (1 H, m), 2.85 (1 H, septet, J = 6.9 Hz), 2.36–1.43 (8 H, m), 1.09 (6 H, d, J = 7.0 Hz); UV (hexanes) 276 nm (ε 300); MS (70 eV) m/e 202 (M + 2, 1), 200 (M^+, 2), 93 (11), 71 (66), 43 (100), 41 (18).

Anal. Calcd for $C_{11}H_{17}ClO$: C, 65.83; H, 8.54. Found: C, 65.70; H, 8.49.

6-Isobutyryl-1,4-dioxaspiro[4.6]undecane (4b). A 12.15-g (60.6 mmol) portion of 2-chloro-3-isobutyrylcycloheptene was added over 5 min to a refluxing mixture of 3.76 g (67.0 mmol) of 85% KOH pellets and 30.14 g (485 mmol) of ethylene glycol in 37 mL of p-dioxane. After refluxing for 40 h, the mixture was added to H_2O and extracted with four portions of Et_2O. The ether solution was dried over $MgSO_4$ and distilled to give 7.27 g (53%), bp 83–85 °C (0.3 mm). An analytical sample was prepared by GC (6 ft, 5% Carbowax 20 M on Chromosorb W, nonacid washed, 105 °C): IR (neat) 1710, 1384, 1310 cm^{-1}; ^1H NMR (CCl_4) δ 3.78 (4 H, s), 3.12–2.92 (1 H, m), 2.65 (1 H, heptet, J = 7 Hz), 2.03–1.19 (10 H, m), 0.99 (6 H, d, J = 7 Hz); UV (hexanes) 286 nm (ε 67); MS (70 eV) m/e 226 (M^+, 9), 183 (61), 113 (11), 100 (10), 99 (100), 55 (34), 43 (52).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.74; H,

9.91.

(*E*)- and (*Z*)-2-(3-Methyl-2-butylidene)cycloheptanone (2d). A 1.56-g portion (7.0 mmol) of keto ketal **4b** in 9.6 mL of dry pentane was reacted at 0 °C with 8.9 mL (14.4 mmol) of 1.62 M MeLi. The reaction solution was stirred at 0 °C for 4 h and was then cautiously quenched with 20 mL of saturated aqueous NH_4Cl solution. The phases were separated and the water solution was extracted twice with ether. The combined organic solutions were dried with Na_2SO_4, filtered, and concentrated to give the tertiary carbinol as a yellow oil: 1.46 g (86%); IR (neat) 3451 (br), 1654 cm^{-1}; ^1H NMR (CCl_4) δ 4.10–3.45 (4 H, m), 2.5–1.3 (13 H, m), 1.3–0.7 (9 H, m with strong signals at 1.20, 1.00, 0.92, and 0.84). The crude product was directly dehydrated and deketalized.

A solution of 8.3 g (34 mmol) of the crude hydroxy ketal and 23.5 mL of 1.3 M H_2SO_4 in 235 mL of MeOH was refluxed for 1.25 h. The solution was cooled, poured into 360 mL of water, and extracted with four portions of ether.

The yellow ether solutions was dried with Na_2SO_4, and the solvent was removed to give 3.51 g (67%) of crude oil which was used in the tosylhydrazone formation. A portion of the enone mixture was distilled, bp 78–78 °C (0.80 mm), GC chromatographed (10 ft, 20% Carbowax 20 M on Chromosorb P, nonacid washed), and redistilled: IR (neat) 1679, 1617, 1391, 1367 cm^{-1}; ^1H NMR (CCl_4) δ 2.82 (1 H, heptet, J = 6.5 Hz), 2.52–2.09 (4 H, m), 1.80–1.42 (6 H, m), 1.61 (1.5 H, s), 1.57 (1.5 H, s), 1.00 (3 H, d, J = 7 Hz), 0.93 (3 H, d, J = 7 Hz); UV (hexanes) 240 (ϵ 4580), 316 nm (ϵ 70).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.31; H, 11.52.

2-Chloro-3-propionylcycloheptene. Following the same procedure as for vinylchloro ketone **4b,** 25.96 g (0.195 mmol) of aluminum chloride, 14.34 g (0.155 mmol) of propionyl chloride, and 20.20 g (0.155 mmol) of 1-chlorocycloheptene in 122 mL of methylene chloride were reacted and gave 16.06 g (56%) of distilled product: bp 69–71 °C (0.30 mm); IR (neat) 3038, 1718, 1643 cm^{-1}; ^1H NMR (CCl_4) δ 6.03 (1 H, t, J = 6.5 Hz), 3.49–3.28 (1 H, m), 2.34 (2 H, q, J = 7.0 Hz), 2.33–1.43 (8 H, m), 1.05 (3 H, t, J = 7.0 Hz); MS (70 eV) m/e 188 (M + 2, 1), 186 (M^+, 3), 95 (10), 93 (6), 79 (6), 77 (5), 57 (100), 39 (5).

6-Propionyl-1,4-dioxaspiro[4.6]undecane (4a). Following the procedure for spiro ketone **4b,** 6.17 g (9.35 mmol) of 85% KOH pellets, 41.93 g (0.676 mmol) of ethylene glycol, and 15.75 g (84.5 mmol) of 2-chloro-3-propionylcycloheptene in 50 mL of *p*-dioxane were heated at reflux for 23 h. Workup as before and distillation gave 10.69 g (60%) of the product: bp 85–95 °C (0.70 mm); IR (neat) 1712 cm^{-1}; ^1H NMR (CCl_4) δ 3.78 (4 H, s), 3.00–2.16 (3 H, m), 1.97–1.29 (10 H, m), 0.94 (3 H, 5, J = 7.5 Hz); MS (70 eV) m/e 212 (M^+, 10), 183 (32), 155 (38), 113 (18), 100 (10), 99 (100), 57 (19), 55 (18), 41 (11).

2-(3-Pentylidene)cycloheptanone (2c). Following the procedure for the preparation of enone **2d,** 12.26 g (57.8 mmol) of keto ketal **4a** in 80 mL of purified pentane was reacted at 0 °C with 121 mL (91.6 mmol) of 0.757 M ethyllithium in benzene to give 14.27 g (102%) of a crude oily tertiary carbinol: ^1H NMR (CCl_4) δ 4.18–3.38 (5 H, m), 2.58–1.10 (15 H, m), 0.81 (6 H, t, J = 7.5 Hz). This oil was used without further purification. A 14.27-g (59 mmol) portion of hydroxy ketal was hydrolyzed and eliminated as for enone **2d** with 38 mL of 1.3 M H_2SO_4 in 363 mL of methanol. The crude product (5.92 g, 56%) was distilled, bp 69–80 °C (0.70 mm). An analytical sample was collected by VPC (10 ft, 20% Carbowax 20 M on Chromosorb P, nonacid washed, 160 °C): IR (neat) 1681, 1608 cm^{-1}; ^1H NMR (CCl_4) δ 2.61–1.82 (8 H, m), 1.82–1.35 (6 H, m), 1.18–0.72 (6 H, m); MS (70 eV) m/e 180 (M^+, 93), 152 (14), 151 (96), 137 (51), 123 (45), 110 (34), 109 (25), 95 (41), 81 (100), 79 (22), 69 (20), 67 (63), 55 (59), 41 (59).

Ozonolysis of $\Delta^{1,7}$-8-Isopropyl-8-methylbicyclo[5.1.0]octene (1d). A 0.1147-g (0.70 mmol) sample of cyclopropene **1d** with 15 mL of spectrograde methylene chloride (Mallinckrodt) was placed in a 25 × 200 mm side-arm test tube. The solution was cooled to −78 °C and ozone (Welsbach T-408 Ozonator) was bubbled through the solution until the solution turned blue. The excess ozone was purged with oxygen and 0.64 g (10.3 mmol) of dimethyl sulfide (Me_2S) was added at −78 °C. The reaction sat at −78 °C for 15 min, then was warmed to room temperature and sat another 15 min. The solvent and excess Me_2S were evaporated and pentane was added. The product solution was washed with water and dried with Na_2SO_4. Concentration left 0.11 g (80%) of a yellow oil. Two products were collected by GC (6 ft, 5% Carbowax 20 M on Chromosorb W, nonacid washed). The major product, conversion ~60%, identified as the expected 2-isopropyl-2-methylcycloocta-1,3-dione, had the following spectra data: IR (CCl_4) 1713, 1687, 1395, 1378 cm^{-1}; ^1H NMR (CCl_4) δ 2.56 (1 H, septet, J = 6.7 Hz), 2.51–2.13 (4 H, m), 1.98–1.40 (6 H, m), 1.16 (3 H, s), 0.79 (6 H, d, J = 6.8 Hz); MS (70 eV) m/e 196 (M^+, 17), 99 (13), 98 (55), 97 (14), 83 (100), 71 (22), 55 (73), 41 (38). The minor product, conversion ~20%, identified as 2-isopropyl-2-methyl-3-oxacyclonona-1,4-dione had the following spectral data: IR (CCl_4) 1740, 1720, 1395, 1381 cm^{-1}; ^1H NMR (CCl_4) δ 2.89–1.50 (11 H, m), 1.52 (3 H, s), 0.99 (3 H, d, J = 6.7 Hz), 0.79 (3 H, d, J = 6.7 Hz); MS (70 eV) m/e 212 (M^+, 0.3), 126 (37), 99 (39), 98 (63), 83 (19), 80 (25), 70 (40), 69 (57), 56 (18), 55 (100).

Products from Epoxidation of Cyclopropenes 1a–d. All product runs were done in CCl_4 at 0 °C with ~0.05 M cyclopropene and 0.05 M 85% *m*-chloroperbenzoic acid. After 2–11 h, the organic solution was washed with 0.6 M of $NaHCO_3$, dried over Na_2SO_4, and concentrated. Analysis by ^1H NMR and GC (Carbowax) showed the respective enones **2a–d** as the major or sole products. Minor signals in the ^1H NMR were attributed to further oxidation of the primary enone products.

Absolute Kinetics. The procedure used was essentially the same as described earlier by Friedrich and Fiato.[4e]

Competitive Kinetics. A mixture of approximately 0.01 M in each cyclopropene, A and B, along with 0.01 M undecane or decane as an internal standard was prepared in CCl_4 (Eastman Spectro ACS) in a 5-mL volumetric flask. The flask was kept at 0 °C. From 10- to 100-μL portions of 0.13 M *m*-chloroperbenzoic acid in CCl_4 (saturated) were added and the flask was shaken. Ten minutes after each addition, aliquots of the solution were analyzed by GC with a flame ionization detector (15 ft, 10% Carbowax 20 M on Chromosorb P, nonacid washed, 120 °C). The areas of the two cyclopropenes were divided by the area of the internal standard. The normalized cyclopropene areas were fitted to the following equation to find the best value of k_A/k_B. A general least-squares program was used which provides weighting for each observable. The data was also visually examined by a plot of ln A_t vs. ln B_t, on which was indicated the calculated slope and intercept.

$$\frac{\ln (A_t/A_0)}{\ln (B_t/B_0)} = \frac{k_A}{k_B}$$

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Registry No.—**2a,** 23438-72-4; **2a** tosylhydrazone, 17826-99-2; (*E*)-**2b,** 64425-35-0; (*E*)-**2b** tosylhydrazone, 64425-36-1; (*Z*)-**2b,** 64425-37-2; (*Z*)-**2b** tosylhydrazone, 64425-38-3; **2c,** 64425-39-4; **2c** tosylhydrazone, 64425-40-7; (*E*)-**2d,** 64425-41-8; (*E*)-**2d** tosylhydrazone, 64425-42-9; (*Z*)-**2d,** 64425-43-0; (*Z*)-**2d** tosylhydrazone, 64425-44-1; **3,** 64440-65-9; **4a,** 64425-45-2; **4a** tertiary carbinol derivative, 64425-52-1; **4b,** 64425-46-3; **4b** tertiary carbinol derivative, 64425-53-2; 2-(dithiomethoxymethylene)cycloheptanone, 61539-01-3; 2,6-di-*tert*-butyl-*p*-cresol, 128-37-0; cycloheptanone, 502-42-1; 1-(1-propen-2-yl)cycloheptene, 64425-47-4; 3-isopropylidenecycloheptene, 53147-82-3; boron trifluoride, 7637-07-2; propionic anhydride, 123-62-6; 1-chlorocycloheptene, 13294-30-9; 1,1-dichlorocycloheptane, 32617-34-8; isobutyryl chloride, 79-30-1; 2-chloro-3-isobutyrylcycloheptene, 64425-48-5; ethylene glycol, 107-21-1; 2-chloro-3-propionylcycloheptene, 64425-49-6; propionyl chloride, 79-03-8; 2-isopropyl-2-methylcycloocta-1,3-dione, 64425-50-9; 2-isopropyl-2-methyl-3-oxacyclonona-1,4-dione, 64425-51-0; methyllithium, 917-54-4; ethyllithium, 811-49-4.

References and Notes

(1) Taken primarily from the Ph.D. thesis of R. A. Leckonby, University of Rochester, 1976.
(2) Taken in part from the Masters thesis of D. M. Stout, University of Rochester, 1971. D. Stout performed the first synthesis of compound **1b.**
(3) Y.-S. Lam performed the competitive kinetics experiments.
(4) (a) L. E. Friedrich and R. A. Cormier, *J. Org. Chem.*, **35,** 450 (1970); (b) *Tetrahedron Lett.*, 4761 (1971); (c) L. E. Friedrich and R. A. Fiato, *J. Org. Chem.*, **39,** 416 (1974); (d) *ibid.*, **39,** 2267 (1974); (e) *J. Am. Chem. Soc.*, **96,** 5783 (1974); (f) see also J. Ciabattoni and P. J. Kocienski, *ibid.*, **91,** 6534 (1969).
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(6) (a) See O. P. Strausz, R. K. Gosavi, A. S. Denes, and I. G. Csizmadia, *J. Am. Chem. Soc.*, **98,** 4784 (1976), and references cited therein; (b) see also J. F. Liebman and A. Greenberg, *Chem. Rev.*, **76,** 311 (1976).
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Synthesis of Epoxides with Electronegative Substituents. Photometric Substrates for Epoxide Hydrase

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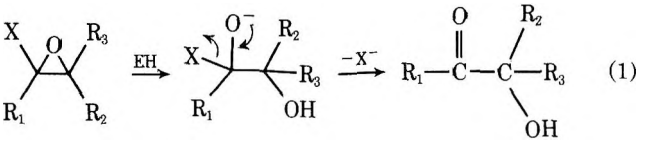
The synthesis of styrene oxides bearing potential leaving groups as α substituents was attempted via peracid epoxidation of the corresponding olefins. Such epoxides were sought as potential photometric substrates for epoxide hydrase. Peracid epoxidations of α-chloro-, α-trimethylsilyloxy-, α-ethoxy-, or α-bromostyrene, as well as α-bromo- or α-(*tert*-butyl)dimethylsilyloxy-*p*-nitrostyrene, lead only to oxidized rearranged products; their epoxides could not be detected among the reaction products. Peracid epoxidation of α-acetoxystyrene and α-methoxy-*p*-nitrostyrene did lead to mixtures containing the desired epoxides, as judged by their NMR spectra, but attempts to isolate these epoxides were unsuccessful due to their great reactivity in the presence of acids or protic solvents. However, using similar methods we were able to synthesize, purify, and characterize the epoxides of α-acetoxy-, α-trifluoroethoxy-, and α-fluoro-*p*-nitrostyrene (**4d**, **4h**, and **4i**, respectively). The half-lives of these oxides (0.25 mM) in 0.1 M phosphate buffer (pH 8.00) were 35, 0.4, and 0.4 min, respectively, and each was cleanly hydrated to α-hydroxy-*p*-nitroacetophenone. The hydration of **4d** (which could be monitored conveniently at 310 nm) was accelerated 11-fold by solubilized liver microsomal epoxide hydrase; this compound was not significantly affected by microsomal esterases. The effects of α substituents on the reactivity of styrene oxides and the mechanisms of their rearrangements are discussed. A mechanism involving a halonium ion–enol π complex is proposed to account for the fact that chloro- and bromooxiranes readily undergo proton-catalyzed halogen migrations, whereas fluorooxirane **4i** was much less reactive and reacted only with loss of fluoride ion.

The recognition of epoxides as cytotoxic, carcinogenic, and mutagenic metabolites of arenes and olefins has over the past few years stimulated considerable interest in both the enzymatic and nonenzymatic reactivity of this class of compounds.[1-3] The enzyme epoxide hydrase is thought to play a protective role in vivo by converting chemically reactive epoxides to relatively nontoxic diols. The relatively broad substrate specificity of epoxide hydrase has led to the development of numerous chromatographic and radiometric assays for this enzyme.[4] Unfortunately these assays do not lend themselves readily to mechanistic studies of the enzyme, because they are rather tedious and often tend to be less precise than one would like. A photometric assay for epoxide hydrase which could provide continuous data rather than data points would be greatly preferred. Since the oxirane ring itself is not a chromophore which can be observed spectrally in the presence of protein, it thus becomes necessary to consider substrates whose enzymatic hydration can be chemically coupled to the unmasking of a suitable chromophore. In contemplating this problem we came upon the idea that a styrene oxide with a suitable leaving group at the α position should, upon enzymatic hydration, generate an aromatic ketone chromophore as shown below (eq 1). Our reasoning was based on the fact that 1,1-disubstituted epoxides are relatively good substrates for epoxide hydrase[5] and that their enzymatic hydration involves exclusive ($\geq$97%) cleavage of the O–CH_2 bond by a nucleophilic mechanism.[6]

Epoxides bearing good leaving groups directly on the oxirane ring are known to be very unstable and highly prone to rearrangement or hydrolysis.[7] Thus it was apparent from the outset that synthesis of epoxides suitable for enzymatic use according to eq 1 would require a delicate compromise be-



(1)

tween the electronic (and possibly steric) properties of the aryl group R_1 and the leaving group X. In this paper we report the synthesis and characterization of three such epoxides, one of which is suitable for photometric assay of epoxide hydrase. We also report the attempted syntheses of several related epoxides and discuss the effects of the substituents on the relative reactivity of epoxides of this type.

Results and Discussion

In designing a photometric substrate for a particular enzyme a number of factors must be taken into consideration. For example, the enzyme catalyzed reaction must generate, at a wavelength not subject to interference by other chromophores in the system, a large enough difference in absorption to give the desired sensitivity. If chromophore generation is to depend on the occurrence of nonenzymatic steps subsequent to the initial enzymatic event, then the former must be considerably faster than the latter. In addition, the substrate should be chemically stable under the assay conditions, so that nonenzymatic background rates are negligible. Finally, the compound should be a good substrate, conforming to the

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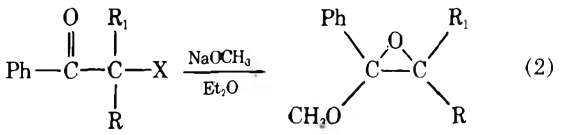
general pattern of structure–activity relationships established for the enzyme.

For the specific case of microsomal epoxide hydrase (EH) we reasoned that if a suitable leaving group X were substituted on the oxirane ring the diol formed by hydration would undergo spontaneous and rapid loss of HX (eq 1) to generate a carbonyl group, which, depending on R_1, might have absorption characteristics suitable for a sensitive photometric assay. A number of tri- or tetrasubstituted chloro- and methoxy oxiranes have been synthesized by various groups,[7-10] but unfortunately epoxide hydrase is extremely selective for mono-, 1,1-di-, or *cis*-1,2-disubstituted epoxides. Since styrene oxide is an efficiently hydrated prototype substrate used in numerous chromatographic and radiometric assays[4] for EH, α-monosubstituted styrene oxides appeared to a logical choice for development as photometric substrates.

In contrast to the numerous syntheses of highly substituted chloro- and methoxyoxiranes, simple styrene oxides bearing an electronegative substituent at the α position are virtually unknown. Our attempts to prepare α-methoxystyrene oxide by analogy (eq 2c) to Stevens' synthesis of α-methoxy-β-substituted styrene oxides (eq 2a,b) were uniformly unsuccessful. Apparently for this reaction to succeed it is important that the halide be on a secondary or tertiary carbon center. This effect has also been noticed[11] in analogous additions of cyanide ion to α-chloroacetaldehyde, -butyraldehyde, and -isobutyraldehyde, in which the yields of epoxynitrile product were 0%, 46%, and 100%, respectively.

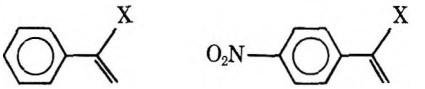


(2)

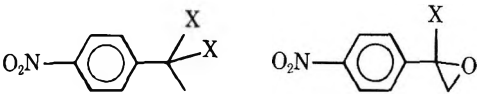
Eq	X	R, R_1	% yield
2a	Br	$-(CH_2)_5-$	83
2b	Cl, Br	CH_3, H	66
2c	Br	H, H	0

Another potential route to the desired α-substituted styrene oxides involved the peracid epoxidation of the corresponding olefins. Thus we synthesized styrenes **1a–e** using standard procedures and attempted their epoxidation under a variety of conditions at room temperature and below. The reagents and conditions employed included CH_3CO_3H–NaOAc–CH_2Cl_2, various peroxyimidic acids, and *m*-chloroperbenzoic acid (MCPBA), the latter being employed both with and without buffers (solid K_2CO_3 or K_2HPO_4) in pentane, CH_2Cl_2, or ether. In only one instance did NMR examination of reaction mixtures or their extracts suggest the presence of an oxirane methylene group, although in all cases the starting materials were rapidly consumed. In general, the NMR spectra of the product mixtures were consistent with the *formation and rearrangement* of the desired epoxide. Similar results have been reported previously for the peracid epoxidations of 1-chlorocyclohexene.[12] In our hands, various attempts at peracid epoxidation of freshly purified **1e** lead to the isolation of 50–70% yields of α-bromoacetophenone. In the case of **1b**, significant amounts of acetophenone, as well as numerous rearranged oxidized products, were obtained upon workup. This was true even when the epoxidations were carried out under rigorously dry conditions. However, in the NMR spectrum of the product mixture from MCPBA epoxidation of α-acetoxystyrene (**1d**) appeared an encouraging sign, a pair of sharp doublets (J = 5 Hz) at δ = 2.92 and 3.23. While this suggested the presence of the desired epoxide in the reaction mixture, attempts to isolate it were unsuccessful.

Since carbonium ion stability usually plays an important role in governing the reactivity of epoxides, particularly epoxides in which a benzylic center is present, we carried out an analogous series of epoxidation attempts on the α-substituted *p*-nitrostyrenes **2c–i**. For the most part the required styrenes were obtained by modification of the syntheses used for olefins **1a–e**. The enol ethers **2c, 2g,** and **2h,** for example, were obtained by the elimination of alcohol from the corresponding ketal of *p*-nitroacetophenone, **3**. Thus styrene **2c** was easily formed by heating diethyl ketal **3c** in toluene containing pTsOH as catalyst for 30 h. However, these conditions were not sufficient to eliminate CH_3OH or CF_3CH_2OH from the corresponding ketals **3g** or **3h**. In fact, heating **3g** with *p*-TsOH in toluene, even under rigorously dry conditions, consistently led to the formation of *p*-nitroacetophenone. The same was true for the bis(trifluoroethyl) ketal **3h**. The mechanism of this reaction is not known, but the formation of ketones from ketals under nonhydrolytic conditions has



1a–e **2c–i**



3c,g,h **4d,h,i**

a, X = Cl
b, X = $OSiMe_3$
c, X = OEt
d, X = OAc
e, X = Br
f, X = $OSi(tBu)Me_2$
g, X = OCH_3
h, X = OCH_2CF_3
i, X = F

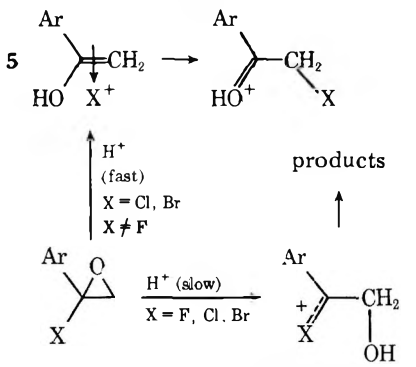
been reported previously.[13] Ultimately these eliminations were effected with $POCl_3$ in refluxing pyridine.[13] Under these conditions dimethyl ketal **3g** reacted smoothly and completely in 6 h, but the bis(trifluoroethyl) ketal **3h** proved exceptionally unreactive and did not react completely even after 1 week. This pattern of reactivity has also been observed, although over a more compressed range, in the acid catalyzed hydrolysis of formaldehyde acetals,[14] and it clearly foretold the properties of the epoxides which eventually were derived from styrenes **2c, 2g,** and **2h.**

As with the α-substituted styrenes **1a–e,** epoxidations of the nitrostyrenes **2c–i** were attempted under a variety of conditions. In general the nitro compounds reacted considerably more slowly, and the reactions were considerably cleaner. For example, epoxidation of **2e** with MCPBA in CH_2Cl_2 over solid K_2CO_3 at 0 °C for 10 min gave an almost quantitative yield of α-bromo-*p*-nitroacetophenone, and epoxidation of **2f** apparently gave only a single product (as judged by the NMR spectrum), the silyl derivative of α-hydroxy-*p*-nitroacetophenone. On the other hand, epoxidation of **2c** led to the formation of α-ethoxy-*p*-nitroacetophenone, along with other unidentified products. In none of these cases did NMR examination of product mixtures suggest the presence of the desired epoxides.

Epoxidation of the methoxystyrene **2g** with MCPBA in CH_2Cl_2 over solid K_2CO_3 not only gave α-methoxy-*p*-nitroacetophenone, but some of the desired epoxide **4h** was also present in the mixture, as judged by a pair of sharp doublets (δ 2.91 and δ 3.43, J = 4.0 Hz) characteristic of oxirane methylene groups. Unfortunately, this epoxide was too reactive to isolate; even on standing in $CDCl_3$ solution in an NMR tube it rearranged completely in 24 h.

Epoxidation of the trifluoroethyl enol ether **2h** using MCPBA in CH_2Cl_2 over solid K_2CO_3 or K_2HPO_4 also gave a mixture of products, but the NMR spectrum suggested that the desired epoxide **4h** comprised ca. 75% of the mixture. The

Scheme I



rest of the mixture appeared to be primarily trifluoroethyl *p*-nitrobenzoate.[15] Attempts to recrystallize **4h** from protic solvents (e.g., MeOH) led to its complete and rapid decomposition; although it could be recrystallized from CCl_4 or chromatographed on silica gel, little purification was achieved in this way. Ultimately **4h** was purified by repeated recrystallization from pentane. Similar results were obtained with the epoxidation of enol acetate **2d.** This olefin was considerably less reactive than the others, and it underwent epoxidation smoothly with *unbuffered* MCPBA in *refluxing* CH_2Cl_2. The resulting epoxyacetate **4d** proved to be an exceptionally stable epoxide and could be recrystallized and chromatographed even more casually than **4h.** No rearrangement products were observed during the epoxidation of **2d** or the subsequent manipulations of **4d;** the only routes of decomposition observed appeared to be hydrolytic, as discussed below.

The final olefin epoxidized in these studies was *p*-nitro-α-fluorostyrene, **2i.** The synthesis of this olefin proved quite straightforward. *p*-Nitrostyrene was fluorobrominated using *N*-bromosuccinimide and polymerized HF in pyridine.[16] Dehydrobromination of the latter using potassium *tert*-butoxide in refluxing *tert*-butyl alcohol afforded **2i** in 80% yield based on *p*-nitrostyrene. Whereas both the epoxidation of bromostyrene **2e** (MCPBA, CH_2Cl_2, 0 °C) and the subsequent rearrangement of the epoxide were complete in less than 10 min, epoxidation of **2i** required 16 h of refluxing in CH_2Cl_2 with an excess of MCPBA. Again, the epoxide was exceptionally stable compared to many of the others discussed above, and it was obtained in good yield despite the fact that no basic buffers were used in the epoxidation. In fact, in our first attempts to epoxidize **2i,** we found that the use of MCPBA–K_2CO_3 in CH_2Cl_2 led mainly to *polymerization* of the olefin. As with epoxyacetate **4h,** but in sharp contrast to the α-chloro or α-bromo epoxides, fluoro epoxide **4i** showed no tendency to rearrange, appearing instead to decompose by solvolytic or hydrolytic mechanisms to compounds devoid of fluorine.

Of the three α-substituted styrene oxides which could be isolated (**4d, 4h,** and **4i**), none proved exceptionally stable in *aqueous* solutions. Their reactions could be conveniently followed at 310 nm. All three epoxides reacted in water to give the same product, as judged by their identical UV spectra. From the reaction of **4i,** the sole reaction product was isolated and shown by IR, UV, and NMR to be α-hydroxy-*p*-nitroacetophenone. In fact, the latter is also somewhat unstable in aqueous solution, decomposing over a period of hours to bright yellow products which were not identified. At a concentration of 0.25 mM in 0.1 M phosphate buffer at pH 8.00, the fluoro epoxide **4i** had a half-life of approximately 0.4 min; the trifluoroethoxy epoxide **4h** was approximately as reactive under the same conditions. In contrast, epoxyacetate **4d** was almost two orders of magnitude *less* reactive, undergoing hydration with a half-life of approximately 35 min.

Although a half-life of 35 min is somewhat less than we had hoped for, this order of reactivity nevertheless gives quite workable nonenzymatic background rates, and using epoxide **4d** with solubilized preparations of epoxide hydrase we have obtained enzymatic hydration rates greater than 11 times the nonenzymatic rate.[17] We have also obtained evidence that microsomal esterases do not affect epoxyacetate **4d,** although enol acetate **2d** is an excellent substrate for these enzymes. The details of these experiments and the development of a photometric assay of epoxide hydrase based on **4d** as the substrate will be reported elsewhere.

From our successes and failures in the attempted syntheses of α-substituted styrene oxides, it is clear that the reactivity of the latter is governed by the effects of the para and α substituents on the stability of the benzylic carbonium ions formed by acid catalyzed opening of the oxirane ring; i.e., H > NO_2, and R_3SiO > EtO > MeO > CF_3CH_2O > AcO. With respect to the halooxiranes, it is interesting that the fluoro compound gave no fluorine-containing rearrangement products, whereas α-haloacetophenones were formed in high yield during the epoxidations of **1a, 1e,** and **2e.** A mechanism which may account for this divergent behavior is given in Scheme I. The essential feature of this mechanism is the intermediacy of the halonium ion π complex, **5.** Its formation provides an obvious role for acid catalysis in these migrations, which has not been accounted for previously.[7] Scheme I *may* also provide an explanation for the paradoxical *decrease*[7] in reactivity of chlorooxiranes as methyl substituents are placed on the ring carbons. The stability of olefin π complexes is a delicate function of electronic, steric, and solvent effects.[18,19] While sufficient data to unravel these effects are not yet available, it may be noted that although increasing the methyl substitution in a series of olefins increases their rates of bromination[20] it *decreases* their affinity for Ag(I)[21] and their rates of hydroxymercuration in solution.[22] The lack of fluorine migration in reaction of **4i** could be a consequence of the extreme electronegativity of F and its reluctance to form fluoronium ions.[23] A related π-complex mechanism may be involved in the NIH shift of a chlorine atom during the hydroxylation of *p*-chlorophenylalanine by phenylalanine hydroxylase to form 3-chlorotyrosine.[2]

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. NMR spectra were determined on a Varian T-60 instrument using Me_4Si as an internal standard.

α-Chlorostyrene (1a). This compound was prepared in 38% yield by the method of Dufraisse and Viel.[24] NMR ($CDCl_3$) δ 5.44 (d, 1 H, J = 1.5), 5.66 (d, 1 H, J = 1.5), 7.15–7.73 (m, 5 H).

α-Bromostyrene (1e). This compound was prepared in 47% yield by dehydrobromination of styrene dibromide with KOH in refluxing ethanol, followed by chromatography on silica gel with ligroin as eluent: NMR ($CDCl_3$) δ 5.65 (d, 1 H, J = 1.5 Hz), 5.98 (d, 1 H, J = 1.5 Hz), 6.90–7.62 (m, 5 H).

***p*-Nitro-α-bromostyrene (2e).** *p*-Nitrostyrene[25] was dissolved in CCl_4 and treated with an equimolar quantity of bromine for 16 h at room temperature to give a 74% yield of *p*-nitrostyrene dibromide (mp 74–75 °C): NMR ($CDCl_3$) δ 3.99 (d, 1 H), 4.13 (s, 1 H), 5.23 (dd, 1 H), 7.64 (d, 2 H), 8.28 (d, 2 H).

This dibromide (2.7 g, 8.75 mmol) was dissolved in *t*-BuOH containing 1.47 g (13.1 mmol) of *t*-BuOK and the solution was refluxed for 15 h. The mixture was then poured into four volumes of water and extracted with CH_2Cl_2. Evaporation of the extract and recrystallization from hexane gave yellow crystals (1.0 g, 50% yield) which decomposed upon storage for several days at room temperature: NMR ($CDCl_3$) δ 5.95 (d, 1 H, J = 2.0), 6.30 (d, 1 H, J = 2.0), 7.70 (d, 2 H), 8.15 (d, 2 H).

α-Trimethylsilyloxystyrene (1b). The compound was prepared using the method of House,[26] except that the reaction was carried out at room temperature for 4 days. This compound was quantitatively hydrolyzed upon column chromatography (alumina or silica) but could be obtained in ≥95% purity by distillation through a Vigreux column (bp 99–100 °C at 5 Torr): NMR ($CDCl_3$) δ −0.12 (s, 9 H), 4.05 (d, 1 H, J = 1.0 Hz), 4.52 (d, 1 H, J = 1.0 Hz), 6.63–7.80 (m, 5 H).

p-Nitro-α-(*tert*-butyldimethylsilyloxy)styrene (2f). The method of House was used.[26] The workup procedure yielded an orange oil which was purified in ca. 65% yield by column chromatography through silica gel, eluting with 90:10 ligroin–ether, yielding a yellow oil: NMR ($CDCl_3$) δ 0.23 (s, 6 H), 1.02 (s, 9 H), 4.58 (d, 1 H, J = 2.0 Hz), 4.86 (d, 1 H, J = 2 Hz), 7.68 (d, 2 H), 8.13 (d, 2 H).

α-Ethoxystyrene (1c). Acetophenone (10.0 mL, 10.3 g, 85.7 mmol) and triethylorthoformate (20.0 mL, 17.8 g, 120.1 mmol) were dissolved in 25 mL of EtOH, and 1 drop of concentrated HCl was added. The mixture was stirred for 1 day at room temperature. The mixture was poured into water and extracted with ether. The solvent was evaporated to give a yellow oil which was filtered through a column of silica gel using 95:5 ligroin–ether: NMR ($CDCl_3$) δ 1.35 (t, 3 H), 4.32 (q, 2 H), 7.42 (m, 3 H), 8.02 (m, 2 H).

Ketals of p-Nitroacetophenone. Ten grams of p-nitroacetophenone and 25.0 mL of the desired trialkylorthoformate were dissolved in 20 mL of the corresponding alcohol and heated to reflux. The alcohol and trialkylorthoformate were then evaporated, and the remaining mixture was taken up in ether and washed with water.

p-Nitroacetophenone diethyl ketal (3c) was obtained with a 6-h reflux. The crude product was used without further purification: NMR ($CDCl_3$) δ 1.25 (t, 6 H), 1.5 (s, 3 H), 3.63 (dq, 4 H), 7.69 (d, 2 H), 8.18 (d, 2 H).

p-Nitroacetophenone dimethyl ketal (3g) was obtained with a 2-h reflux and used without further purification: yield, 79%; NMR ($CDCl_3$) δ 1.55 (s, 3 H), 3.19 (s, 6 H), 7.68 (d, 2 H), 8.18 (d, 2 H).

p-Nitroacetophenone bis(trifluoroethyl)ketal (3h) was obtained with a 24-h reflux and used without further purification: yield, 61%; mp 50–51 °C; NMR ($CDCl_3$) δ 1.79 (s, 3 H), 3.91 (dq, 4 H), 7.79 (d, 2 H), 8.32 (d, 2 H).

Tris(trifluoroethyl)orthoformate. This orthoformate was prepared by the method of Hill[27] from trifluoroethanol, ferric chloride, and chloroform: yield, 17%; bp 132–133 °C; NMR (CCl_4) δ 4.03 (m, 6 H), 5.57 (s, 1 H).

p-Nitro-α-ethoxystyrene (2c). Crude ketal **3c** was heated to a gentle reflux in toluene with 500 mg of p-toluenesulfonic acid for 30 h. The mixture was cooled and stirred over solid $NaHCO_3$, and the toluene was evaporated to give yellow crystals which were recrystallized from ligroin and then from CH_3OH: yield, 47% (from p-nitroacetophenone); mp 49–51 °C; NMR ($CDCl_3$) δ 1.62 (t, 3 H), 3.95 (q, 2 H), 4.38 (d, 1 H, J = 3.0), 4.78 (d, 1 H, J = 3.0), 7.75 (d, 2 H), 8.15 (d, 2 H).

p-Nitro-α-methoxystyrene (2g). The enol ether was prepared by the method of Rappaport[13] from dimethyl ketal **3g**, $POCl_3$, and pyridine by heating for 6 h at 100 °C. The compound was purified by recrystallization once from methanol and once from ligroin: yield, 95%; NMR ($CDCl_3$) δ 3.78 (s, 3 H), 4.42 (d, 1 H, J = 3.5), 4.83 (d, 1 H, J = 3.5), 7.73 (d, 2 H), 8.13 (d, 2 H).

p-Nitro-α-trifluoroethoxystyrene (2h). The enol ether was made by a modification of the procedure of Rappaport.[13] The ketal **3h** (1.5 g, 4.3 mmol) and $POCl_3$ (3.2 mL, 5.3 g, 34.6 mmol) were heated to reflux in 30 mL of pyridine and 10 mL of toluene for 7–10 days. The reaction was stopped by adding 10% aqueous NaOH *dropwise* at 0 °C until the solution was neutralized and then extracting with two portions of $CHCl_3$. The solvent was dried and evaporated to yield brown crystals which were filtered through a column of silica gel using 80:20 ether–ligroin as an eluent. Finally, the compound was recrystallized from ligroin: yield, 0.79 g (31%); mp 83–84 °C; NMR ($CDCl_3$) δ 4.33 (q, 2 H), 4.51 (d, 1 H, J = 4.0), 5.05 (d, 1 H, J = 4.0), 7.83 (d, 2 H), 8.27 (d, 2 H). Anal. Calcd for $C_{10}H_8F_3NO_3$: C, 48.53; H, 3.26; N, 5.67. Found: C, 48.85; H, 3.16; N, 5.47.

p-Nitro-α-fluoro-β-bromoethylbenzene. This compound was prepared by the method of Olah[16] from p-nitrostyrene, N-bromosuccinimide, and pyridine·$(HF)_x$ in ether. The reaction was stirred in a polyethylene bottle overnight at room temperature: yield, 85%; mp 73–74 °C; NMR ($CDCl_3$) δ 3.70 (dd, 2 H, J_{HF} = 20), 5.80 (dt, 1 H, J_{HF} = 57.5), 7.62 (d, 2 H), 8.27 (d, 2 H).

α-Fluoro-p-nitrostyrene (2i). The α-fluoro-β-bromo compound (7.5 g., 30.2 mmol) and 4.1 g (36.2 mmol) of potassium *tert*-butoxide were dissolved in 150 mL of *t*-BuOH and stirred at room temperature for 30 min. The mixture was poured into water, the crystals were filtered, and the mixture was then recrystallized first from 80:20 MeOH–H_2O and then from ligroin: yield, 4.6 g (94%); mp 62–63 °C; NMR ($CDCl_3$) δ 4.90 (dd, 1 H, J_{HF} = 7), 5.44 (dd, 1 H, J_{HF} = 30.0), 7.68 (d, 2 H), 8.23 (d, 2 H). Anal. Calcd for $C_8H_6FNO_2$: C, 57.49; H, 3.62; N, 8.38. Found: C, 57.20; H, 3.62; N, 8.23.

p-Nitro-α-acetoxystyrene (2d). The compound was made by the method of Pollack and Noyce.[28] Purification was achieved by first reducing the unreacted p-nitroacetophenone to the corresponding alcohol using sodium cyanoborohydride in 95% EtOH, keeping the pH between 3 and 4 with an AcOH/NaOAc buffer. The mixture was then poured into water and extracted with ether. After solvent evaporation, the crystals were recrystallized once from ethanol and once from ligroin, giving pure **2d:** yield, 20%; mp 51–52 °C (lit.[28] 52–53 °C); NMR ($CDCl_3$) δ 2.32 (s, 3 H), 5.17 (d, 1 H, J = 2.0), 5.52 (d, 1 H, J = 2.0), 7.55 (d, 2 H), 8.12 (d, 2 H).

Epoxidation Methods. m-Chloroperbenzoic acid was dissolved in ether and extracted with pH 8.0 phosphate buffer before use.

Method A. The styrene derivative and a 1.5 molar excess of MCPBA were dissolved in CH_2Cl_2 and stirred at either 0 °C (enol ethers), room temperature (α-halo- and α-acetoxystyrenes), or at reflux (α-fluoro- and α-acetoxy-p-nitrostyrenes). The reaction was stopped by washing once with 10% aqueous $Na_2S_2O_3$ and then with aqueous $NaHCO_3$.

Method B. The styrene derivative and a 1.5 molar excess of MCPBA were dissolved in CH_2Cl_2 at 0 °C and then an excess of solid K_2CO_3 or K_2HPO_4 was added to the mixture. The mixture was stirred at room temperature for ca. 48 h. Periodic additions of small amounts of MCPBA were needed to drive the reaction to completion. After each addition, the mixture was chocked with moist pH paper to make sure it was not acidic. The reaction was stopped by washing once with 10% aqueous $Na_2S_2O_3$.

p-Nitro-α-trifluoroethoxystyrene oxide (4h) was made using method B. The compound was purified by three recrystallizations from pentane and gave satisfactory mass spectral analysis: yield of purified material, 10%; mp 50–51 °C; NMR ($CDCl_3$) δ 2.90 (d, 1 H, J = 4); 3.50 (d, 1 H, J = 4), 3.93 (q, 2 H, J = 9), 7.68 (d, 2 H), 8.28 (d, 2 H). Anal. Calcd for $C_{10}H_8F_3NO_4$: C, 45.62; H, 3.04; N, 5.32. Found: C, 45.69; H, 3.18; N, 5.00.

p-Nitro-α-fluorostyrene oxide (4i) was made using method A. Purification was achieved by recrystallization from ligroin: yield, 73%; mp 62–63 °C; NMR ($CDCl_3$) δ 3.03 (d, 1 H, J = 4.0), 3.55 (dd, 1 H, J_{HF} = 5.0), 7.63 (d, 2 H), 9.27 (d, 2 H). Anal. Calcd for $C_8H_6FNO_3$: C, 52.47; H, 3.30; N, 7.65. Found: C, 52.60; H, 3.25; N, 7.59.

p-Nitro-α-Acetoxystyrene oxide (4d) was synthesized by method A. Purification was achieved by recrystallization from CCl_4 and then from EtOH: mp 100–101 °C; yield, 58%; NMR ($CDCl_3$) δ 2.16 (s, 3 H), 3.01 (d, 1 H, J = 4.5), 3.40 (d, 1 H, J = 4.5), 7.58 (d, 2 H), 8.21 (d, 2 H). Anal. Calcd for $C_{10}H_9NO_5$: C, 53.81; H, 4.06; N, 6.28. Found: C, 53.40; H, 3.90; N, 6.03.

Formation and Rearrangement of α-Methoxy-p-nitrostyrene Oxide (4g). The epoxidation was carried out using method B and solid K_2CO_3 buffer. After workup, the NMR spectrum ($CDCl_3$) contained peaks corresponding to unreacted starting material, as well as the following peaks which were attributed to either α-methoxy-p-nitrostyrene oxide or α-methoxy-p-nitroacetophenone: δ 2.91 (d, J = 4 Hz, epoxide methylene), 3.35 (s, epoxide α-methoxyl), 3.43 (d, J = 4 Hz, epoxide methylene), 3.74 (s, acetophenone α-methoxyl), 5.61 (s, acetophenone methylene), 7.17–8.45 (m, aromatic protons).

The $CDCl_3$ solution was allowed to stand for 24 h in the NMR tube and the spectrum was retaken. It was identical with the above spectrum except that the peaks at δ 2.91, 3.35, and 3.43 had disappeared.

Hydrolysis of 4i. A solution of 200 mg of the epoxide in 15 mL of THF and 30 mL of H_2O was stirred for 10 min at room temperature. The reaction was extracted with two portions of CH_2Cl_2. The solvent was evaporated and the crystals were recrystallized once from CCl_4: mp 120–125 °C; NMR (CD_3COCD_3) δ 5.01 (s, 2 H); 8.35 (q, 4 H); IR ($CHCl_3$) 3505 m (OH), 1710 s(C=O); UV (H_2O) λ_{max} 267 nm (ε 9100).

The solid from the above reaction was subjected to the same conditions except that the time was extended to 8 h. The resulting solid was bright yellow and showed several new spots on TLC.

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Registry No.—**1a,** 618-34-8; **1b,** 13735-81-4; **1c,** 6230-62-2; **1d,** 2206-94-2; **1e,** 98-91-7; **2c,** 59938-04-4; **2d,** 22391-01-1; **2e,** 64600-19-7; **2f,** 64600-20-0; **2g,** 3440-23-1; **2h,** 64600-21-1; **2i,** 64600-22-2; **3c,** 64600-23-3; **3g,** 53577-98-3; **3h,** 64600-24-4; **4d,** 64600-25-5; **4g,** 64600-26-6; **4h,** 64600-27-7; **4i,** 64600-28-8; α-hydroxy-p-nitroacetophenone, 64611-67-2; styrene dibromide, 6607-46-1; p-nitrostyrene, 100-13-0; p-nitrostyrene dibromide, 64600-29-9; acetophenone, 98-86-2; triethylorthoformate, 122-51-0; p-nitroacetophenone, 100-19-6; trimethyl orthoformate, 149-73-5; tris(trifluoroethyl)orthoformate, 58244-27-2; p-nitro-α-fluoro-β-bromoethylbenzene, 64600-30-2; α-methoxy-p-nitroacetophenone, 7714-12-7.

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π-Complexed β-Arylalkyl Derivatives. 5. Polar Effects in the Formolysis of π-Complexed 9-Benzonorbornenyl and 9-Benzonorbornadienyl Methanesulfonates[1]

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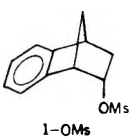
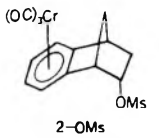
In a search for possible neighboring-group (direct d-orbital) participation by the metal, the formolysis rates of *anti*-9-benzonorbornenyl and *anti*-9-benzonorbornadienyl methanesulfonates (**6**- and **11**-OMs) have been compared with those of the π-complexed derivatives *endo*-tricarbonylchromium (**7**- and **12**-OMs), *exo*-tricarbonylchromium (**8**- and **13**-OMs) and, in the case of **6**-OMs only, the *endo*- and *exo*-trimethyl phosphite dicarbonylchromium derivatives (**9**- and **10**-OMs). At 60 °C the relative reactivities of **6**–**13**-OMs are 1.0, 0.005, 0.02, ~1.6, ~3.4, ~70, 0.06, and 0.07. All appear to yield unrearranged esters as the exclusive primary formolysis product, although formolysis of the complexes is accompanied by extensive oxidative decomplexation which prevents the determination of accurate titrimetric rate constants. It is suggested that the observed rate effects reflect differing ion-dipole interactions in the transition state of the rate-limiting step, rather than direct d-orbital participation by chromium.

In earlier papers in this series[2] we have reported several chromium tricarbonyl complexed β-arylalkyl methanesulfonates which solvolyze with partial or complete π-(aryl)-chromium tricarbonyl migration at rates that exceed those of their noncomplexed counterparts. To rationalize these and other observations, we suggested the possibility of direct d-orbital participation and/or σ–π homoconjugation. Each of these reaction paths, illustrated diagrammatically for the acetolysis of 2-[π-(phenyl)chromium tricarbonyl]-2-methyl-1-propyl methanesulfonate in Scheme I, suggests that the metal moiety should stabilize intermediates in which a positive charge is concentrated in the vicinity of the metal and requires that it precede the migrating aryl in a geometric sense during the rearrangement. We have shown that these conditions are fulfilled by demonstrating that at 75 °C the acetolysis of *exo*-2-[*endo*-π-(benzonorbornenyl)chromium tricarbonyl] methanesulfonate (**4**-OMs) is about 300 times as rapid as that of the exo-complexed methanesulfonate, **5**-OMs, that a portion of the former internally returns to the latter during acetolysis, and that both complexes yield the thermodynamically less stable endo-complexed *exo*-acetate, **4**-OAc, as the major product; cf. Scheme II.[3] We were able to demonstrate conclusively that tricarbonylchromium inductively retards acetolysis in cases where the aryl ring itself cannot participate anchimerically by comparing the acetolysis rate of *endo*-2-[*exo*-π-(norbornenyl)chromium tricarbonyl] methanesulfonate (**2**-OMs) with that of its noncomplexed analogue, **1**-OMs.[3] We were unable, however, to distinguish between direct metal bridging and σ–π homoconjugation as the mode of the metal-complex participation since either interpretation (Scheme I) appeared compatible with our data. In an effort to make such a distinction we have prepared and examined the solvolysis rates and products of a series of exo-π-complexed, *anti*-9-benzonorbornenyl and -norbornadienyl methanesulfonates designed to maximize the possibility of direct metal interaction.



1-OMs



2-OMs

Results

Preparation of Starting Materials. The π-complexed, 9-substituted benzonorbornenyl and -norbornadienyl derivatives were prepared from the known[4] noncomplexed alcohols

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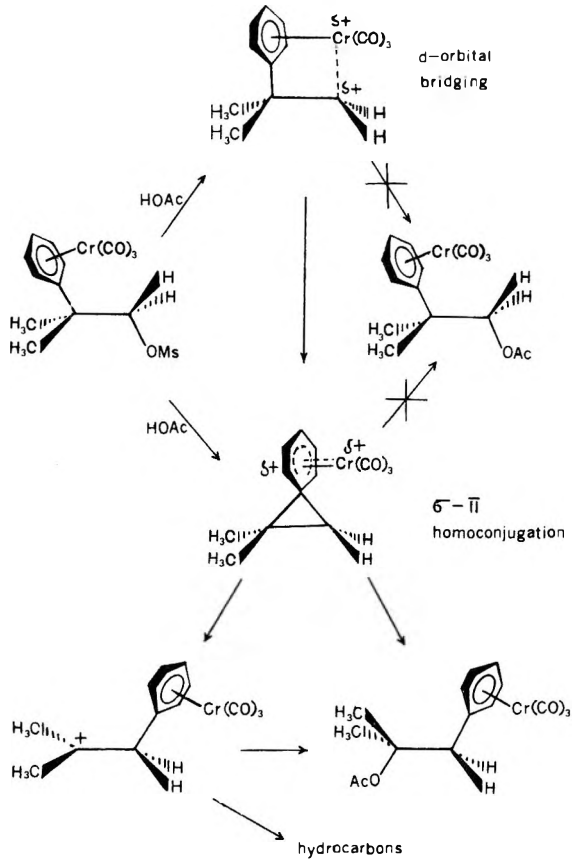
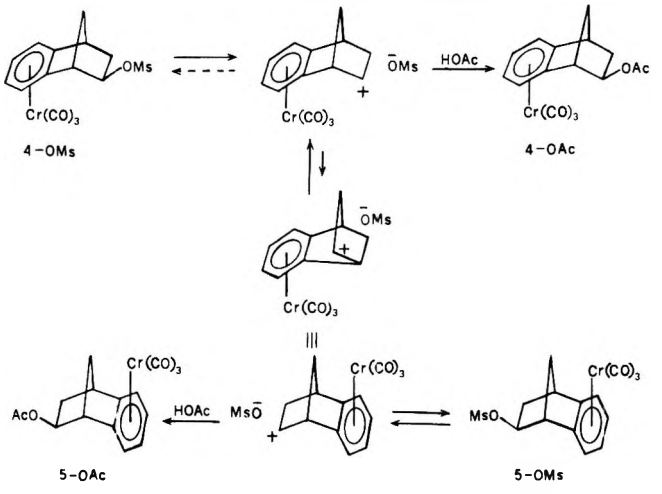
Scheme I. Possible Modes of Chromium Participation

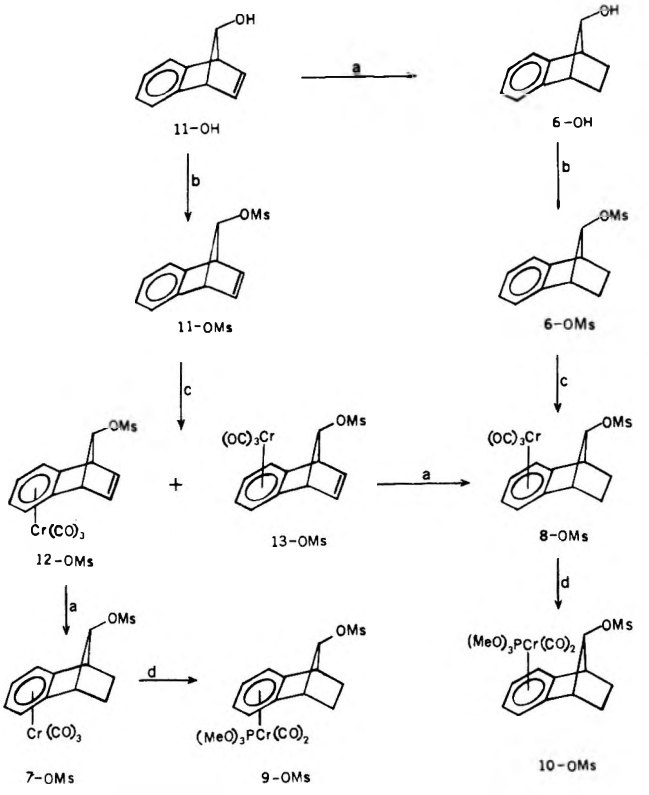


Scheme II. Stereochemistry of π-Arylchromium Tricarbonyl Migration



6- and 11-OH as outlined in Chart I. As indicated, the chromium tricarbonyl complexed benzonorbornadienyl methanesulfonates are most conveniently prepared by direct complexation of *anti*-9-benzonorbornadienyl methanesulfonate (**11-OMs**) with chromium hexacarbonyl in refluxing *n*-butyl ether–heptane. The resulting 60/40 mixture of *endo*- and *exo*-tricarbonylchromium derivatives, **12-** and **13-OMs**, respectively, can be separated by preparative thin-layer chromatography (TLC). While both **11-OH** and **11-OAc** can also be complexed in this manner,[5] the yields are lower, the resulting mixtures are more difficult to separate, and the complexes themselves appear to be less stable than their methanesulfonate counterparts. The use of more reactive complexing agents such as tris(acetonitrile)- or tris(pyridine)-chromium tricarbonyl[6] appears to offer no advantage either in convenience or yield. Since direct complexation of *anti*-

Chart I. Preparation of the π Complexes[a]

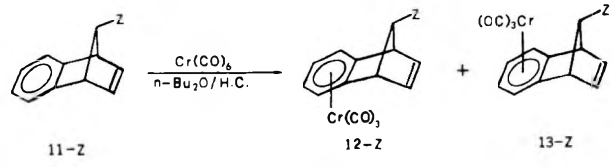


[a] a: H_2, Pd(C), EtOAc. b: MsCl, pyridine. c: $Cr(CO)_6$. d: $P(OMe)_3$, C_6H_6, $h\nu$.

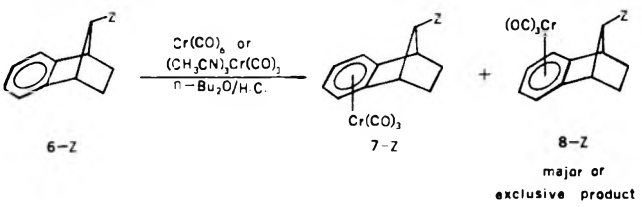
9-benzonorbornenyl alcohol (**6-OH**) or methanesulfonate (**6-OMs**) with chromium hexacarbonyl in *n*-butyl ether–heptane produces the corresponding exo complex exclusively, *anti*-9-[*endo*-π-(benzonorbornenyl)chromium tricarbonyl] methanesulfonate (**7-OMs**) is best prepared by catalytic hydrogenation of the endo-complexed norbornadienyl derivative, **12-OMs**; cf. Chart I.

The chromium trimethyl phosphite dicarbonyl complexes **9-** and **10-OMs** were prepared by photolysis of the chromium tricarbonyl complexes, **7-** and **8-OMs**, in the presence of excess trimethyl phosphite;[7] cf. Chart I. The phosphite complexes are markedly less stable than their tricarbonyl precursors and decompose extensively when preparative chromatography on active alumina or silica gel is attempted.

Structure of the Complexes. The stereochemistry of the metal moiety in each complex follows from its method of preparation and its proton magnetic resonance spectra. Except in cases where 9-substituted benzonorbornadienes form *exo*-chromium tetracarbonyl complexes,[5,8] direct complexation of benzonorbornadiene (**11-H**) (or its anti derivatives **11-Z**, Z = OH, OMs, or OAc) with chromium hexacarbonyl in



an ether–hydrocarbon solvent mixture gives the *endo*-π-arene tricarbonyl complex preferentially.[5,8a,9a] Benzonorbornene



(6-H)[9a] and its 2-[3,8a,9] and anti-9-substituted derivatives (3-Z and 6-Z, respectively, Z = OH, OMs, or OAc) complex predominantly or exclusively for the less hindered exo side.[5,8a]

The proton magnetic resonance spectra of exo- and endo-complexed benzonorbornenyl and -norbornadienyl derivatives exhibit characteristic differences which reflect the configuration of the metal moiety. The four aromatic hydrogens, which show the usual upfield shifts associated with the aromatic hydrogens of a π-(arene)chromium tricarbonyl,[10] appear as a complex AA'BB' or A_2B_2 pattern in the spectrum of each benzonorbornenyl or -norbornadienyl complex. In the spectrum of *exo*-2-[*exo*-π-(benzonorbornenyl)chromium tricarbonyl] acetate (5-OAc), whose structure is unequivocally known from the single-crystal x-ray diffraction studies of Amma et al.,[11] the chemical shifts of the A- and B-type protons differ by ~0.25 ppm while those of the endo complex, 4-OAc, differ by ~0.48 ppm. This characteristically greater difference in chemical shift is apparent in the proton spectra of all known endo-complexed benzonorbornenyl and -norbornadienyl derivatives;[3,5,8a,9] cf. Figure 1. As Wege and Wilkinson have noted,[5,8a] an additional feature of the proton spectra of exo-complexed 9-substituted benzonorbornenyl and -norbornadienyl derivatives which serves to differentiate them from those of their endo-complexed counterparts is the strong deshielding of the *syn*-9-hydrogen which is shifted 0.3–1.0 ppm downfield by the proximate tricarbonylchromium; cf. Figure 1. This effect is also evident, though less obvious, in the spectra of the 2-substituted benzonorbornenyl complexes.

Solvolysis Products. *anti*-9-Benzonorbornenyl brosylate (6-OBs) is reported to undergo acetolysis without rearrangement.[12] We find that the formolysis of 6-OMs also produces unrearranged product as do both the acetolysis and formolysis of *anti*-9-benzonorbornadienyl methanesulfonate (11-OMs).

Solvolyses of the complexes were conducted in the usual manner[2a,c] in buffered, deoxygenated acetic and formic acids. Where possible π-complexed products were isolated by crystallization or chromatographic techniques and identified by comparison of their infrared, NMR, and/or mass spectra. In cases where the instability of the complex or the small amount available precluded its isolation, the identity of a reaction product was inferred from a comparison of its TLC R_f value with that of a known complex and by analysis of the organic material resulting from its oxidative decomplexation with ceric ammonium nitrate[2a] and, in some cases, subsequent reduction with lithium aluminum hydride.[2a] Product compositions where mixtures result were estimated from analytical TLC plates, from integrated NMR spectra of the mixture, and from gas chromatographic analysis of decomplexed reaction mixtures.[2a]

As best we have been able to determine, all of the chromium tricarbonyl complexed *anti*-9-benzonorbornenyl and -norbornadienyl methanesulfonates solvolyze in acetic and formic acids without rearrangement. The *anti*-9-[*endo*-π-(benzonorbornenyl)chromium trimethyl phosphite dicarbonyl] methanesulfonate (9-OMs) appears to yield the endo-complexed formate, 9-OCOH, exclusively when formolized for ~10 half-lives at 70 °C, although some decomplexation accompanies the reaction. The exo-complexed methanesulfonate, 10-OMs, under these conditions, yields the exo-complexed formate 10-OCOH predominantly but also produces about 10% of a noncomplexed formate of unknown structure. Since the relative amount of this latter product appears to increase with time, we doubt that it is a primary solvolysis product.

Solvolysis Rates. Titrimetric solvolysis rate constants for the noncomplexed methanesulfonates 6- and 11-OMs were determined in the usual manner.[2] Both give first-order plots which are linear through greater than 2 half-lives and titrimetric rate constants which are generally reproducible to within ±10%. Rate constants for the complexed methanesulfonates (cf. Table II) were determined in degassed solvents as described previously,[2a] the progress of the reaction being monitored by potentiometric titration.[2c] Most of these solvolyses, even in deoxygenated solvents, are accompanied by some oxidative decomplexation in the latter stages of the reaction as evidenced by the development of an orange to green color in the normally yellow solutions.[13] Decomplexation is so rapid at the higher temperatures required for the acetolyses of these relatively unreactive 9-substituted complexes that solvolysis constants for most of them could not be determined in this solvent.

Since the complexes solvolyze more rapidly in formic acid, lower temperatures can be utilized and approximate solvolysis rates can be established in this solvent. Even so, decomplexation during solvolysis is still a problem and the use of experimental infinity titers gives first-order plots which are far from linear, the rates appearing to decrease with time in a fairly regular manner. Since the complexes have been shown to solvolyze without rearrangement and are known to be pure initially, we rule out the usual possibilities of impure starting material and/or internal return to a less reactive methanesulfonate as the cause of this behavior and attribute it instead to decomplexation accompanying solvolysis.[13] because the first-order rate plots do not approach linearity at extended reaction times and since with but two exceptions the complexes are less reactive than their noncomplexed analogues, the nonlinearity of the first-order plots cannot be due simply to the presence of both complexed and noncomplexed methanesulfonates in the reaction mixture. Instead, it appears that the decomplexation actually produces formate ion[13] and, thus, causes the titrimetric formolysis rate of the complexed methanesulfonate to appear to decrease with time.

Since the extent of decomplexation during solvolysis varies irregularly from one run to another, the experimental titrimetric infinity values are meaningless as a basis for calculation of a solvolytic rate constant. In an effort to get some idea of the relative reactivity of the isomeric complexes, we utilize instead a hypothetical infinity titer adjusted to give the best fit of our data within an individual run to an assumed first-order rate law.[15] In this manner it is possible to produce highly linear first-order plots whose slopes are reproducible in duplicate runs to within about ±30%. While this method probably does not yield true formolysis rate constants—we suspect it underestimates them in most instances—we believe that it provides relative rate constants for isomeric complexes which are accurate to within at least an order of magnitude.

The apparent first-order titrimetric solvolysis constants and activation parameters for the noncomplexed 9-benzonorbornenyl and -norbornadienyl methanesulfonates are collected in Table I, while the relative rates of the complexes at 60 °C derived as described above are given in Table II.

Discussion

Our kinetic data (Tables I and II) indicate that direct d-orbital participation by chromium is minimal in the solvolysis of *exo*-tricarbonylchromium complexed *anti*-9-benzonorbornenyl and -norbornadienyl methanesulfonates. In direct contrast to the effect of endo complexation which increases the acetolytic reactivity of *exo*-2-benzonorbornenyl methanesulfonate (4-OMs/3-OMs ≈ 1000/250 ≈ 4), exo complexation *decreases* the reactivity of the *anti*-9-benzonorbornenyl derivative [8-OMs/6-OMs ≈ 0.3 (HOAc); 8-OMs/6-OMs ≈ 0.02 (HCOOH)]. An even greater decrease is estimated in the benzonorbornadienyl case: 13-OMs/11-OMs ≈ 0.07/70 ≈ 0.001 (HCOOH). While it is true that in both the *anti*-9-benzonorbornenyl and -norbornadienyl series the *exo*-tricarbonylchromium complexes are formolytically slightly more reactive than their endo counterparts (8-OMs/7-OMs ≈

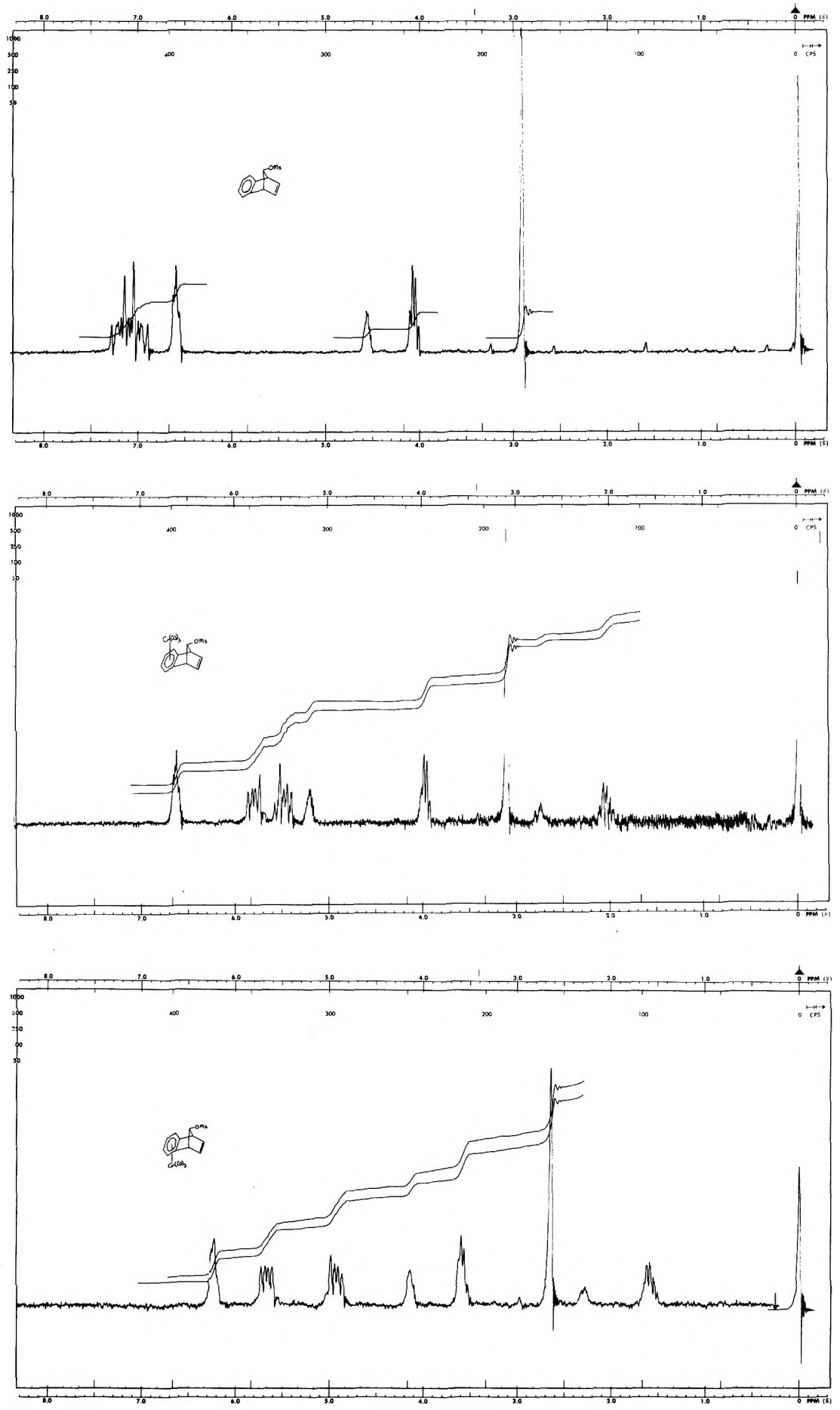


Figure 1. The 60-MHz proton magnetic resonance spectra of (upper) *anti*-9-benzonorbornadienyl methanesulfonate (**11**-OMs), (middle) *anti*-9-[*exo*-π-(benzonorbornadienyl)chromium tricarbonyl] methanesulfonate (**13**-OMs), and (lower) *anti*-9-[*endo*-π-(benzonorbornadienyl)chromium tricarbonyl] methanesulfonate (**12**-OMs).

Table I. Apparent First-Order Solvolysis Constants and Activation Parameters for Noncomplexed Benzonorbornenyl and Benzonorbornadienyl Methanesulfonates

Compd[a]	Solvent	Temp, °C	k,[b] s^{-1}	ΔH^*, kcal/mol	ΔS^*, eu
1	HOAc[c]	60.0[d]	1.69×10^{-4}	27.5	−10.3
3	HOAc[c]	60.0[d]	3.52×10^{-8}	24.0	−3.9
6	HOAc	114.4	$2.09 \pm 0.30 \times 10^{-4}$	26.6	−7.1
		97.7	$4.97 \pm 0.26 \times 10^{-5}$		
		84.1	$1.02 \pm 0.06 \times 10^{-5}$		
		60.0	6.68×10^{-7}		
6	HCOOH	59.1	1.09×10^{-3}	25.5	4.3
		59.0	1.03×10^{-3}		
		50.1	$3.62 \pm 0.30 \times 10^{-4}$		
		40.0	$9.58 \pm 1.17 \times 10^{-5}$		
		60.0	1.20×10^{-3}		
11	HOAc	84.7	$6.70 \pm 0.06 \times 10^{-4}$	25.8	−1.1
		84.3	7.93×10^{-4}		
		69.3	$1.44 \pm 0.06 \times 10^{-4}$		
		60.1	3.89×10^{-5}		
		59.2	$4.36 \pm 0.04 \times 10^{-5}$		
		60.0	4.61×10^{-5}		

[a] Refer to Chart I for numbering; note that -OMs has been omitted for simplicity. [b] ± one standard deviation for replicate runs at the same temperature. [c] See ref 3 for raw data. [d] Estimated from data at other temperatures.

0.02/0.005 ≈ 4; **13**-OMs/**12**-OMs ≈ 0.07/0.06 ≈ 1.2), the consequence of having the chromium closer to the reactive site is much more pronounced in the *exo*-2-benzonorbornenyl case [**4**-OMs/**5**-OMs ≈ 1000/3 ≈ 330 (HOAc)].

The absence of an appreciable direct d-orbital interaction in the case of **8**-OMs may be due in part to the relatively large Cr–C_9 distance, ~3.6 Å—the Cr–C_2 distance in **4**-OMs is ~3.1 Å[11]—but this is probably not the whole story. The replacement of a strongly back-bonding carbonyl with a less strongly back-bonding trimethyl phosphite[16] should increase the electron density on chromium and render direct d-orbital participation more likely in **10**-OMs; yet, the effect of such a substitution is to increase substantially the formolytic reactivity of *both* the exo- *and* the endo-complexed *anti*-9-benzonorbornenyl derivatives: **10**-OMs/**8**-OMs ≈ 3.4/0.02 ≈ 170; **9**-OMs/**7**-OMs ≈ 1.6/0.005 ≈ 320. Thus, while **10**-OMs is actually slightly more reactive than *anti*-9-benzonorbornenyl methanesulfonate itself (**10**-OMs/**6**-OMs ≈ 3.4), it would appear incorrect to attribute this effect to direct d-orbital participation since it is also evident in the endo complex, **9**-OMs/**6**-OMs ≈ 1.6, where such interaction is not possible.

If a difference in the extent of direct d-orbital participation is not the cause of the changes in solvolytic rate which result when a carbonyl ligand is replaced by trimethyl phosphite, what is? Each of the π-complexed *anti*-9-benzonorbornenyl and -norbornadienyl derivatives solvolyses without significant rearrangement; hence, σ–π homoconjugation is an unlikely possibility. Because the partial bond moments associated with the ligand-to-metal bonds in some π-arene and π-cyclopentadienyl complexes can be appreciable,[16] it occurred to us that the formolytic rate enhancements which we observe in going from a tricarbonyl to a dicarbonyl trimethyl phosphite complex might be due to differences in the electrostatic interactions between the ligand-to-metal dipole and the developing charge at C_9. Since the unusual geometry of the π complexes precludes the use of σ-bound substituents to mimic the dipolar effect of the metal ligands, we have utilized a modified Kirkwood–Westheimer treatment[18] to estimate whether rate effects of the magnitude which we observe could possibly be due to electrostatic interactions alone. The results of such calculations, carried out as described in the Experimental Section, may be compared with the observed rate ratios; cf. Table III.

Apparently the substantial rate enhancements observed upon going from tricarbonylchromium to trimethyl phosphite dicarbonylchromium complexes of comparable geometry *could* derive, from electrostatic effects alone![19]

This possibly fortuitous congruity of theory and experiment raises some interesting questions. Could similar electrostatic interactions determine the relative reactivities of other benzonorbornenyl derivatives (cf. Table II)? Is the demonstrated tendency of tricarbonylchromium to precede the ring of a migrating π-complexed aryl,[3] in fact, a manifestation of such electrostatic effects rather than the consequence of either σ–π homoconjugation or d-orbital bridging?[20] We do not presently have answers to these questions but are hopeful that studies now in progress may provide them.

The introduction of an additional double bond into the benzonorbornenyl ring results in a more reactive anti-9 methanesulfonate: thus, **11**-OMs/**6**-OMs = 69 (HOAc, 60 °C). The acetolysis of **6**-OBs, which is 10^5 times more facile than that of 7-norbornyl brosylate,[12] is thought to occur with π-arene participation via a symmetric transition state.[12] The additional anchimeric effect of the double bond in **11**-OMs in the absence of σ delocalization[21] (no rearranged products) may be a consequence of laticyclic type participation similar to that observed in the solvolysis of 7-norbornadienyl derivatives.[22] It is reasonable to expect the additional double bond to shift π-electron density toward the arene as it does in benzocyclobutadiene[23] for benzonorbornadiene may be thought of as a weakly coupled bis(homobenzocyclobutadiene).[24]

In the light of this conjecture it is of interest to note that π complexation apparently decreases the solvolytic reactivity of *anti*-9-benzonorbornadienyl methanesulfonate (**11**-OMs) to a much greater extent than it does the benzonorbornenyl analogue, **6**-OMs: vis., **12**-OMs/**11**-OMs ≈ 0.06/70 ≈ 0.0009; **13**-OMs/**11**-OMs ≈ 0.07/70 ≈ 0.001. Apparently, by utilizing the aromatic π MOs that would normally interact weakly with the isolated double bond, the more strongly bound tricarbonylchromium is able to obliterate all bis(homobenzocyclobutadiene)-like character and, hence, any laticyclic stabilization of the intermediate cation by the isolated double bond.

Experimental Section[25]

Preparation of the Methanesulfonates. In the manner of Veazey,[2a] the appropriate alcohol was allowed to react with methanesulfonyl chloride in cold, dry pyridine. The reaction mixtures were maintained at −10 °C for 2 days prior to workup.

Preparation of *anti*-9-Benzonorbornadienyl Methanesulfonate (11-OMs). A white crystalline solid (mp 92–94 °C) was obtained from **11**-OH[4] in 94% yield: IR ($CHCl_3$) 3075, 3025, 2940, 1470 (CH), 1380, 1350, 1173 cm^{-1} (–OSO_2–); NMR ($CDCl_3$) δ 7.10 (m, 4 H, aromatic), 6.70 (m, 2 H, olefinic), 4.59 (m, 1 H, syn C-9), 4.08 (m, 2 H, bridgehead C-1 and C-4), 2.93 (s, 3 H, CH_3SO_2–) (cf. Figure 1). Anal. Calcd for $C_{12}H_{12}O_3S$: C, 61.00; H, 5.12; O, 20.31; S, 13.57. Found: C, 61.03; H, 5.03; O, 20.18; S, 13.76.

Preparation of *anti*-9-Benzonorbornenyl Methanesulfonate (6-OMs). White needles obtained from **6**-OH[4] were purified by recrystallization from ether–pentane in an overall yield of 74%: mp 53–55 °C; IR (CCl_4) 3040, 3018, 2970, 2950, 2900, 2868, (CH), 1470 (–CH_2), 1460 (–CH_3), 1163, 1182 (–SO_2–), 886, 864, 830, 816 cm^{-1} (S–O); NMR ($CDCl_3$) δ 7.14 (s, 4 H, aromatic), 4.42 (m, 1 H, syn C-9), 3.42 (m, 2 H, bridgehead C-1 and C-4), 3.00 (s, 3 H, –SO_2CH_3), 2.17 (m, 2 H, endo C-2 and C-3), 1.23 (distorted q, 2 H, exo C-2 and C-3). Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92; O, 20.14; S, 13.46. Found: C, 60.37; H, 5.81; O, 20.42; S, 13.20.

Preparation of *anti*-9-Benzonorbornadienyl Acetate (11-OAc). Employing the general procedure of Winstein and Trifan,[26] **11**-OH[4] was acetylated with acetic anhydride in glacial acetic acid at 75 °C. Distillation afforded a clear, oily liquid: bp 81–84 °C (0.3 mm); IR ($CHCl_3$) 3075, 3020, 3005 (CH), 1745 (C=O), 1220, 1038 (C–O), 698 cm^{-1} (cis olefin); NMR ($CDCl_3$) δ 7.05 (m, 4 H, aromatic), 6.55

Table II. Approximate Relative Solvolysis Rates of Benzonorbornenyl and Benzonorbornadienyl Methanesulfonates at 60 °C

Compd	Registry no.	Solvent	Rel rate	Compd	Registry no.	Solvent	Rel rate
6		HOAc	1.00	6	64425-80-5	HCOOH	1.00
1	31351-15-2	HOAc[a]	0.053	7	64440-61-5	HCOOH	0.005
2	33220-89-2	HOAc[b]	<0.004	8	64519-53-5	HCOOH	0.02
3	31351-14-1	HOAc[a]	250	9	64475-08-7	HCOOH	~1.6
4	33218-83-6	HOAc[b]	>1000	10	64440-64-8	HCOOH	~3.4
5	33247-11-9	HOAc[b]	3	11	64425-79-2	HCOOH	(69)[c]
8		HOAc	~0.3	12	64440-60-4	HCOOH	0.06
11		HOAc	69	13	64519-52-4	HCOOH	0.07

[a] See Table I; note that -OMs has been omitted for simplicity. [b] Estimated from data in ref 3. [c] Estimated from the relative acetolysis rates of 11 and 6.

Table III. Formolysis Rate Ratios of Isogeometric Trimethyl Phosphite Dicarbonyl- and Tricarbonylchromium π-Arene Complexes

	Obsd[a]	Predicted[b]
9-OMs/7-OMs	~300	~100
10-OMs/8-OMs	~200	~300

[a] Estimated from the relative formolysis rates at 60 °C; cf. Table II. [b] Calculated from the electrostatic model at 60 °C; cf. Experimental Section and Table IV.

(m, 2 H, olefinic), 4.85 (m, 1 H, syn C-9), 3.95 (m, 2 H, bridgehead C-1 and C-4), 1.96 (s, 3 H, CH_3CO_2–). These spectra are in reasonable agreement with the reported literature values.[4]

Preparation of *anti*-9-Benzonorbornenyl Acetate (6-OAc). When the general acetylation procedure of Winstein and Trifan[26] was employed, 6-OH was converted to 6-OAc, a colorless liquid [bp 81–84 °C (0.25 mm)] in 86% yield: IR ($CHCl_3$) 3050, 2975, 2955, 2910, 2875 (CH), 1750 (C=O), 1490 (–CH_2–), 1480, 1395, 1380 (–CH_3), 1228, 1113, 1042 (C–O), 912 cm^{-1} (aromatic);[4] NMR ($CDCl_3$) δ 7.09 (m, 4 H, aromatic), 4.52 (br s, 1 H, syn C-9), 3.28 (m, 2 H, bridgehead C-1 and C-4), 2.1–1.9 (m, 2 H, endo C-2 and C-3) superimposed on a singlet at 1.98 (3 H, CH_3CO_2–), 1.13 (distorted q, 2 H, exo C-1 and C-4). The above spectra are in good agreement with published values.[4]

Preparation of *anti*-9-Benzonorbornadienyl Formate (11-OCOH). Solvolysis of 1.00 g (4.23 mmol) of 11-OMs in 50 mL of 0.10 M sodium formate in formic acid afforded the desired product in greater than 90% yield. GLC of the crude reaction mixture showed only one product: bp 115–118 °C (oil bath) (0.8 mm); IR ($CHCl_3$) 3067, 3007, 3002, 2940 (CH), 1750 (C=O), 1487, 1482, 1332 (–CH_2–), 1230, 1182, 1155 (C–O), 704 cm^{-1} (cis olefin); NMR ($CDCl_3$) δ 7.86 (s, 1 H, –OCOH), 7.08 (m, 4 H, aromatic), 6.55 (m, 2 H, olefinic), 4.77 (m, 1 H, syn C-9), 3.98 (m, 2 H, bridgehead C-1 and C-4). Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41; O, 17.19. Found: C, 77.26; H, 5.40; O, 17.34.

Preparation of *anti*-9-Benzonorbornenyl Formate (6-OCOH). Catalytic hydrogenation at atmospheric pressure of 11-OCOH with 10% Pd/C in ethyl acetate afforded the desired formate in greater than 90% yield: bp 79 °C (0.45 mm); IR ($CHCl_3$) 3005, 2975, 2950, 2880 (–CH–), 1745 (C=O), 1495, 1485 (–CH_2–), 1212, 1190, 1110 cm^{-1} (C–O); NMR ($CDCl_3$) δ 7.94 (s, 1 H, –OCOH), 7.10 (s, 4 H, aromatic), 4.60 (m, 1 H, syn C-9), 3.32 (m, 2 H, bridgehead C-1 and C-4), 2.03 (m, 2 H, endo C-2 and C-3), 1.14 (distorted q, 2 H, exo C-2 and C-3). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43; O, 17.00. Found: C, 76.46; H, 6.56; O, 16.97.

Preparation of the Tricarbonylchromium π-Complexed Compounds. All tricarbonylchromium complexes were prepared in a Strohmeier apparatus[27] using the general procedure of Veazey.[2a] Optimum yields were obtained when reaction mixtures, saturated with inert gas, were allowed to reflux for about 24 h. The samples were purified by recrystallization from benzene–ether–pentane mixtures.

Preparation of *anti*-9-[*exo*-π-(Benzonorbornenyl)chromium tricarbonyl] Methanesulfonate (8-OMs). Reaction of 6-OMs yielded the desired yellow, crystalline complex in 65% yield. TLC (eluent: ether–pentane, 75:25) indicated a single isomer (R_f 0.75): mp 151–153 °C dec; IR ($CHCl_3$) 3015, 2950 (CH), 2030, 1955 (C=O), 1390, 1370, 1208, 1173 (–SO_2–), 668, 636, 538 cm^{-1} (Cr–C); NMR ($CDCl_3$) δ 5.75 and 5.45 (m, 4 H, aromatic), 4.70 (m, 1 H, syn C-9), 3.28 (perturbed q, 2 H, bridgehead C-1 and C-4), 3.19 (s, 3 H, CH_3SO_2–), 2.18 (m, 2 H, endo C-2 and C-3), 1.36 (perturbed q, J = 4 Hz, 2 H, exo C-2 and C-3). Anal. Calcd for $C_{15}H_{14}O_6CrS$: C, 48.13; H, 3.77; O, 25.65; S, 8.57; Cr, 13.89. Found: C, 48.21; H, 3.95; O, 25.47; Cr, 13.97.

Preparation of *anti*-9-[*exo*-π-(Benzonorbornadienyl)chromium tricarbonyl] Methanesulfonate (13-OMs). Reaction of 11-OMs produced a yellow, microcrystalline complex in 62% yield. TLC of the solid [eluent: ether–pentane, 80:20 (0.5 mm)] revealed the presence of two complexes (R_f 0.20 and 0.30) in a 60/40 ratio. Separation of these two products was effected by preparative TLC in the absence of light. A typical run utilized about 250 mg of the mixture in 1 mL of acetone on a TLC plate (20 × 40 cm) which had been coated with silica gel (PF-254, ca. 2 mm) and conditioned for 2.5 h at 120 °C.

Elution of this plate was accomplished in a sandwich developing chamber fitted for continuous elution using an ether–pentane solution (75:25). Following the separation of the two isomers, the eluent was removed, and with the aid of a UV lamp, the yellow bands were scraped from the plate. Extraction of the separated bands from silica gel with acetone afforded yellow solutions which when concentrated and diluted with pentane at −10 °C yielded yellow crystalline precipitates. Spectral analysis of the yellow needles isolated from the TLC band of shorter retention time (R_f 0.30) indicated them to be the desired *exo*-tricarbonylchromium isomer 13-OMs: mp 179 °C dec; 25% yield; IR ($CHCl_3$) 3010 (CH), 1990, 1920 (C=O), 1400, 1210 (–SO_2–), 670, 635 cm^{-1} (Cr–C); NMR (CD_3COCD_3) δ 6.63 (m, 2 H, olefinic), 5.30 and 5.56 (m, 4 H, aromatic), 5.20 (m, 1 H, syn C-9), 3.89 (m, 2 H, bridgehead C-1 and C-4), 3.09 (s, 3 H, CH_3SO_2–) (cf. Figure 1); parent ion at *m/e* 372. Anal. Calcd for $C_{15}H_{12}O_6CrS$: C, 48.39; H, 3.25; O, 25.78; Cr, 13.97; S, 8.61. Found: C, 48.25; H, 3.26; O, 25.36; S, 8.41.

Preparation of *anti*-9-[*endo*-π-(Benzonorbornadienyl)-chromium tricarbonyl] Methanesulfonate (12-OMs). This complex, a component of the isomeric mixture obtained from the Strohmeier complexation of 11-OMs, was isolated via preparative TLC (vide supra) from the band of lower R_f value in about 30% yield. Analytical TLC indicated an isomer distribution of 12-OMs/13-OMs in the crude reaction mixture of ca. 60/40. The *endo*-tricarbonylchromium isomer exhibits the following properties: mp 167–170 °C dec; IR ($CHCl_3$) 3020 (CH), 1988, 1910 (C=O), 1390, 1370, 1200, 1171 (–SO_2–), 706 (cis olefin), 669, 634 cm^{-1} (Cr–C); NMR (CD_3COCD_3) δ 6.63 (m, 2 H, olefinic), 6.06 and 5.32 (m, 4 H, aromatic), 4.54 (m, 1 H, syn C-9), 3.99 (distorted q, 2 H, bridgehead C-1 and C-4) (cf. Figure 1), 3.04 (s, 3 H, CH_3SO_2–); parent ion *m/e* 372. Anal. Calcd for $C_{15}H_{12}O_6CrS$: C, 48.39; H, 3.25; O, 25.78; Cr, 13.97; S, 8.61. Found: C, 48.25; H, 3.24; O, 25.52; S, 8.45.

Preparation of *anti*-9-[*endo*-π-(Benzonorbornenyl)chromium tricarbonyl] Methanesulfonate (7-OMs). Catalytic hydrogenation of 12-OMs at atmospheric pressure employing 10% Pd/C in ethyl acetate required several days at 55 °C. The yield of the desired complex was about 60%. The endo complex of the saturated methanesulfonate, 7-OMs, exhibits the following properties: mp 152–154 °C; IR ($CHCl_3$) 3010, 2955 (CH), 1985, 1908 (C=O), 1480 (–CH_2–), 1395, 1375, 1208, 1172 (–SO_2–), 669, 638 cm^{-1} (Cr–C); NMR ($CDCl_3$) δ 5.52 and 5.13 (m, 4 H, aromatic), 437 (m, 1 H, syn C-9), 3.19 (distorted q, 2 H, bridgehead C-1 and C-4), 3.00 (s, 3 H, CH_3SO_2–), 2.21 (m, 2 H, endo C-2 and C-3), 1.72 (distorted q, 2 H, exo C-2 and C-3); parent ion at *m/e* 374. Anal. Calcd for $C_{15}H_{14}O_6CrS$: C, 48.13; H, 3.77; O, 25.65; Cr, 13.89; S, 8.57. Found: C, 48.33; H, 3.71; O, 25.33; S, 8.74.

Preparation of *anti*-9-[*exo*-π-(Benzonorbornenyl)chromium dicarbonyl trimethyl phosphite] Methanesulfonate (10-OMs). Following the general procedure for photolytic ligand substitution first developed by Strohmeier,[10c,28] an inert gas saturated benzene

solution of 8-OMs containing excess trimethyl phosphite was irradiated in a Pyrex vessel for 2–3 h employing a 250-W sunlamp. The water-washed and magnesium sulfate dried, yellow-orange solution was concentrated to ca. 20 mL, and crystallization was initiated by the addition of pentane at 0 °C. TLC (eluent benzene) of the resulting yellow-orange crystals revealed one major component (R_f 0.16) along with several minor ones. Recrystallization afforded pure **10**-OMs in 64% yield: mp 132–134 °C; IR ($CHCl_3$) 3010, 2990, 2950, 2840 (CH), 1915, 1860 (C≡O), 1390, 1360, 1205, 1172 (–SO_2–), 1015 (C–O), 710 (P–C), 652, 624 cm^{-1} (Cr–C); NMR (CD_3COCD_3) δ 5.12 (m, 4 H, aromatic), 4.88 (m, 1 H, syn C-9), 3.60 and 3.49 [d, J_{CP} = 11 Hz, 9 H, $P(OCH_3)_3$], 3.14 (s, 3 H, CH_3SO_2–) superimposed on a multiplet at 3.10 (2 H, bridgehead C-1 and C-4), 2.08 (m, 2 H, endo C-2 and C-3), 1.30 (distorted q, 2 H, exo C-2 and C-3). Anal. Calcd for $C_{17}H_{23}O_8CrPS$: C, 43.41; H, 4.93; O, 27.21; Cr, 11.05; P, 6.58; S, 6.82. Found: C, 43.58; H, 4.94; P, 6.52; S, 6.72.

Preparation of *anti*-9-[*endo*-π-(Benzonorbornenyl)chromium dicarbonyl trimethyl phosphite] Methanesulfonate (9-OMs). Employing the same procedure outlined for the preparation of **10**-OMs (vide supra), **7**-OMs was converted to the desired trimethyl phosphite derivative in 52% yield: mp 115–116 °C; IR ($CHCl_3$) 2990, 2945, 2840 (CH), 1910, 1855 (C≡O), 1390, 1370, 1172 (–SO_2–), 1016 (C–O), 653, 624 cm^{-1} (Cr–C); NMR ($CDCl_3$) δ 5.20 and 4.83 (m, 4 H, aromatic), 4.36 (m, 1 H, syn C-9), 3.62 and 3.41 [d, J = 12 Hz, 9 H, $P(OCH_3)_3$], 3.19 (m, 2 H, bridgehead C-1 and C-4), 3.02 (s, 3 H, CH_3SO_2–), 2.06 and 1.91 (m, 4 H, exo/endo C-2 and C-3). Anal. Calcd for $C_{17}H_{23}O_8CrPS$: C, 43.41; H, 4.93; O, 27.21; Cr, 11.05; P, 6.58; S, 6.82. Found: C, 43.51; H, 4.72; P, 6.44; S, 6.92.

Preparation of exo-π-(Benzonorbornene)chromium Dicarbonyl Trimethyl Phosphite (10-H). Irradiation of a benzene solution of 8-H[8a,9a] containing excess trimethyl phosphite yields the desired monosubstitution product, an orange-yellow oil, in 48% yield: IR ($CHCl_3$) 3015, 2980, 2950, 2875, 2845 (CH), 1905, 1850 (C≡O), 1380, 1368 (CH_2, CH_3), 1205, 1030 (P–O), 660, 622 cm^{-1} (Cr–C); NMR ($CDCl_3$) δ 5.05 and 4.83 (m, 4 H, aromatic), 3.62 and 3.43 [d, J_{CP} = 11 Hz, 9 H, $P(OCH_3)_3$], 3.02 (m, 2 H, bridgehead C-1 and C-4), 1.95 (m, 4 H, endo C-2 and C-3 plus syn and anti C-9), 1.23 (m, 2 H, exo C-2 and C-3). Anal. Calcd for $C_{16}H_{21}O_5CrP$: C, 51.07; H, 5.63; O, 21.26; Cr, 13.82; P, 8.23. Found: C, 51.01; H, 5.23; Cr, 13.65; P, 8.39.

Acetolysis Product Studies of Noncomplexed Methanesulfonates. In a typical run 10 mL of acetic acid, which was about 0.20 M in methanesulfonate and 0.30 M in sodium acetate, was sealed in a large test tube and heated in a thermostated oil bath at a temperature used for the rate study. After 10 half-lives, the tube was cooled and opened, and its contents was poured over ice water. The mixture was extracted with ether. The ether extract was washed sequentially with 10% sodium carbonate and water, dried over sodium sulfate, and concentrated to produce the expected acetate in ca. 90% yield.

The purity and structure of the sole product detected by GLC was established by comparison of its IR and NMR spectra with authentic samples of **6**- or **11**-OAc.

Acetolysis Product Study of *anti*-9-[*exo*-π-(Benzonorbornenyl)chromium tricarbonyl] Methanesulfonate (8-OMs). Under an inert atmosphere, 0.074 g (0.20 mmol) of 8-OMs was added to 15 mL of a solution of 0.0505 M sodium acetate in deoxygenated anhydrous acetic acid. This yellow solution was sealed in an ampule under nitrogen and heated for 9.5 half-lives at 98 °C. The cool, orange-brown solution, which turned green when exposed to air, was poured over 75 mL of crushed ice and extracted with four 50-mL portions of ether–pentane. The combined extracts were washed with a 10% sodium carbonate solution and with water. A TLC check of this solution (Kodak plates, ether–pentane 80:20) revealed the presence of only one complex (R_f 0.34, ether–pentane 70:30), whose retention time was less than that of the starting material, 8-OMs. To the slightly yellow extract was added, with stirring, 5 mL of a saturated solution of ceric ammonium nitrate in acetone.[2a] The resultant mixture was washed three times with cold water and dried over anhydrous magnesium sulfate. After concentration to ca. 10 mL, a molar excess of lithium aluminum hydride was added. The etheral mixture was allowed to reflux overnight and worked up by addition of water and 2 N sulfuric acid, followed by extraction with three 50-mL portions of ether–pentane (50:50). After washing with a 10% sodium carbonate solution and with water, the product was dried over anhydrous magnesium sulfate. The IR of the sole component detected and collected by GLC (85% yield by internal standard) is identical with that of authentic **6**-OH.

Formolysis Product Studies of Noncomplexed Methanesulfonates. As with the acetolysis product studies, 10-mL samples of a buffered formic acid solution ca. 0.02 M in **6**- or **11**-OMs were solvolyzed. In each case the IR and NMR of the sole product, detected by GLC and collected by distillation (90% yield), are consistent with those expected of **6**- or **11**-OCOH, respectively.

Formolysis Product Studies of Chromium Tricarbonyl Complexed Methanesulfonates. The same general procedure outlined for the acetolysis product studies of π complexes was employed, except that, because of the small amount of material available, the complexes were run in pairs of equimolar mixtures: **7**- and 8-OMs or **12**- and **13**-OMs. In each case a TLC run prior to oxidative decomplexation with ceric ammonium nitrate indicated the presence of two complexed products in approximately equal amounts. The tricarbonyl complexed products from **7**- and 8-OMs were found to have R_f values of 0.51 and 0.66 (ether–pentane, 80:20), respectively; those from **12**- and **13**-OMs had R_f values of 0.51 and 0.63 (ether–pentane, 80:20), respectively. The overall yield of unrearranged alcohol—**6**-OH from **7**- and 8-OMs, **11**-OH from **12**- and **13**-OMs—isolated by GLC following ceric oxidation and hydride reduction was 75% in each case by GLC with an internal standard. The identity of the noncomplexed alcohol was established in each case by comparison of the IR and NMR spectra of a collected sample with those of the known compound.

Formolysis Product Study of Chromium Dicarbonyl Trimethyl Phosphite Complexed Methanesulfonates. The formolysis of equimolar mixtures of the trimethyl phosphite complexes **9**- and **10**-OMs was carried out in the manner described previously for the tricarbonyl complexes. In each case TLC analyses of the crude formolysis mixtures indicate the presence of approximately equal amounts of two π-complexed products, R_f 0.22 and 0.32 (benzene), presumed to be the endo- and exo-complexed formates **9**- and **10**-OCOH. A GLC analysis following ceric oxidation of the product mixtures indicated the presence of two noncomplexed components, whose ratio appeared to depend upon the reaction time. The overall yield of decomplexed products, determined gas chromatographically using an internal standard, was ~75% in all runs. The major decomplexed product (that of longer retention time) was collected and found to be identical with authentic *anti*-9-benzonorbornenyl formate (**6**-OCOH). The second component (that of shorter retention time) could not be characterized except by its IR and mass spectrum which indicated a formate ester with a molecular ion of *m/e* 192.

To obtain an accurate ratio of these two noncomplexed products, a 30-mL formolysis sample, ca. 0.02 M in **10**-OMs, was placed in a thermostated bath at 70 °C. Aliquots (10 mL) were withdrawn at 5, 10, and 15 half-lives and examined by GLC following oxidative decomplexation with ceric ammonium nitrate. The ratio of the unknown product relative to **6**-OCOH varied with time, being 0.11 at 5 half-lives, 0.15 at 10 half-lives, and 0.16 at 15 half-lives, implying that the unknown ester is not a primary formolysis product. Because of the small amount of material available, we were unable to determine whether it is also produced in the formolysis of **9**-OMs.

Kinetic Studies and Data Treatment. Acetolysis and formolysis rates on the noncomplexed methanesulfonates were determined titrimetrically as described previously.[2c] For the complexed derivatives acetolysis and/or formolysis rates were obtained from potentiometric titrations of ~0.02 M solutions of the methanesulfonates in degassed, buffered acetic or formic acid. Degassed rate solvents were prepared by passing dry, oxygen-free nitrogen through them for 10–20 min at 70–80 °C and then allowing them to cool under the same inert atmosphere. All rate-sample preparations were carried out in a glovebag under a nitrogen atmosphere. In a typical run, the appropriate amount of complex was weighed into a 10-mL volumetric flask, and this flask, along with the open rate tubes, was placed in a glovebag. All of the apparatus was flushed with a stream of dry nitrogen, the glovebag was closed, and the rate solution was prepared in the following manner. The well-mixed solution was pipetted in slightly greater than 1-mL quantities into each rate tube. These tubes were flushed with a stream of N_2, corked, removed from the glovebag, cooled in ice water, and sealed as quickly as possible. The sealed tubes were placed in a thermostated oil bath (±0.05 °C) and removed at regular intervals. After cooling, the rate tubes were opened, and a 1-mL aliquot of solution was removed, placed in a titration vessel, and diluted with 5 mL of glacial acetic acid. Titration was accomplished with a perchloric–acetic acid solution using a Radiometer-Copenhagen pH stat–autoburette combination.[25]

Because of the oxidative decomplexation which accompanies the solvolyses of the complexed methanesulfonates,[13] titrimetric infinity titers obtained in this manner are of limited utility for the calculation of the rate constants for individual runs. Instead, the curved first-order plots were adjusted to give the best straight lines (assuming first-order kinetics) by varying the "infinity titer" until the coefficient of determination of the least-squares linear regression line through the experimental points was maximized. A FORTRAN IV computer program derived originally from that of Wiberg[15] was used to ac-

Table IV. Parameters for the Charge–Dipole Calculation

Compd	μ^a	θ, deg	R, Å
7-OMs	0.6	1.95	5.06
8-OMs	0.6	13.8	4.49
9-OMs	3.2	1.81	5.29
10-OMs	3.2	13.2	4.71

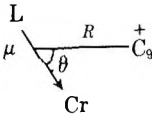
[a] In debyes directed toward chromium.

complish this. In every case the coefficient of determination of an individual run exceeded 0.98. In almost all cases the "rate constant" derived in this manner was considerably greater than that which would have resulted had the experimental infinity titer been utilized. Rate constants of replicate runs were generally reproducible to within ±30%, and the activation parameters computed in the usual manner[29] from replicate runs at three or more temperatures had standard deviations that did not exceed 0.25 kcal/mol in the case of ΔH^* or 0.7 eu in the case of ΔS^*. These approximate activation parameters were used to estimate the *relative* solvolysis rates of the individual complexes at 60 °C (Table II).

Charge–Dipole Calculations. To estimate the effect of changes in the magnitude and direction of a ligand dipole, e.g., the substitution of a trimethyl phosphite for a carbonyl, upon the relative solvolysis rate of a complexed methanesulfonate, we have assumed a point-dipole model[18d] similar to that originally developed by Westheimer[18a] and modified by Stock.[18b] This calculation utilizes the equation[18b]

$$\log (k_2/k_1) = (e/2.3kTD_E)\left[\left(\frac{\mu \cos\theta}{R^2}\right)_2 - \left(\frac{\mu \cos\theta}{R^2}\right)_1\right]$$

and requires values of the bond moments of the Cr–CO (μ_1) and Cr–P(OMe)$_3$ (μ_2) bonds, the angles, θ_1 and θ_2, which these moments make with respect to a line joining their midpoints with C_9 (the site of developing positive charge), the distances from the midpoint of the Cr–CO and Cr–P(OMe)$_3$ bonds from C_9, R_1 and R_2, respectively, and an estimate of the effective dielectric constant D_E.



For purposes of this calculation we used values of the bond moments suggested by Strohmeier et al. ($\mu_1 \approx 0.6$ D,[17b] $\mu_2 \approx 3.2$ D),[17d] directed toward the metal in each case, and ligand-to-chromium bond lengths of 1.85 (Cr–CO)[11b] and 2.31 Å (Cr–P).[30] The required angles (θ) and distances (R) were derived from the single-crystal x-ray data of Amma et al.[11b] on *exo*-2-[*exo*-π-(benzonorbornenyl)chromium tricarbonyl] acetate (**5**-OAc) by assuming that the atomic coordinates of all the carbons which make up the bicyclic framework of the π-complexed *anti*-9-benzonorbornenyl methanesulfonates are identical with those of the corresponding carbons in **5**-OAc, that trimethyl phosphite, being a more bulky ligand, replaces the carbonyl which lies in the plane defined by C_9, Cr, and the center of the aromatic ring, and that the atomic coordinates of the endo-complexed metal moieties may be derived from those of the exo by reflection of the latter in the plane of the aromatic ring. The resulting parameter values are summarized in Table IV.

The substitution of these values, together with an assumed effective dielectric constant, D_E, of 2[18d] into the defining equation, permits estimates to be made of the relative solvolysis rates at 60 °C of **9**- and **7**-OMs and of **10**- and **8**-OMs; cf. Table III. If the effective dielectric constant is actually greater than 2, then, of course, the predicted rate ratios are smaller.

Registry No.—**6**-OH, 1198-20-5; **6**-OCOH, 64425-81-6; **6**-OAc, 1207-28-9; **8**-H, 64440-62-6; **10**-H, 64457-61-0; **11**-OCOH, 64425-82-7; **11**-OAc, 16031-35-9; **11**-OH, 6991-42-0; trimethyl phosphite, 121-45-9.

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Polyamines from Cyanobutadienes[1a]

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Hydrazine reacts with 1-cyanobutadiene to produce 3-(cyanomethyl)pyrazolidine (**2**), whose reduction gives 1,3,5-pentanetriamine (**4**). Pyrazolidine **2** reacts with a wide variety of compounds to give 1:1 and 1:2 open-chain and cyclic adducts. Amines react with 1- and 2-cyanobutadienes to give products ranging from 1:1 to 4:3 adducts depending on the nature of the amine and the reaction conditions.

The 1,4 addition of many HX such as amines, alcohols, and thiols to either 1- or 2-cyanobutadienes has been described.[1,2] Either acid or base catalysis can equilibrate 2- and 3-pentenenitriles. With some HX a second addition occurs to give 2:1 adducts.

$$CH_2{=}CHCH{=}CHCN \xrightarrow{HX} XCH_2CH{=}CHCH_2CN$$

$$\rightleftarrows XCH_2CH_2CH{=}CHCN \xrightarrow{HX} XCH_2CH_2CHXCH_2CN$$

$$CH_2{=}CHC(CN){=}CH_2 \xrightarrow{HX} XCH_2C(CN){=}CHCH_3$$

$$\xrightarrow{HX} XCH_2CH(CN)CHXCH_3$$

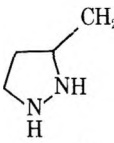
The reaction of hydrazine with 1-cyanobutadiene has been reported to give only hydrazinobutenenitrile **1**.[1]

We find that the general sequence is continued intramolecularly and 3-(cyanomethyl)pyrazolidine **2**, a reactive heterocycle, can be isolated in good yield.

$$N_2H_4 + CH_2{=}CHCH{=}CHCN \longrightarrow H_2NNHCH_2CH{=}CHCH_2CN$$

1

$$H_2NNHCH_2CH_2CH{=}CHCN \longrightarrow$$



2

In this paper, we describe the synthesis and chemistry of **2** and related compounds derived from the reactions of amines with cyanobutadienes.

Results

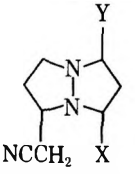
Combining methanol solutions of 1-cyanobutadiene and hydrazine at −25 °C and removing the solvent under vacuum at 0 °C gives 5-hydrazino-3-pentenenitrile **1**.[1] The infrared spectrum shows a primary amine and the NMR spectrum shows resonances for four allylic and two unconjugated vinyl protons.

The structure proof offered by Kurtz[1] for the *distilled* product does not distinguish between **1** or its cyclic isomer **2**. We find that any attempt to purify **1** involving temperature only slightly above ambient results in double-bond isomerization and subsequent ring closure.

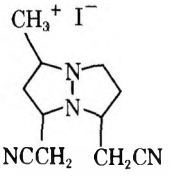
If the alcohol solution is refluxed before the solvent is removed, the NMR spectrum shows no vinyl absorptions. Distilling the viscous residue gives two fractions, the lower boiling being 3-(cyanomethyl)pyrazolidine **2**. Lower temperatures during the initial exothermic addition of hydrazine to 1-cyanobutadiene and excess hydrazine favor the formation of **2** over the higher boiling 2:1 adduct **3**. Either hydrazine hydrate or anhydrous hydrazine can be used.

The structure of **2** follows from its elemental analysis and NMR spectrum which shows no vinyl absorptions. At 220 MHz, all the ring protons are resolved and all the coupling constants can be obtained.

The gross structure of the higher boiling fraction **3a** or **3b** as an adduct of two cyanobutadienes to one hydrazine follows from its elemental analysis and proton NMR spectrum. Reacting pyrazolidine **2** with excess 1-cyanobutadiene also gives **3a, b.** There are several isomeric possibilities for **3a, b,** and the



3a, X = CH_2CN; Y = H
b, X = H; Y = CH_2CN



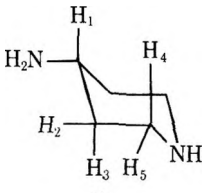
3c

carbon NMR spectrum shows that of the four plausible isomers two are present in the ratio of 2:1. Similar heterocycles have been isolated from hydrazine and 1,3-dibromopropane.[3] Reaction of the isomeric diazabicyclooctanes with methyl iodide in THF gives one crystalline product **3c** whose carbon NMR spectrum shows only six peaks in the ratio 2:2:2:2:2:1 which fixes the structure of its precursor as *cis*-**3a.** Any other isomer of **3** would have given a salt with 11 nonequivalent carbons. A logical assignment for the structure of the second isomer of **3** is *trans*-**3a** rather than a **3b** isomer. Only one of the four possible methiodides of *cis*-**3a** was isolated and the evidence is not sufficient to identify it.

Hydrogenations. Hydrogenating pyrazolidne **2** at room temperature and 40 psi with a Raney nickel catalyst gives 1,3,5-pentanetriamine **4**.[4] At higher temperatures loss of ammonia and intramolecular cyclization to 4-aminopiperidine **5**[5] becomes an important side reaction.

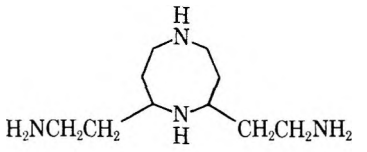
$$H_2NCH_2CH_2CH(NH_2)CH_2CH_2NH_2$$

4



5

Compound **3a** is reduced with a Raney nickel catalyst to tetramine **6,** but slightly more stringent conditions are required.



6

Chemistry of 3-(Cyanomethyl)pyrazolidine. Much of the chemistry of pyrazolidine **2** is typical of that of a dialkylhydrazine. It reacts with aldehydes such as formaldehyde or benzaldehyde to give 2:2 adducts **7**. Kurtz's benzaldehyde

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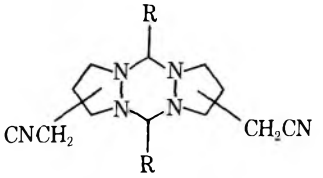
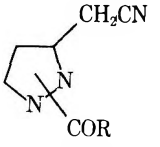
adduct of hydrazinopentenenitrile[1] may have been a slightly different isomer mix than our **7b.**



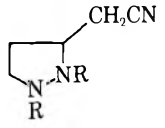
7a, R = H
b, R = C_6H_5

Phenyl isocyanate and isobutyl chloroformate give 1:1 adducts **8.**

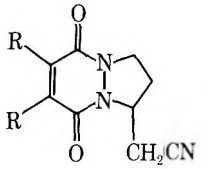


8a, R = NHC_6H_5
b, R = $OCH_2CH(CH_3)_2$

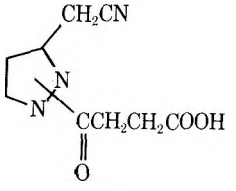
Benzoyl chloride and methyl isocyanate give 2:1 adducts **9.** Maleic and phthalic anhydrides give 1:1 adducts **10.** Succinic anhydride gives a 1:1 adduct **11,** where the ring isomer closure has not occurred. The site of acylation in **8** and **11** is unknown.



9a, R = COC_6H_5
b, R = $CONHCH_3$

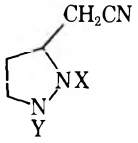


10a, R = H
b, R,R = benzo ring



11

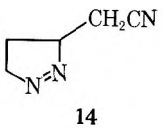
Pyrazolidine **2** gives a mixture of two 1:1 Michael adducts **12** with dimethyl acetylenedicarboxylate and a 2:1 adduct **13** with hexafluoro-2-butyne.



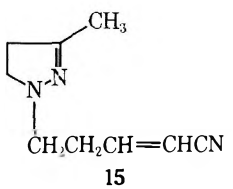
12, X = CR=CHR; Y = H
X = H; Y = CR=CHR
R = $COOCH_3$

13, X = Y = CR=CHR
R = CF_3

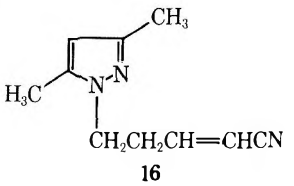
Mild oxidation with mercuric oxide gives the azo compound **14.** The products of the reaction of pyrazolidine **2** with methyl vinyl ketone and acetylacetone are pyrazoline **15** and pyrazole **16,** respectively. Both are formally derived from the open-chain hydrazinonitrile **1,** but the mechanism of these reactions is unknown and could involve either addition–elimination or elimination–addition.



14

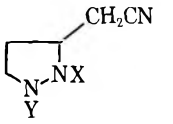


15



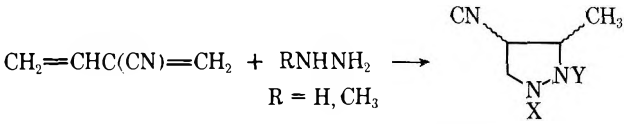
16

Other Hydrazines. The formation of cyanomethylpyrazolidines can be extended to monosubstituted hydrazines. Both phenyl- and methylhydrazines gives mixtures of 1(2)-substituted 3-(cyanomethyl)pyrazolidines **17.**



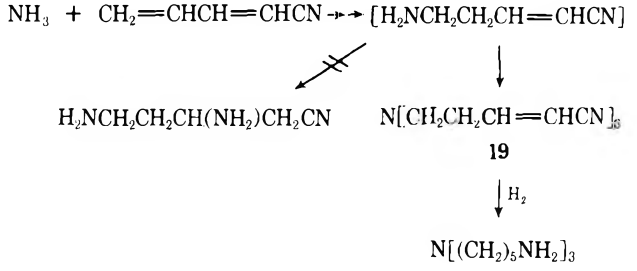
17a, X, Y = H, C_6H_5
17b, X, Y = H, CH_3

Reactions of Hydrazines with 2-Cyanobutadiene. Although the first addition of amines to 2-cyanobutadiene occurs easily, the second Michael addition is much more difficult than the corresponding reaction with 1-cyanobutadiene. Both hydrazine and methylhydrazine give a pyrazolidine from 2-cyanobutadiene, but strong base catalysis is required for the ring closure and the reaction proceeds poorly. Both *cis*- and *trans*-3-methyl-4-cyanopyrazolidine (**18a**) are formed from hydrazine.



18a, X = Y = H
b, X, Y = CH_3, H

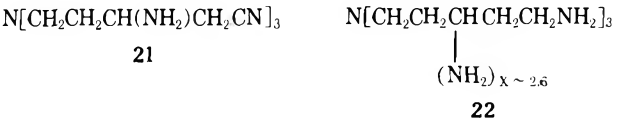
Reactions of Amines with Cyanobutadienes. An alternate route to pentanetriamine **4** might involve the addition of 2 mol of ammonia to 1-cyanobutadiene followed by reduction; however, the reaction follows a different course. Even in the presence of excess ammonia, the initial 1:1 adduct reacts with additional cyanobutadiene to form the adduct of three cyanobutadienes per ammonia **19.**[1] Even adding 1-cyanobutadiene slowly to hot ammonia did not produce 3,5-diaminopentanenitrile. Hydrogenation of amine **19** gives tetramine **20.** If **19** is heated with additional ammonia, the expected



19

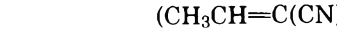
20

Michael reaction occurs and the product isolated (**21**) consists of a mixture with an average of 2.6 primary amines. Reduction gave a septamine **22** with (nominally) six primary and one tertiary amine.



21 **22**

Ammonia reacts with 2-cyanobutadiene to give mixtures of 1:1 and 1:2 adducts **23.** The 1:1 adduct could not be pre-



23a, x = 1; y = 2
b, x = 2; y = 1

pared in analytically pure form because it rapidly lost NH_3 on standing. No 1:3 adduct was isolated, nor were any products found corresponding to a Michael addition to the initially formed materials.

No distinct products could be isolated from the reaction of methylamine with 1-cyanobutadiene because extensive cross-linking apparently occurs. Methylamine reacts smoothly with 2 mol of 2-cyanobutadiene to give adduct **24** which can be reduced to triamine **25**. Dimethylamine reacts smoothly with 1-cyanobutadiene to give 1:1 adducts which react with more dimethylamine to give 2:1 adduct **26**.[1] This compound can be reduced to a triamine **27** with two tertiary and one primary amines. Triamine **27** can be alkylated with formaldehyde and formic acid to give a tris(tertiary amine) **28** which can also be prepared from pentanetriamine **4**.

$CH_3N[CH_2C(CN)=CHCH_3]_2$

24

$CH_3N[CH_2CH(C_2H_5)CH_2NH_2]_2$

25

$XCH_2CH_2CHXCH_2Y$

26, X = $N(CH_3)_2$; Y = CN

27, X = $N(CH_3)_2$; Y = CH_2NH_2

28, X = $N(CH_3)_2$; Y = $CH_2N(CH_3)_2$

Experimental Section

Instrumentation. All melting and boiling points are uncorrected. NMR spectra were obtained on Varian A-60 and HR-220 spectrometers. Infrared spectra were measured on a Perkin-Elmer 21 instrument and mass spectra on a Du Pont CEC 21-103C instrument.

Materials. 1- and 2-cyanobutadienes were prepared by literature methods.[6]

Caution: Extensive outgassing during distillation of **2** and **3** can lead to loss of vacuum and rapid decomposition of the product. The distillation should be carried out at the lowest pressure and temperature possible.

5-Hydrazino-3-pentenenitrile (1).[1] To a solution of N_2H_4·H_2O in CH_3OH at −25 °C was added dropwise 1-cyanobutadiene. The internal temperature was maintained at less than −20 °C. Solvent and starting materials were removed at 0 °C and 1 mm, leaving a colorless oil: IR 3.05, 3.44, 3.56, 4.46, 6.23, 10.32 μm; NMR δ 5.7 (m, 2 H, =CH), 3.1–3.4 (m, 7 H, CH_2 + NH).

The product cyclized to **2** during attempts at purification and on standing at room temperature.

3-(Cyanomethyl)pyrazolidine (2). To a solution of 30 g of hydrazine hydrate and 30 mL of methanol at 0 °C was added dropwise 30 g of 1-cyanobutadiene in 1 h. The exotherm was kept below 25 °C by ice-bath cooling. Solvent and excess hydrazine were removed on a rotary evaporator and the product was distilled: bp 88 °C (0.25 mm); yield 11 g; ^{1}H NMR ($CDCl_3$/Me_4Si), on HR220, δ 1.60 (d, d, t, J = 13, 6, 7 Hz, 1 H), 2.22 (d, d, t, J = 13, 3, 8, Hz, 1 H), 2.51 (d, d, J = 6, 1 Hz, CH_2), 2.72 (d, t, J = 12, 8 Hz, 1 H), 3.14 (d, d, d, J = 12, 8, 3 Hz, 1 H), 3.58 (q, J = 6 Hz, 1 H), 3.89, (s, 2 NH); IR 3.03, 3.38, 3.45, 4.44 μm. Anal. Calcd for $C_5H_9N_3$: C, 54.0; H, 8.2; N, 37.8. Found: C, 54.1; H, 8.0; N, 37.7.

1,7-Bis(cyanomethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole (3a). Continued distillation from the preparation of 3-(cyanomethyl)pyrazolidine gave 4.5 g of product as a light yellow liquid: bp 156 °C (0.2 mm); ^{1}H NMR ($CDCl_3$/Me_4Si) δ 1.78 (m, 1 H), 2.36–2.63 (m, 3 H), 2.85 (m, 1 H), 3.11 (m, 1 H), 3.34 (m, 1 H); ^{13}C NMR (neat/Me_4Si) major, δ 66.0, 72.7, 92.6, 100.8, 160.6; minor, 65.2, 76.0, 91.1, 97.9, 161.2. Anal. Calcd for $C_{10}H_{14}N_4$: C, 63.2; H, 7.4; N, 29.5; Found: C, 62.9; H, 7.6; N, 29.5.

1,7-Bis(cyanomethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole Methiodide (3c). A solution of cyclic hydrazine **3a** in THF was treated at room temperature with methyl iodide until no further exotherm occurred. A heavy phase separated. THF was decanted and the oil recrystallized (slowly) from ethanol, giving the salt as white needles: mp 200 °C (dec); IR 3.30, 3.38, 3.43, 4.45 μm; ^{1}H NMR (Me_2SO-d_6/Me_4Si) δ 3.4 (s, CH_3), remainder is an aliphatic multiplet; ^{13}C NMR (Me_2SO-d_6/Me_4Si) δ 118.1 (2 CN), 64.5 (2 C), 63.4 (2 C), 56.6 (CH_3), 29.8 (2 C), 22.1 (2 C). Only one of the four possible isomers is present in this particular sample. Anal. Calcd for $C_{11}H_{17}N_4I$: C, 39.8; H, 5.2; N 16.9. Found: C, 39.1; H, 5.1; N, 16.9.

1,3,5-Pentanetriamine (4). A slurry of 8.6 g of pyrazolidine **2**, 20 mL of EtOH, and 5 g of Raney nickel was shaken with 35 psi of H_2 at room temperature for 4 h. Catalyst was removed and the residue distilled, giving 6.1 g of pentanetriamine: bp 67 °C (0.12 mm);[4] NMR ($CDCl_3$/Me_4Si) δ 1.24 (s, 6 NH), 1.27–1.58 (m, 4 H, AB further split), 2.72 (t, J = 7 Hz, 4 H), 2.85 (t, J = 4 Hz, t, J = 8 Hz, 1 H). The IR spectrum was consistent with an aliphatic primary amine.

4-Aminopiperidine (5). If the Raney nickel catalyzed hydrogenation of pyrazolidine **2** is carried out above room temperature, some 4-aminopiperidine[5] is formed, bp 28–32 °C (0.4 mm). GC on any nonpolar column separates the diamine and the triamine conveniently. The diamine has the shorter retention time: ^{1}H NMR ($CDCl_3$/Me_4Si) δ 1.148 (d, J = 4 Hz, q, J = 12 Hz, H-3), 1.42 (s, NH), 1.75 (d, J = 12 Hz, br, H-2), 2.52 (d, J = 2 Hz, t, J = 12 Hz, H-4), 2.66 (t, J = 4 Hz, t, J = 10 Hz, H-1), 2.99 (t, J = 3 Hz, d, J = 12 Hz, H-5). The IR spectrum was consistent with a primary aliphatic amine.

2,8-Bis(2-aminoethyl)octahydro-1,5-diazocine (6). Ten grams of **3a**, 20 mL of CH_3OH, 10 g of NH_3, and 5 g of Raney nickel were pressured to 1000 psi of H_2 heated at 75 °C/6 h. The catalyst was filtered and the residue distilled, giving 3.9 g of light yellow liquid: bp 122–125 °C (0.18 mm); IR 3.04, 3.42, 3.49, 6.25 μm; ^{1}H NMR (CCl_4/Me_4Si) δ 1.07 (s, 6 NH), 1.42 (q, J = 6.5 Hz, 4 H), 1.0–2.1 (m, 4 H), 2.77 (t, J = 6.5 Hz, 4 H), 2.5–3.3 (m, 6 H). Anal. Calcd for $C_{10}H_{24}N_4$: C, 60.0; H, 12.1; N, 28.0. Found: C, 60.1; H, 11.6; N, 27.9.

1,7(9)-Bis(cyanomethyl)tetrahydro-1*H*,5*H*,7*H*,11*H*-dipyrazolo[1,2-*a*:1′,2′-*d*]-*S*-tetrazine (7a). To 5.5 g of pyrazolidine **2** in 25 mL of CH_3OH was added at room temperature 4 mL of formalin. The exothermic reaction was controlled by an ice bath. The solution became viscous and deposited a white solid which was filtered and recrystallized from $CHCl_3$/C_6H_{12}: yield 1.5 g; mp 154–158 °C; IR 3.37, 3.46, 3.52, 3.57, 4.45 μm; ^{1}H NMR ($CDCl_3$/Me_4Si) δ 4.02, 3.45 (2 AB, J = 9 Hz, 4 H), 2.57 (d, J = 5 Hz, 4 H), 1.7–3.4 (m, 10 H). Anal. Calcd for $C_{12}H_{18}N_6$: C, 58.5; H, 7.4; N, 34.1. Found: C, 58.5; H, 7.3; N, 34.3.

1,7(9)-Bis(cyanomethyl)-5,11-diphenyltetrahydro-1*H*,5*H*,7*H*,11*H*-dipyrazolo[1,2-*a*:1′,2′-*d*]-*S*-tetrazine (7b). A solution of 2.2 g of pyrazolidine **2** and 5 g of benzaldehyde in 25 mL of CH_3OH was stirred at room temperature. After 10 min a white precipitate formed. The suspension was stirred for 30 min and filtered, and the product was washed with CH_3OH and air-dried: yield 1.5 g; mp 165–185 °C; mol wt (mass spec) 398; IR 3.24, 3.27, 3.34, 3.46, 3.50, 4.44, 6.22, 6.28, 6.68, 13.28, 14.27 μm. Anal. Calcd for $(C_{12}H_{13}N_3)_n$: C, 72.3; H, 6.6; N, 21.1. Found: C, 72.2; H, 6.75; N, 21.4.

3-(Cyanomethyl)pyrazolidinecarboxanilide (8a). To 7.2 g of phenyl isocyanate in 20 ml of benzene was added dropwise at room temperature 3 g of pyrazolidine **2**. The initial exotherm was controlled by ice-bath cooling. The white precipitate which formed was filtered and washed with pentane, yield 6 g. The analytical sample was recrystallized from CH_3OH/H_2O: mp 140–141 °C; IR 2.97, 3.07, 3.37, 3.42, 4.44, 5.94, 6.26, 6.57, 13.26, 14.35 μm; ^{1}H NMR ($CDCl_3$/Me_4Si) δ 1.5–2.45 (m, 2 H), 2.58 (d, J = 6 Hz, 2 H), 3.05–4.06 (m, 3 H), 5.69 (d, J = 7 Hz, 1 H), 6.85–7.81 (m, 5 H), 8.72 (s, NH). Anal. Calcd for $C_{12}H_{14}N_4O$: C, 62.6; H, 6.1; N, 24.3. Found: C, 62.6; H, 6.1; N, 24.0.

Isobutyl 3-(Cyanomethyl)pyrazolidinecarboxylate (8b). To pyrazolidine **2** (3.3 g) and triethylamine (3.1 g) in 50 mL of benzene was added at 0 °C with stirring 4.1 g of isobutyl chloroformate. An exothermic reaction deposited a white solid. After stirring at room temperature overnight, 50 mL of pentane was added and the solid was filtered. The liquid was stripped on a rotary evaporator and the residue distilled, giving 3 g of product as a light yellow liquid: bp 170 °C (0.25 mm); IR 3.07, 3.36, 3.43, 4.45, 5.87, 7.21 μm; ^{1}H NMR ($CDCl_3$/Me_4Si) δ 4.90 (s, NH), 3.4–4.1 (m, 5 H, CHN, CHO), 1.7–2.5 (m, 3 H), 2.58 (d, J = 6 Hz, CH_2CN), 0.92 [d, J = 7 Hz, $CH(CH_3)_2$]. Anal. Calcd for $C_{10}H_{17}N_3O_2$: C, 56.8; H, 8.1; N, 19.9. Found: C, 57.0; H, 8.1; N, 19.8.

1,2-Dibenzoyl-3-(cyanomethyl)pyrazolidine (9a). To 2 g of pyrazolidine **2** and 2 g of triethylamine in 50 mL of benzene was added at 0 °C with stirring 6 g of benzoyl chloride. After a vigorous exotherm, a white solid deposited. The slurry was stirred overnight at room temperature, filtered, washed with pentane and water, and air-dried, giving 2.3 g of product as white solid. The analytical sample was recrystallized from methanol/water, mp 151.5–152 °C; IR 3.24, 3.34, 4.44, 5.95, 6.05, 6.22, 6.31, 6.68, 13.42, 14.40 μm; ^{1}H NMR (Me_2SO-d_6) δ 7.35–7.88 (10 H, m, aromatic), 4.66 (br, NH), 3.84 (pentet, J = 7 Hz, 2 H), 3.09 (d, J = 6 Hz, 2 H), 1.78–2.64 (m, 2 H). Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.5; H, 5.4; N, 13.2. Found: C, 71.4; H, 5.4; N, 13.5.

3-(Cyanomethyl)-1,2-bis(methylcarbamoyl)pyrazolidine (9b). To 3 g of pyrazolidine **2** in 20 mL of benzene was added dropwise 5 g of methyl isocyanate in 20 mL of benzene. The vigorous exotherm was

controlled by ice-bath cooling. The solution was stirred overnight at room temperature. Cooling deposited white needles which were filtered and washed with pentane, yield 1.8 g. The analytical sample was recrystallized from DMF: mp 238–240 °C; IR 3.01, 3.38, 4.44, 5.97, 6.42, 6.58 μm; ^{1}H NMR (Me_2SO) δ 6.9 (br m, 2 NH), 3.95–4.97 (m, 2 H), 1.5–3.2 (m, 9 H), 2.6 (d, J = 5 Hz, 2 H). Anal. Calcd for $C_9H_{15}N_5O_2$: C, 48.0; H, 6.7; N, 31.1. Found: C, 47.8; H, 6.4; N, 31.1.

1-Cyanomethyl-2,3-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-dione (10a). To 5 g of maleic anhydride in 20 mL of THF was added in portions 5.5 g of pyrazolidine **2**. After a mild exotherm subsided, the product was deposited as a sticky yellow solid. Methanol recrystallization gave 5 g of product as a white crystalline solid: mp 139.5–143 °C (dec); IR 3.26, 3.31, 3.40, 4.44, 5.95, 6.15, 6.36 μm; ^{1}H NMR (Me_2SO/Me_4Si) δ 6.86 (s, 2 =CH), 4.87 (m, NCH), 4.16 (m, NCH_2), 3.13 (4 lines, CH_2CN), 1.97–2.90 (m, CCH_2C). Anal. Calcd for $C_9H_9N_3O_2$: C, 56.5; H, 4.7; N, 22.0. Found: C, 56.7; H, 4.9; N, 22.2.

1-(Cyanomethyl)-2,3-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione (10b). To 7.6 g of phthalic anhydride in 50 mL of THF was added in portions 5.5 g of pyrazolidine **2**. After a mild exotherm subsided, the solution was refluxed overnight. Solvent was removed on a rotary evaporator and the product recrystallized from water, giving 6.4 g of white crystalline solid: mp 140–143 °C; IR 3.24, 3.41, 3.49, 4.45, 6.14, 6.23, 6.78 μm; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 8.20 (m, 2 H), 7.82 (m, 2 H), 5.00 (m, 1 H), 4.34 (m, 2 H), 2.95 (d, J = 6 Hz, 2 H), 1.50 (m, 2 H). Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.7; H, 4.6; N, 17.4. Found: C, 64.6; H, 4.6; N, 17.1.

3-(Cyanomethyl-γ-oxopyrazolidinebutyric Acid (11). To 5 g of succinic anhydride in 50 mL of THF was added 5.5 g of pyrazolidine **2**. After a slight exotherm subsided the solution was refluxed 4 h. Solvent was removed on the rotary evaporator and the residual oil was triturated with methanol to give 6 g of white crystalline solid; mp (CH_3OH) 110–112.5 °C; IR 3.05, 3.37, 3.5–4.0, 4.42, 5.83, 6.25 μm; NMR δ 1.7–3.8 with (2.50, d, J = 6 Hz, CH_2, 11 H), 5.4, 7.3 (br, NH + OH). Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.2; H, 6.2; N, 19.9. Found: C, 51.2; H, 6.2; N, 20.0.

Dimethyl 2-[3-(Cyanomethyl)pyrazolidinyl]fumarate (12). To 5.5 g of pyrazolidine **2** in 25 mL of CH_3OH was added dropwise 7.1 g of dimethyl acetylenedicarboxylate. After the initial exotherm at 50 °C subsided, the solution was heated at 50 °C/2 h. On standing overnight the bulk of the solvent evaporated, leaving a crystalline residue which was triturated with benzene, filtered, washed with pentane, and air-dried to give 5.7 g of light yellow solid: mp 100–102 °C; mol wt calcd for $C_{11}H_{15}N_3O_4$, 253; found (mass spec), 253; IR 3.11, 3.25, 3.39, 3.47, 4.46, 5.70, 5.97, 6.36, 8.65 μm; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 3.62, 3.65, 3.72, 3.82 (s, OCH_3), 2.43, 2.68 (d, J = 6 Hz), the rest is broad. Anal. Calcd for $C_{11}H_{15}N_3O_4$: C, 52.2; H, 6.0; N, 16.6. Found: C, 51.8; H, 6.1; N, 16.8.

3-(Cyanomethyl)-1,2-bis[3,3,3-trifluoro-1-(trifluoromethyl)-1-propenyl]pyrazolidine (13). Pyrazolidine **2** (5.5 g), THF (10 mL), and hexafluorobutyne (20 g) were heated in an 80-cm^3 bomb at 50 °C/3 h. Distillation gave 14.3 g of product: bp 98–104 °C (0.6 mm); IR 3.36, 3.45, 4.43, 6.09, 8–9 μm; ^{1}H NMR ($CDCl_3/Me_4Si$) aliphatic absorption and 1 multiplet at δ 4.2; ^{19}F NMR ($CDCl_3/CFCl_3$) ϕ −70.4 (m), −61.0 (q, J = 10 Hz), −60.5 (m), −56.7 (pentet J = 10 Hz), ca. equal intensities. Anal. Calcd for $C_{13}H_9N_3F_{12}$: C, 35.9; H, 2.1; F, 52.4. Found: C, 36.2; H, 2.2; F, 52.0.

3-(Cyanomethyl)-Δ1-pyrazoline (14). To a refluxing solution of 5.5 g of pyrazolidine **2** in 100 mL of CH_3OH was added in portions 11 g of HgO (yellow). The yellow color was replaced by the dark gray of metallic mercury. After refluxing for 2 h, the solution was decanted from metallic residues, stripped on a rotary, and distilled, giving 4.4 g of product as a colorless liquid, bp 72–80 °C (0.25 mm); IR 3.36, 4.43, 6.42 μm; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 0.9–2.2 (m, 2 H), 2.92 (d, d, J = 6, 2 Hz, 2 H), 3.8–5.0 (m, 3 H). Anal. Calcd for $C_5H_7N_3$: C, 55.0; H, 6.5. Found: C, 55.3; H, 6.3.

1-(4-Cyano-3-butenyl)-3-methyl-Δ2-pyrazoline (15). To 5.5 g of pyrazolidine **2** in 25 mL of CH_3OH was added in portions 3.5 g of methyl vinyl ketone. After a mild exotherm subsided, the yellow solution was refluxed 0.5 h, solvent was removed on a rotary evaporator, and the product was distilled to give 3.5 g of colorless liquid bp 90 °C (0.05 mm); IR 3.27, 3.42, 3.53, 4.51, 6.17, 7.22 μm; ^{1}H NMR δ 6.4–7.0 (m, 1 H), 5.2–5.6 (m, 1 H), 2.3–3.2 (m, 8 H), 1.92 (s, CH_3). Anal. Calcd for $C_9H_{13}N_3$: C, 66.2; H, 8.0; N, 25.7. Found: C, 65.2; H, 8.0; N, 26.3.

1-(4-Cyano-3-butenyl)-3,5-dimethylpyrazole (16). To 5.5 g of pyrazolidine **2** in 25 mL of CH_3OH was added in portions 5.0 g of acetylacetone. After the initial mild exotherm subsided, the yellow solution was heated at 50 °C/2 h. Solvent was removed on a rotary evaporator and the residue distilled, giving 6 g of colorless liquid; bp 89–92 °C (0.07 mm); IR 3.24, 3.37, 4.47, 6.08, 6.42 μm; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 2.08 (s, CH_3), 2.18 (d, J = 2 Hz, CH_3), 2.71 (AA′), 3.93 (XX′), 5.08 (d, J = 14 Hz, m, 1 H), 5.60 (s, =CH), 6.44 (m, 1 H). Anal. Calcd for $C_{10}H_{13}N_3$: C, 68.5; H, 7.5; N, 24.0. Found: C, 68.3; H, 7.2; N, 24.3.

1(2)-Phenyl-3-(cyanomethyl)pyrazolidine (17a). A solution of 38 g of phenylhydrazine and 28 g of 1-cyanobutadiene in 100 mL of dioxane was refluxed for 3 h. Triton B (1 mL) and 25 mL of 1-cyanobutadiene were added and the solution was refluxed again. Distillation gave 20 g of yellow liquid, bp 140 °C (0.04 mm); IR 2255 cm^{-1}; NMR (CCl_4/Me_4Si) δ 6.5–7.3 (m, 5 H), 1.3–4.2 (m, 6 H), 2.43 (d, J = 6 Hz, CH_2). Anal. Calcd for $C_{11}H_{13}N_3$: C, 70.6; H, 7.0. Found: C, 70.7; H, 7.0.

1(2)-Methyl-3-(cyanomethyl)pyrazolidine (17b). Sixteen grams of 1-cyanobutadiene was added dropwise to 15 g of methylhydrazine in 20 mL of methanol. The internal temperature was kept below 15 °C by ice-bath cooling. The solution was stirred for 1 h at room temperature. Solvent was removed on a rotary evaporator and the residue distilled, giving 14.1 g of colorless liquid, bp up to 90 °C (0.06 mm).

A crude ^{1}H NMR spectrum showed that the product was not extensively cyclized. The product was added to 10 mL of triethylamine and the homogeneous solution refluxed for 2 h. Distillation gave 9.8 g of a light yellow liquid: bp 68–76 °C (0.25 mm); ^{1}H NMR ($CDCl_3/Me_4Si$) resembles 3-(cyanomethyl)pyrazolidine with sharp CH_3N singlets at δ 2.53 and 2.82. Anal. Calcd for $C_6H_{11}N_3$: C, 57.6; H, 8.9; N, 33.6. Found: C, 57.5; H, 8.5; N, 33.8.

4-Cyano-3-methylpyrazolidine (18a). A solution of 25 g of 95% N_2H_4, 25 g of 2-cyanobutadiene, and 200 mL of EtOH was refluxed for 3 h. A few grams of strong base ion-exchange resin was added and the solution refluxed overnight. The resin was filtered and the solution distilled. The bulk decomposed, but a 20% yield of product could be obtained from small-scale distillations; bp ~120 °C (2 mm); IR 3.1, 3.4, 4.5, 9.0, 9.2, 12.0 μm; NMR ($CDCl_3/Me_4Si$) δ 1.40, 1.32 (d, J = 6 Hz CH_3CH), 3.1–3.6 (m, 6 H). Two isomers are present in the ratio of ca. 2:1. Anal. Calcd for $C_5H_9N_3$: C, 54.0; H, 8.2; N, 37.8. Found: C, 53.7; H, 8.1; N, 37.8.

1(2),3-Dimethyl-4-cyanopyrazolidine (18b). A solution of 16 g of 2-cyanobutadiene, 10 g of methylhydrazine and 100 mL of EtOH was mixed at room temperature. After a mild exotherm subsided, 1 mL of Triton B was added and the dark solution was refluxed for 4 h. NMR examination of the crude product showed uncyclized material, so more Triton B was added and the solution again heated. Distillation gave 5 g of colorless liquid, bp 88–90 °C (2.5 mm), and other unidentified higher boiling fractions. IR 2.95, 3.05, 6.07, 3.36, 3.49, 3.57, 4.45, 7.21 μm; NMR δ 1.34 (several d, J = 7 Hz, CH_3CH), 2.48, 2.53 (s, s, NCH_3), 2.6–3.7 (m, 5 H). There are at least three isomers present in the ratio of 1:2:3. Anal. Calcd for $C_6H_{11}N_3$: C, 57.6; H, 8.9. Found: C, 57.2; H, 9.2.

Tris(5-aminopentyl)amine (20). A slurry of 38 g of crude adduct **19**,[1] 25 g of Raney nickel, and 25 g of NH_3 was heated at 100 °C/8 h under 2000 psi of H_2. Distillation at 180 °C (0.15 mm) gave 20 g of a colorless liquid. IR 2.96, 3.03, 3.39, 3.47, 6.23 μm; NMR (CCl_4/Me_4Si) δ 0.87 (s, 3 NH_2), 1.37 (m, 9 CH_2), 2.33 (t, J = 7 Hz, 6 H), 2.62 (t, J = 7 Hz, 6 H). Anal. Calcd for $C_{15}H_{36}N_4$: C, 66.1; H, 13.2; N, 20.6; mol wt 272. Found: C, 66.2; H, 13.2; N, 20.7; mol wt 262.

Tris(3-amino-4-cyanobutyl)amine (21). A 400-mL bomb was charged with 120 g of ammonia and heated to 90 °C. A solution of 1:1 1-cyanobutadiene in THF was injected at the rate of 10 mL/30 min. After the addition was complete (6 h), the solution was heated at 90 °C for an additional 2 h. Solvent was removed on a rotary evaporator leaving a yellow oil. ^{1}H NMR analysis gave a ratio of vinyl/aliphatic of 38:200, suggesting that the fourth ammonia had added ~60%. The sample was purified by falling film distillation, bp 160–165 °C/<5 μm. Anal. Calcd for $C_{15}H_{27}N_7$: C, 59.0; H, 8.9; N, 32.1. $C_{15}H_{24}N_6$: C, 62.4; H, 8.3; N, 29.2. Found: C, 60.9; H, 8.9; N, 30.0.

Tris(3,5-diaminopentyl)amine (22). A suspension of 75 g of Raney nickel, 150 g of amine **21**, and 500 mL of THF was loaded into a bomb, cooled, and evacuated. To this was added 100 g of NH_3 and 1000 psi of H_2. The mixture was heated at 100 °C/8 h. Catalyst was filtered and solvent removed on a rotary evaporator. The residue was passed through a falling film evaporator and the fraction, bp 135–140 °C/<2 μm, was analyzed: IR primary aliphatic amine; NMR ($CDCl_3/Me_4Si$) δ 1.28 (5, NH), 1.0–1.9 (m, CH_2CH_2C), 2.2–3.4 (m, CHN). Anal. Calcd for $C_{15}H_{39}N_7$ (average of five primary amines): C, 59.2; H, 13.1; N, 27.6. Found: C, 61.3; H, 11.5; N, 27.1.

Bis(2-cyano-2-butenyl)amine 23b. To a solution of 2.5 g of NH_3 in 25 mL of EtOH at 0 °C was added dropwise 34 g of 2-cyanobutadiene in 75 mL of EtOH. The solution was stirred at room temperature for 2 h and refluxed overnight. Solvent was removed on a rotary evaporator and the residual oil was distilled on a spinning-band col-

umn, giving, among others, 5 g of dinitrile as a colorless liquid; bp 138 °C (0.4 mm); IR 3.01, 3.28, 3.42, 3.49, 4.51, 6.09, 7.23 μm; NMR ($CDCl_3/Me_4Si$) δ 1.59 (s, NH), 1.88, 2.02 (d, J = 7 Hz, CH_3), 3.41 (s, CH_2), 6.48, 6.60 (q, J = 7 Hz, m, J = 1 Hz, =CH). Anal. Calcd for $C_{10}H_{13}N_3$: C, 68.5; H, 7.4; N, 24.0. Found: C, 68.0; H, 7.7; N, 24.8.

2-Cyano-2-butenylamine (23a). The fraction, bp 68–75 °C (2.1 mm) (17.5 g), showed: IR 3.0, 3.5, 3.6, 4.5, 6.1, 6.2, 6.9, 7.3 μm; ^1H NMR (CCl_4/Me_4Si) δ 1.21 (s, 2 NH), 2.00 (d, J = 7 Hz, t, J = 1.5 Hz, CH_3), 3.38 (m, J = 1.5 Hz, CH_2), 6.39 (q, J = 7 Hz, t, J = 1.5 Hz, =CH). Elemental analyses were unsatisfactory because the ammonia addition is apparently reversible.

Bis(2-cyano-2-butenyl)methylamine (24). To a solution of 5 g of methylamine in 25 mL of EtOH at 0 °C was added dropwise a solution of 28 g of 2-cyanobutadiene in 25 mL of EtOH over a 0.5-h period. The red solution was refluxed overnight and distilled, giving 20 g of colorless liquid: bp 113–120 °C (0.05 mm); IR 3.25, 3.37, 3.48, 3.55, 4.49, 6.07 μm; ^1H NMR δ 1.91, 2.05 (d, J = 6 Hz, CH_3CH), 2.30 (s, CH_3N), 3.20 (s, CH_2N), 6.48, 6.60 (q, J = 6 Hz, br, =CH). Anal. Calcd for $C_{11}H_{15}N_3$: C, 69.8; H, 8.0; N, 22.2. Found: C, 70.0; H, 8.0; N, 22.5.

Bis[2-(aminomethyl)butyl]methylamine (25). A slurry of 15 g of dinitrile **24**, 60 mL of THF, 25 g of NH_3, and 20 g of Raney nickel was shaken under 2000 psi of H_2 at 135 °C/8 h. The catalyst was separated, solvent was removed on a rotary evaporator, and the product was distilled through a small spinning-band column; bp 75–77 °C (0.02 mm); yield 9 g; IR 2.99, 3.06, 3.44, 3.49, 3.58, 6.26, 7.26 μm; ^1H NMR (CCl_4/Me_4Si) δ 2.13 (s, CH_3), 2.05–2.7 (m, CH_2N), 0.9 (t, J = 6 Hz, CH_3CH_2), 1.05–1.8 (m, CH_2). Anal. Calcd for $C_{11}H_{27}N_3$: C, 65.6; H, 13.5; N, 20.9. Found: C, 66.4; H, 13.2; N, 20.1.

3,5-Bis(dimethylamino)valeronitrile (26) was prepared by the addition of dimethylamine to 1-cyanobutadiene:[1] ^1H NMR (CCl_4/Me_4Si) δ 1.62 (q, J = 6.5 Hz, CH_2CN), 2.19, 2.30 (s, s, NCH_3), 2.42 (m, CH_2N), 2.90 (m, CHN).

1,3-Bis(dimethylamino)-5-aminopentane (27). A slurry of 18 g of nitrile **26**, 50 mL of THF, 20 g of NH_3, and 10 g of Raney cobalt was shaken under 1000 psi of H_2 at 135 °C/6 h. Distillation gave 7 g of triamine, bp 84–90 °C (2 mm); IR primary aliphatic amine; ^1H NMR δ 1.12 (s, NH_2), 1.2–1.8 (m, 4 H), 2.11, 2.17 (s, s, NCH_3), 2.27–2.79 (m, 5 H). Anal Calcd for $C_9H_{23}N_3$: C, 62.4; H, 13.4; N, 24.2. Found: C, 62.2; H, 13.4; N, 24.2.

1,3,5-Tris(dimethylamino)pentane (28). To 17 g of **27** at 0 °C was added 40 g of formic acid and then 40 g of formalin. The solution was refluxed, giving off 4.5 L of CO_2 in 2 h. After the addition of 5 mL of concentrated HCl, the solution was stripped on the rotary and poured onto ice. The solution was made basic with 50% NaOH, and the organic phase was extracted into ether, dried, and distilled, giving 12 g of colorless liquid: bp 68–70 °C (0.6 mm); IR saturated tertiary amine; NMR ($CDCl_3/Me_4Si$) δ 1.30 (m, $CH_2CH_AH_BCH$), 1.57 (m, $CH_2CH_AH_BCH$), 2.13 (s, 12 H, CH_3N), 2.19 (s, 6 H, CH_3N), 2.20 (m, J = 6 Hz, CH_2N), 2.40 (pentet, J = 6, CHN). Anal. Calcd for $C_{11}H_{27}N_3$: C, 65.6; H, 13.5; N, 20.9. Found: C, 66.1; H, 13.5; N, 21.0.

Registry No.—**1**, 64413-80-5; **2**, 64413-76-9; **3a**, 64413-74-7; **3c**, 64413-75-8; **4**, 59821-81-7; **5**, 13035-19-3; **6**, 64413-73-6; **7a**, 64414,07-9; **7b**, 64414-06-8; **8a**, 64414-05-7; **8b**, 64414-09-1; **9a**, 64413-85-0; **9b**, 64413-84-9; **10a**, 64413-83-8; **10b**, 64413-82-7; **11**, 64414-08-0; **12** isomer 1, 64413-81-6; **12** isomer 2, 64413-79-2; **13**, 64413-78-1; **14**, 64413-77-0; **15**, 64398-03-4; **16**, 64398-02-3; **17a** isomer 1, 64398-01-2; **17a** isomer 2, 64397-86-0; **17b** isomer 1, 64398-00-1; **17b** isomer 2, 64397-85-9; *cis*-**18a**, 64397-99-5; *trans*-**18a**, 64397-98-4; **18b** isomer 1, 64414-30-8; **18b** isomer 2, 64397-84-8; **19**, 64397,87-1; **20**, 64397-97-3; **21**, 64397-96-2; **22**, 64397-95-1; **23a**, 64397-94-0; **23b**, 64397,93-9; **24**, 64397-92-8; **25**, 64397-91-7; **26**, 64397-90-6; **27**, 64397-89-3; **28**, 64397-88-2; hydrazine, 302-01-2; 1-cyanobutadiene, 1615-70-9; benzaldehyde, 100-52-7; phenyl isocyanate, 103-71-9; isobutyl chloroformate, 17462-58-7; benzoyl chloride, 98-88-4; methyl isocyanate, 624-83-9; maleic anhydride, 108-31-6; phthalic anhydride, 85-44-9; succinic anhydride, 108-30-5; dimethyl acetylene dicarboxylate, 762-42-5; hexafluorobutyne, 692-50-2; methyl vinyl ketone, 78-94-4; acetylacetone, 123-54-6; phenylhydrazine, 100-63-0; methylhydrazine, 60-34-4; 2-cyanobutadiene, 5167-62-4; methylamine, 74-89-5; formalin, 50-00-0.

References and Notes

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(6) Research Disclosure 11516, Nov., 1973.

Reactions of 1,1-Disubstituted Olefins Containing Electron-Attracting Substituents with Methylphenyldiazomethanes

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Reactions of 1,1-disubstituted olefins 3 which carry cyano, carboalkoxy, halogen, etc. as a substituent with methyl-para-substituted-phenyldiazomethanes (2) in dichloromethane at −5–0 °C produce 1,1-disubstituted-3-phenyl-1-butene (4) and 1,1-disubstituted-2-methyl-2-phenylcyclopropane (5). Product ratios of 4 to 5 seem to depend upon the substituents on 3. In the case of 3 with both cyano and carboalkoxy groups, product 4 is more favorable than 5; on the other hand, when using 3 with both either a cyano or carboalkoxy group and either a halogen or hydrogen, product 5 is more favorable than 4. The product ratios of 4 to 5 also depend upon the substituents of 2; e.g., when the substituent is an electron-attracting group product 4 is more favorable than 5, and when the substituent is an electron-donating group 5 is more likely than 4.

It has been reported[1-3] that the reactions of 2-cyano-3-phenylacrylates with diazomethane give various products, including 2-cyano-3-methyl(or ethyl)-3-phenylacrylates, 2-cyano-3-methyl-3-benzylacrylates, and 1-cyano-2-methyl-2-phenylcyclopropanecarboxylates (**5a,b**). **5** (X = NO_2, R = H, Y = CN, Z = COOMe) has been isolated in pure form[4] but **5a** and **5b** have not.[5] We wished to obtain **5b** in its pure form and tried the following reactions.

Methylphenyldiazomethane (**2a**)[6,7] reacted with 2-cyanoacrylates **3a,b** in dichloromethane at −5–0 °C readily, and the crude products obtained were applied to a column of silicic acid (eluted with chloroform) and afforded 2-cyano-4-methyl-4-phenylcrotonates **4a,b**. In the case of **2a** with **3b**, **5b** was afforded, mp 105–106 °C, in 9.8% yield together with **6b** (X = H), mp 160–161 °C, in 2.7% yield. From its NMR, **6** was recognized as a geometrically simple compound.

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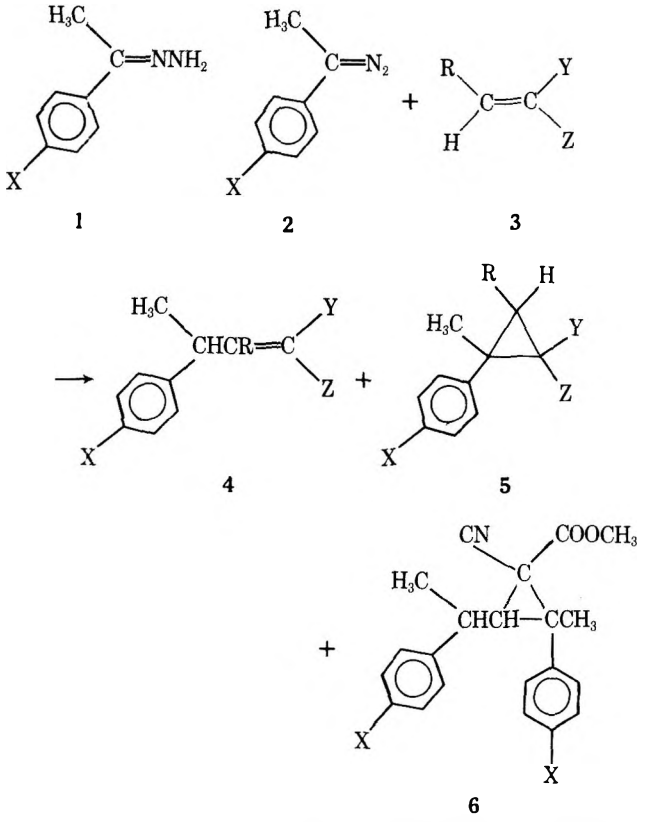
Table I. Product Yields and Geometric Isomer Ratios of the Reactions

2		3				4							5						
Compd 2	X	Compd 3	R	Y	Z	Compd 4	X	R	Y	Z	Yield %	Yield c:t	Compd 5	X	R	Y	Z	Yield %	Yield c:t
a	H	a	H	CN	COOEt	a	H	H	CN	COOEt	29.3	1:3.3	a	H	H	CN	COOEt	None	
	H	b	H	CN	COOMe	b	H	H	CN	COOMe	27.8	Only *t*	b	H	H	CN	COOMe	9.77	Only *t*
	H	c	H	CN	Cl	c	H	H	CN	Cl	None		c	H	H	CN	Cl	33.7	1:1
	H	d	H	Br	COOMe	d	H	H	Br	COOMe	None		d	H	H	Br	COOMe	25.9	1:1.5
	H	e	H	H	COOMe	e	H	H	H	COOMe	7.81	Only *t*	e	H	H	H	COOMe	21.5	Only *t*
	H	f	CH_3	CN	COOMe	f	H	CH_3	CN	COOMe	16.4	1:10	f	H	CH_3	CN	COOMe	23.8	1:1.8
b	Cl	b	H	CN	COOMe	g	Cl	H	CN	COOMe	33.5	1:6.7	g	Cl	H	CN	COOMe	None	
	Cl	c	H	CN	Cl	h	Cl	H	CN	Cl	None		h	Cl	H	CN	Cl	39.5	1:1.2
c	CH_3	b	H	CN	COOMe	i	CH_3	H	CN	COOMe	3.9	Only *t*	i	CH_3	H	CN	COOMe	14.8	Only *t*



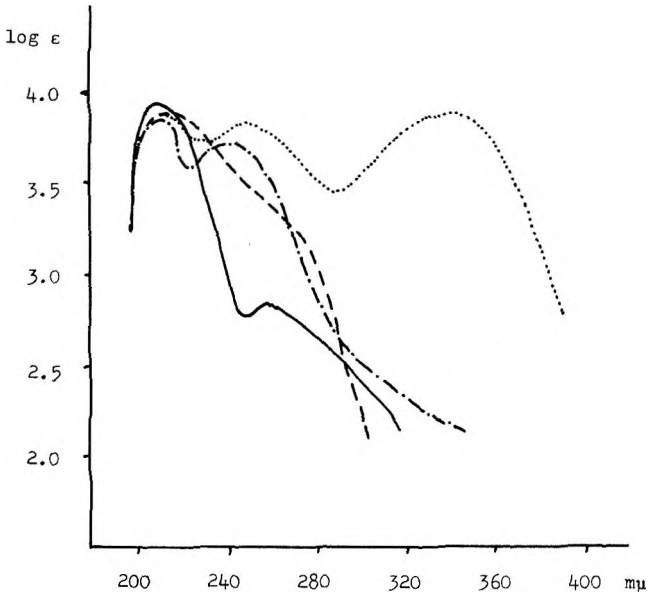
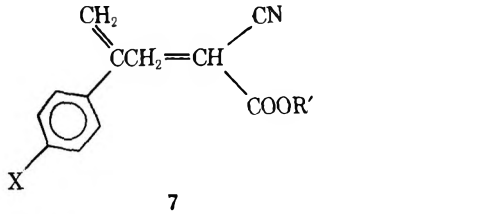
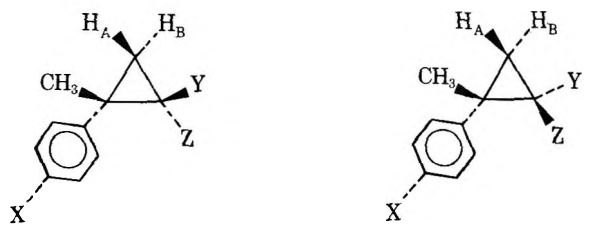


Figure 1. UV spectra of **4b** and **5b**: (- - -) **4b** in neutral medium; (···) **4b** in basic medium; (– • –) **4b** in acidic medium; (—) **5b** in neutral medium.

To obtain **5** in a better yield, we varied the substituents Y or Z of the olefin **3**, and their reactions gave the products **4a–i** and **5b–i**. The yields (%) based on acetophenone hydrazones **1**[8] and isomeric ratios[9] of these products are shown in Table I. The products **4–6** were characterized on the basis of their MS, IR, NMR, and UV spectra and analyses. Table II shows NMR spectral data of **4**, Table III shows NMR spectral data of **5**, and Table IV shows UV spectral data of **4** and **5**.[10] (For Tables II–IV, see paragraph concerning supplementary material.)

The differences between **4** and **5** have been apparently recognized on NMR and UV spectra. From the NMR spectra of these compounds, **4b** and **5b** are geometrically simple, and the constitution of the trans form only was estimated. A vinyl proton of **4b** appears at δ 7.63 (d), but two hydrogens of the cyclopropane ring of **5b** appear at δ 2.40 (d) and 2.01 (d). On the UV absorption curve, **4b** shows a marked variation with a change in the acidity of the medium, as shown by a new absorption maximum at 340 nm (log ϵ 3.85) in alkaline medium, but the UV spectra of **5b** does not show a marked variation (Figure 1). The UV spectra of **4a** and **4g** are similar to that of **4b**, and those of **5c–i** are similar to that of **5b**.





5 cis (5f: CH_3 instead of H_A)

5 trans (5f: CH_3 instead of H_B)

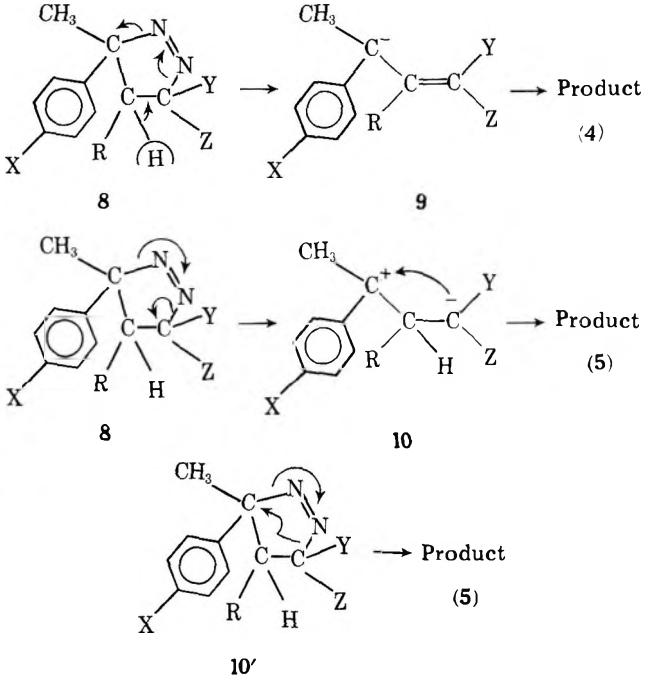
When **5b** is kept at 180 °C for 3 h it changes completely to **7b** (X = H; R′ = Me): NMR ($CDCl_3$) δ 5.30 and 5.42 (nearly two s, 2 H), δ 3.5 (ABX type, 1 H), 3.2 (ABX type, 2 H, J_{AX} = 8.6 Hz, J_{BX} = 6.4 Hz, J_{AB} = 13.6 Hz), 3.72 (s, 3 H). This fact suggests that **4** has not been produced from **5**; the products **4** and **5** have been produced via a separate route.

Reaction of methyl-*p*-chlorophenyldiazomethane (**2b**) with

3b only produces olefin compound **4g**, but reaction of **2b** with 2-chloroacrylonitrile (**3c**) only produces cyclopropane compound **5h**. On the other hand, reaction of methyl-*p*-methylphenyldiazomethane (**2c**) with **3b** produces both olefin compound **4i** and cyclopropane compound **5i**, mp 103–104.5 °C,[11] with the result that the latter will give a better yield than the former. In this case, the products were refined carefully with a column of silicic acid (eluted with chloroform and petroleum ether) to produce **4i** and **5i** in their pure forms, respectively; in spite of refining which was repeated four to five times, **4i** was obtained as an equivalent mixture with **6i**.

The IR spectrum of **5e** agrees with that of the product from the reaction of α-methylstyrene with diazoacetic ester.[12] On the UV spectra of **4f** a marked variation has never been shown with a change in the acidity of the medium, because the CH_3 group attaching to the C=C bond decreases the acidity of the vinyl hydrogen. In comparing the mass spectra of **4** with those of **5**, it is observed that all base peaks of **4** are made of $M^+ - R'OH$ but those of **5** are made of the fragments which lack a substituent in the cyclopropane ring.

From the reports of Carrie et al.[13] concerning pyrazoline compounds, we guess that these reactions which are treated under no irradiation at low temperature proceed by way of the pyrazoline compounds **8**. McGreer et al.[14] have suggested that the pyrolyses of pyrazolines at 70 or 140 °C proceeded through ionic mechanisms and were affected by the polarity of solvents. Also, we guess that when **8** loses nitrogen through an ionic mechanism, according to the nature of the substituent X, Y, and Z, they take either a path to product **4** easily or the other path to produce **5** easily. From the above results, 1,1-disubstituted olefin which carries the electron-attracting substituents such as COOR′ and CN conjugated with C=C is ordinarily unfavorable for cyclopropane ring formation, but our experiments show that it proceeded together with chain-extended olefin formation. The ratios of **4** to **5** in the reaction products seem to depend upon the substituents (Y, Z) of **3**; namely, in the case of **3** with both CN and COOR′ groups, product **4** is more favorable than **5**; on the other hand, in the case of **3** with both either a CN or COOR′ group and either a halogen or hydrogen, product **5** is more favorable than **4**. The details are as follows: **3** (R = H, Y = CN, Z = COOR′), **4** > **5**; **3** (R = H, Y = H, Z = COOR′), **4** < **5**; **3** (R = CH_3, Y = CN, Z = COOR′), **4** < **5**; **3** (R = H, Y = Br, Z = COOR′), **4** ≪ **5**; **3** (R = H, Y = CN, Z = Cl), **4** ≪ **5**.

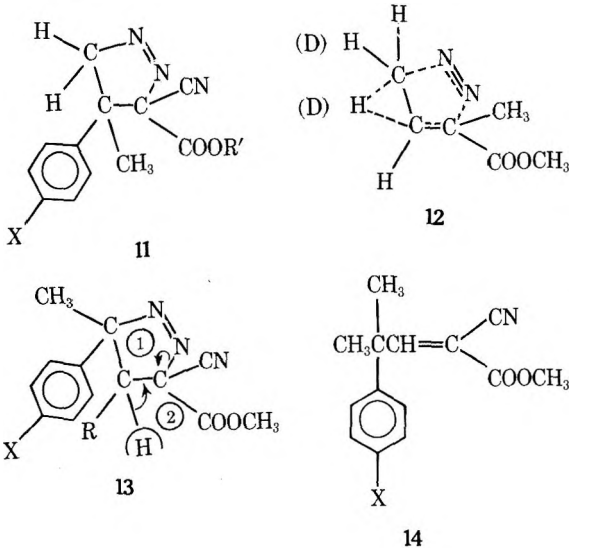


On the reaction of methyl-para-substituted-phenyldiazomethanes (**2**) with methyl α-cyanoacrylate (**3b**), the substituents (X) of **2** control the product ratios of **4** to **5** in the reaction products as follows: **2** (X = Cl), **4** ≫ **5**; **2** (X = H), **4** > **5**; **2** (X = CH_3), **4** < **5**.

In the case of **8** (X = Cl, R = H, Y = CN, Z = COOR′), the carbanion at the benzyl site is stable. When, therefore, a nitrogen molecule misses from **8**, a hydrogen on the allyl site of Y or Z will leave off **8** as a proton, and then the residue will produce **4** through an intermediate **9**. In the case of **8** (X = CH_3, R = H, Y = CN, Z = COOR′), the carbonium ion at the benzyl site is stable. When, therefore, a nitrogen molecule misses from **8**, the residue will produce the carbanion at the α position of Y or Z in **10**. If the carbanion has a certain stability, though a zwitter ion **10** is difficult to exist, it will produce **5** by way of a concerted mechanism (**10′**).

Discussion

Hamelin et al.[15] and McGreer et al.[16] considered the mechanisms of olefin formation by pyrolyses of the pyrazolines **11**, and they suggested that the driving force which was caused by the formation of the zwitter ion of $^+$N-2 and $^-$C-3 (shifting ① in **13**) was the result of an aromatic or methyl



group migrating from C-4 to C-5. From the kinetic study[16,17] using the deuterated pyrazolines, McGreer et al. suggested that the olefin formation proceeded by way of the concerted mechanism which transformed the σ bond between N-2 and C-3 into the π bond between C-3 and C-4 in **12**. They also suggested that the olefin formation was a stereospecific reaction, but that the cyclopropane formation was not.[16-18] Their products-yield data[4] showed that **11** (X = NO_2) produced much more corresponding cyclopropane compound than **11** (X = MeO) did, but, in both cases, more olefins were produced than cyclopropane compounds, but these facts are opposite to our results, and their data were obtained regardless of whether C-4 was charged negative or positive in the transition state of the decomposition reaction of **11**.

In the case of our study, the bond shifting in the decomposition reactions of pyrazoline takes place in the reverse direction to the cases in the study of Hamelin et al. and McGreer et al. In our case, the formation of olefin **4** from pyrazoline **8** occurred through intermediate **9** owing to the bond shifting (**13**, ② →), and a hydrogen at C-4 came off as a proton. Consequently, it is difficult to consider that a hydrogen at C-4 migrates to C-5 in the form of a hydrogen atom or a hydride ion. A methyl migration from C-4 to C-5 is also difficult to consider because the olefin of the type **14** is not given.

In our study, when a pyrazoline **8** produced a zwitterion **10**

of ^{+}C and ^{-}C, the bond shifting (**13**, ← ①) which is also shown by Hamelin et al. and McGreer et al. occurred; but in our case it should be considered that a pyrazoline **8** produces a cyclopropane compound **5**.

Experimental Section[19]

Methyl α-Cyanoacrylate (3b). In a 200-mL round-bottomed flask with a reflux condenser a mixture of 25 g (0.25 mol) of methyl cyanoacetate, 10 g of paraformaldehyde, and 3 drops of piperidine was heated and stirred on a oil bath at 80 °C for 1 h. The content of the flask became a pale-yellow resinous material. The material was cooled down to room temperature and was dissolved into 300 mL of dichloromethane, into which 100 g of anhydrous sodium sulfate was added for dryness. This solution contained 0.92 g (0.0082 mol) of methyl α-cyanoacrylate per 10 mL. Ethyl α-cyanoacrylate (**3a**) was prepared in the same way.

Methyl 2-Cyano-4-methyl-4-phenylcrotonate (4b), Methyl 1-Cyano-2-methyl-2-phenylcyclopropanecarboxylate (5b), and Methyl 1-Cyano-2-α-methylbenzyl-3-methyl-3-phenylcyclopropanecarboxylate (6b). To the stirred mixture of 8 g (0.06 mol) of acetophenone hydrazone (**1**, X = H), 60 mL of dichloromethane, and 6.2 g of anhydrous magnesium sulfate, cooled in an ice bath, 28 g of active manganese dioxide[20] was added portionwise in 20 min, and then the whole material was stirred for 1 h at room temperature. The inorganic salts were filtered off with a Buchner funnel packed with hyflo super-cel (Johns-Manvills Sales Corp.), being washed with 30 mL of dichloromethane. The combined filtrates were cooled down to −35 °C, and then a small amount of precipitates was separated off by decantation. The deep red-purple solution contained methylphenyldiazomethane (**2a**). To this cooled dichloromethane solution of **2a** in a 200-mL round-bottomed flask, 70 mL of a dichloromethane solution of **3b** (0.0574 mol) was added and stirred at −5–0 °C for 1 h, the solution changed its color to yellow, and stirring was continued overnight at room temperature. The solvent was distilled off under reduced pressure at 40–50 °C. Fourteen grams of crude oily products was obtained. A solution of 14 g of the crude products in the minimum volume of chloroform was applied to a column of silicic acid (500 g, 100 mesh), and the column was eluted with chloroform. The crude products resolved into four or five bands in the column; the pale-yellow fastest moving band (500 mL of chloroform solution) gave 5 mL of oily product. When 3 mL of 95% ethanol was added to this product, 5.72 g of **6b** was given as the crystals which gave 0.51 g (yield 2.7%) of the colorless prisms of **6b**, mp 160–161 °C, by recrystallization from ethanol, and the mother liquid, being applied to a column of silicic acid (three times chromatographied), gave the solution of **4b**.

The second fastest moving band (500 mL of chloroform solution) gave 3 mL of oily product. Two milliliters of 95% ethanol was added to this product and then 1.303 g of **5b** as the colorless prisms, mp 105–106 °C, was given. These prisms gave 1.25 g (yield 9.8%) of **5b**: mp 105–106 °C; NMR ($CDCl_3$) δ 2.17 (d, H_A), 2.10 (d, H_B, J_{AB} = 6 Hz), 1.67 (s, CH_3); MS *m/e* (rel intesity) 215 (27), 200 (4), 183 (70), 156 (100); IR (nujol) 2248 (CN), 1764 cm^{-1} (C=O), by recrystallization from ethanol; Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.37; H, 5.98; N, 6.68. The mother liquid, being applied to a column of silicic acid (three times chromatographed), gave the solution of **4b**.

A combined solution of **4b** gave 3.56 g (yield 27.8%) of pure **4b** as a pale-yellow oil: $n^{20}D$ 1.5396; NMR ($CDCl_3$) δ 4.16 (m, H_A), 7.62 (d, H_B, J_{AB} = 11 Hz), 1.53 (d, CH_3); MS *m/e* (rel intensity) 215 (47), 183 (100), 155 (37); IR (neat) 2230 (CN), 1740 cm^{-1} (C=O). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.29; H, 5.90; N, 6.23. From the third and fourth bands, 0.7 g of acetophenonazine, mp 122 °C (lit.[21] mp 121 °C), was given.

6b: mp 160–161 °C; IR (nujol) 2218 (CN), 1740 cm^{-1} (C=O); UV (EtOH), λ_{max}, nm (log ε), in neutral medium 213 (4.05), 252 (2.16), 260 (2.38), 264 (2.38); UV absorption spectrum of **6b** does not show a marked variation with a change in the acidity of the medium; NMR ($CDCl_3$) δ 7.32 (arom, 5 H), 7.12 (arom, 5 H), 3.49 (s, 3 H), 2.72 (d, 1 H, J_{AB} = 12 Hz), 2.51 (m, 1 H, $J_{A\text{-}CH_3}$ = 6 Hz), 1.35 (d, 3 H), 1.50 (s, 3 H). Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.96; H, 6.58; N, 4.39. Found: C, 78.84; H, 6.60; N, 4.48.

In the same way the above **4a** was given as oil: $n^{20}D$ 1.5292; NMR (Me_2SO-d_6) cis form δ 7.05 (d, H_B, J_{AB} = 11 Hz, H_A is obscure), 1.51 (d, CH_3, $J_{A\text{-}CH_3}$ = 7 Hz); trans form δ 4.00 (m, H_A), 7.77 (d, H_B, J_{AB} = 11 Hz), 1.49 (d, CH_3, $J_{A\text{-}CH_3}$ = 7 Hz); MS *m/e* (rel intensity) 229 (46), 183 (100), 156 (50). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.28; H, 6.56; N, 6.07.

Methyl 2-Cyano-4-methyl-4-*p*-methylphenylcrotonate (4i), Methyl 1-Cyano-2-methyl-2-*p*-methylphenylcyclopropanecarboxylate (5i), and Methyl 1-Cyano-2-α-methyl-*p*-methylbenzyl-3-methyl-3-*p*-methylphenylcyclopropanecarboxylate (6i). Methyl-*p*-methylphenyldiazomethane (**2c**) was prepared from 9.4 g (0.06 mol) of *p*-methylacetophenone hydrazone (**1**, X = CH_3), 6.2 g of anhydrous magnesium sulfate in 70 mL of dichloromethane, and 28 g of active manganese dioxide. In the same way as the reaction of **2a** with **3b**, **2c** reacted with 90 mL of a dichloromethane solution of **3b** (0.06 mol) and gave 12.6 g of the crude products. The solution of the crude products in the minimum volume of chloroform was applied to a column of silicic acid (400 g, 100 mesh) and eluted with chloroform. From the faster moving bands, 1 L of chloroform solution gave 10.3 g of an orange-yellow oily substance. The oily substance was applied repeatedly (five times) to a column of silicic acid (each 400 g, 100 mesh) and eluted at first with petroleum ether only (boiling range 30–70 °C) and then with the solvent which was gradually changed to the mixture of petroleum ether and chloroform (10:1).

The fastest moving band, being distilled off the solvent under reduced pressure at 40 °C, gave 1.514 g of a pale-yellow oil. From NMR, this oil (1.514 g) proved to consist of 0.536 g (yield 3.9%) of **4i** and 0.978 g (yield 4.7%) of **6i**. The second fastest moving band, being distilled off the solvent under reduced pressure at 40 °C, gave white crystallines, which gave 2.03 g (yield 14.8%) of **5i** by recrystallization from a mixed solvent of petroleum ether and methanol (1:1): mp 103–104.5 °C; NMR ($CDCl_3$) δ 2.11 (d, H_A), 2.05 (d, H_B, J_{AB} = 6 Hz), 1.57 (s, CH_3); MS *m/e* (rel intensity) 229 (41), 197 (48), 170 (100); IR (nujol) 2250 (CN), 1732 cm^{-1} (C=O). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.46; H, 6.56; N, 6.03. The third and fourth fastest moving bands gave 3.15 g of *p*-methylacetophenonazine, mp 131–132 °C (lit.[21] mp 131 °C). **4i:** NMR ($CDCl_3$) δ 4.00 (m, H_A), 7.40 (d, H_B, J_{AB} = 11 Hz), 1.45 (d, CH_3, $J_{A\text{-}CH_3}$ = 7 Hz). **6i:** NMR ($CDCl_3$) δ 6.98 (arom, 4 H), δ 6.83 and 6.70 (A_2B_2, 4 H, *J* = 9 Hz), 3.80 (s, 3 H), 2.58 (d, 1 H), 2.46 (m, 1 H, J_{AB} = 10.8 Hz, $J_{A\text{-}CH_3}$ = 6.3 Hz), 2.34 (s, 3 H), 2.20 (s, 3 H), 1.45 (s, 3 H), 1.18 (d, 3 H).

Methyl 1-Bromo-2-methyl-2-phenylcyclopropanecarboxylate (5d). Methylphenyldiazomethane (**2a**) was prepared, in the above-mentioned method, from 0.06 mol of acetophenone hydrazone (**1**, X = H). To the dichloromethane solution of **2a**, 13 g (0.08 mol) of methyl α-bromoacrylate[22] was added under stirring at −5–0 °C, and stirring was continued overnight at room temperature. When the solvent was distilled off under reduced pressure at 40–50 °C, 19.8 g of crude products was given, and then they were applied to a column of silicic acid (500 g, 100 mesh) and eluted with chloroform. That is to say, for the purification of the products, column-chromatography was applied repeatedly six times with silicic acid columns. The fastest moving band gave 1.4 g (yield 5.93%) of the orange-red colored crystals of ω,ω′-dibromoacetophenonazine (**15**):[23] mp 151–152 °C; NMR ($CDCl_3$) δ 4.51 (s, 2 H), 8.0 and 7.5 (arom, 5 H); MS *m/e* (rel intensity) 396 (27), 394 (51), 392 (27), 315 (41), 313 (44), 314 (99), 312 (99), 234 (100). Anal. Calcd for $C_{16}H_{14}N_2Br_2$: C, 48.75; H, 3.55; N, 7.11; Br, 40.61. Found: C, 48.68; H, 3.51; N, 7.03; Br, 40.66. A combined solution of the faster moving bands of each column chromatogram, especially the fastest moving band, gave 4.15 g (yield 25.9%) of **5d** (NMR pure substance, this sample was six times column chromatographed): $n^{20}D$ 1.5444; NMR ($CDCl_3$) cis form δ 2.02 (d, H_A), 1.70 (d, H_B, J_{AB} = 6 Hz), 1.45 (s, CH_3); trans form δ 2.49 (d, H_A), 1.34 (d, H_B, J_{AB} = 6 Hz), 1.70 (s, CH_3); MS *m/e* (rel intensity) 270 (4), 268 (4), 189 (23), 157 (19), 192 (100); IR (neat) 1730 cm^{-1} (C=O);[24] and any olefin compound was not given.

Methyl 4-Methyl-4-phenylcrotonate (4e) and Methyl 2-Methyl-2-phenylcyclopropanecarboxylate (5e). In the above-mentioned method, from 4 g (0.03 mol) of acetophenone hydrazone (**1**, X = H) was prepared **2a**, which was reacted with 2.2 g (0.025 mol) of methyl acrylate (**3e**) in dichloromethane at −5–0 °C. Crude products (2.1 g) were applied to a column of silicic acid and eluted with chloroform. The fastest moving band (column chromatographed repeatedly two times) gave 0.863 g of a pure oil of **5e**: $n^{20}D$ 1.5196; NMR (CDl_3) δ 1.36 (cd, H_A), 1.53 (dd, H_B), 1.96 (dd, H_X, J_{AB} = 5 Hz, J_{AX} = 7 Hz, J_{BX} = 8 Hz), 1.51 (s, CH_3); MS *m/e* (rel intensity) 190 (25), 159 (17), 131 (100); IR (neat) 1725 cm^{-1} (C=O). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.64; H, 7.36. The second fastest moving band (column chromatographed repeatedly six times) gave 0.842 g of mixed oil; from NMR, the oil proved to consist of **4e** and **5e** in the ratio 1:0.9. **4e:** NMR ($CDCl_3$) δ 3.55 (m, H_A), 7.66 (dd, H_B), 5.78 (d, H_C, J_{AB} = 11 Hz, J_{AC} = 2 Hz, J_{BC} = 15 Hz), 1.62 (d, CH_3, $J_{A\text{-}CH_3}$ = 7 Hz). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.75; H, 7.42. Found: C, 75.22; H, 7.44.[25] The third and fourth fastest moving bands gave 1.69 g of acetophenonazine, mp 122 °C. As a result, the reaction of **2a** with **3e** gave eventually 12.2 g (yield 21.5%) of **5e** and 0.44 g (yield 7.81%) of **4e**.

Methyl 2-Cyano-3,4-dimethyl-4-phenylcrotonate (4f) and Methyl 1-Cyano-2,3-dimethyl-2-phenylcyclopropanecarboxylate (5f). In the above-mentioned method, from 4 g (0.03 mol) of acetophenone hydrazone (**1**, X = H) was prepared **2a**, which was reacted with 5.1 g (0.042 mol) of methyl α-cyanocrotonate (**3f**) in dichloromethane at −5–0 °C. There was 8.5 g of crude products given, and they were applied to a column of silicic acid and eluted with chloroform. The fastest moving band (column chromatographed repeatedly two times) gave 1.12 g (yield 16.4%) of **4f:** n^{20}D 1.5427; NMR ($CDCl_3$) cis form δ 1.62 (d, CH_3, $J_{A\text{-}CH_3}$ = 7 Hz, H_A is obscure); trans form δ 5.84 (m, H_A), 1.49 (d, CH_3, $J_{A\text{-}CH_3}$ = 7 Hz), 1.99 (s, CH_3); MS *m/e* (rel intensity) 229 (35), 197 (100), 170 (40); IR (neat) 2220 (CN), 1722 and 1730 cm^{-1} (C=O). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.16; H, 6.62; N, 5.91. The second fastest moving band (column chromatographed repeatedly two times) gave 1.63 g (yield 23.8%) of **5f:** n^{20}D 1.5298; NMR ($CDCl_3$) cis form δ 1.24 (d, CH_3), 2.30 (q, H_B, $J_{B\text{-}CH_3}$ = 7 Hz); 1.46 (s, CH_3); trans form δ 1.42 (d, CH_3), 2.63 (q, H_B, $J_{B\text{-}CH_3}$ = 7 Hz), 1.69 (s, CH_3); MS *m/e* (rel intensity) 229 (55), 197 (100), 170 (79); IR (neat) 2230 (CN), 1735 and 1740 cm^{-1} (C=O). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.35; H, 6.59; N. 6.11. Found: C, 73.64; H, 6.57; N, 6.02. The third and fourth fastest moving bands gave 0.6 g of acetophenonazine.

1-Chloro-1-cyano-2-methyl-2-phenylcyclopropane (5c). In the above-mentioned method, from 4 g (0.03 mol) of **1** (X = H) was prepared **2a**, which was reacted with 2.2 g (0.025 mol) of α-chloroacrylonitrile (**3c**) and gave 4.12 g of crude products which contained some yellow crystals. The crude products gave 0.46 g of acetophenonazine by filtration, and then the mother liquid was applied to a column of silicic acid (eluted with chloroform), giving a pure oil, 1.94 g (yield 33.7%), of **5c** (column chromatographed repeatedly two times): n^{20}D 1.5737; NMR ($CDCl_3$) cis form δ 2.10 (d, H_A), 1.42 (d, H_B, J_{AB} = 6 Hz), 1.64 (s, CH_3); trans form δ 1.78 (d, H_A), 1.72 (d, H_B, J_{AB} = 6 Hz), 1.62 (s, CH_3); MS *m/e* (rel intensity) 191 (32), 156 (100), 129 (99); IR (neat) 2220 cm^{-1} (CN). Anal. Calcd for $C_{11}H_{10}NCl$: C, 68.93; H, 5.26; N, 7.31; Cl, 18.50. Found: C, 69.01; H, 5.09; N, 7.52; Cl, 18.79. Any olefin product was not given.

Methyl 2-Cyano-4-methyl-4-*p*-chlorophenylcrotonate (4g). In the above-mentioned method, from 8.5 g (0.05 mol) of *p*-chloroacetophenone hydrazone (**1**, X = Cl), was prepared **2b**, which was reacted with 50 mL of a dichloromethane solution of **3b** (0.04 mol) at −5–0 °C. The reaction gave 12.7 g of crude products as a mixture of oil and crystals. From the crude products, 1.27 g of *p*-chloroacetophenonazine, mp 148–149 °C (lit.[21] mp 151 °C), was given by filtration, and the mother liquid was applied to a column of silicic acid and eluted with chloroform. The fastest moving band (column chromatographied repeatedly two times) gave 4.22 g (yield 33.5%) of **4g:** n^{20}D 1.5555; NMR (CCl_4) cis form δ 1.33 (d, CH_3, $J_{A\text{-}CH_3}$ = 7 Hz), 3.93 (s, CH_3); trans form δ 4.09 (m, H_A); 7.49 (d, H_B, J_{AB} = 11 Hz), 1.51 (d, CH_3, $J_{A\text{-}CH_3}$ = 7 Hz), 7.22 (arom), 3.82 (s, CH_3); MS *m/e* (rel intensity) 249 (30), 217 (100); IR (neat) 2220 (CN), 1740 cm^{-1} (C=O). Anal. Calcd for $C_{13}H_{12}NO_2Cl$: C, 62.51; H, 4.81; N, 5.61; Cl, 17.03. Found: C, 62.75; H, 4.77; N, 5.56; Cl, 17.42; and the slower moving bands gave 2.86 g of **3b**.

1-Chloro-1-cyano-2-methyl-2-*p*-chlorophenylcyclopropane (5h). In the above-mentioned method, from 8.5 g (0.05 mol) of **1** (X = Cl) was prepared **2b**, which was reacted with 4.4 g (0.05 mol) of **3c** in a dichloromethane solution at −5–0 °C. Crude products (7.39 g) were applied to a column of silicic acid and eluted with chloroform. The fastest moving band gave 4.23 g (yield 39.5%) of **5h** (column chromatographied repeatedly three times): n^{20}D 1.5526; NMR (CCl_4) cis form δ 2.11 (d, H_A), 1.47 (d, H_B, J_{AB} = 8 Hz), 1.67 (s, CH_3); trans form δ 1.80 (d, H_A), 1.70 (d, H_B, J_{AB} = 8 Hz), δ 1.64 (s, CH_3); MS *m/e* (rel intensity) 225 (7), 190 (100); IR (neat) 2233 cm^{-1} (CN). Anal. Calcd for $C_{11}H_9NCl_2$: C, 58.43; H, 4.01; N, 6.20; Cl, 31.36. Found: C, 58.21; H, 3.84; N, 6.18; Cl, 31.18. The slower moving bands gave 0.21 g of *p*-chloroacetophenonazine.

Isomerization of Methyl 1-Cyano-2-methyl-2-phenylcyclopropanecarboxylate (5b). In a glass tube, for the NMR measurement, 50 mg of **5b** was kept at 180 °C for 3 h on an oil bath. The content became a light brown oil, and it was cooled down to room temperature and dissolved into 0.4 mL of chloroform-*d* for the NMR measurement. From NMR, **5b** changed completely to 4-cyano-4-methoxycarbonyl-2-phenyl-1-butene (**7b**).

Registry No.—**1** (X = H), 13466-30-3; **1** (X = CH_3), 64242-53-5; **1** (X = Cl), 40137-41-5; **2a**, 22293-10-3; **2b**, 61185-76-0; **2c**, 64252-52-4; **3a**, 7095-85-0; **3b**, 137-05-3; **3c**, 920-37-7; **3d**, 4519-46-4; **3e**, 96-33-3; **3f**, 51977-58-3; *cis*-**4a**, 64252-51-3; *trans*-**4a**, 38323-11-4; **4b**, 64252-50-2; **4e**, 64252-40-9; *cis*-**4f**, 64252-47-7; *trans*-**4f**, 64252-45-5; *trans*-**4g**, 64252-46-6; **4i**, 64252-44-4; **5b**, 64252-43-3; *cis*-**5c**, 64265-07-2; *trans*-**5c**, 64252-38-6; *cis*-**5d**, 62360-17-2; *trans*-**5d**, 62360-16-1; **5e**, 64252-37-5; *cis*-**5f**, 64252-36-4; *trans*-**5f**, 64312-48-7; *cis*-**5h**, 64252-35-3; *trans*-**5h**, 64252-42-2; **5i**, 64252-41-1; **6b**, 64265-06-1; **6i**, 64252-40-0; **7b**, 64252-39-7; **15**, 35635-90-6; methyl cyanoacetate, 105-34-0; paraformaldehyde, 30525-89-4; *p*-methylacetophenonazine, 21399-33-7; acetophenonazine, 729-43-1; *p*-chloroacetophenonazine, 5326-15-8.

Supplementary Material Available. Full NMR data (Tables II and III) and UV spectral data (Table IV) for compounds 4 and 5 (3 pages). Ordering information is given on any current masthead.

References and Notes

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(2) J. Hamelin and R. Carrie, *Bull. Soc. Chim. Fr.*, 2513 (1968).
(3) Y. Hirata and W. Nagai, *Bull. Nagoya Inst. Tech.*, **21**, 123 (1969).
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(5) In the report[2] by J. Hamelin et al., the reaction products were applied to distillation so that the NMR data were shown as a mixture of **5** (X = CH_3 or CH_3O, R = H, Y = CN, Z = COOEt) and **7** (X = CH_3 or CH_3O, R′ = Et). McGreer et al.[4] isolated **5** (X = NO_2, R = H, Y = CN, Z = COOMe) in pure form by means of preparative thin-layer chromatography, but they obtained **5** (X = H or CH_3O, R = H, Y = CN, Z = COOMe) which still remains as a mixture with the cinnamates.
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(8) Yields are for the NMR pure substances which were purified two or three times (or if circumstances require five or six times) by means of the column of silicic acid. One cause of a poor yield is due to the production of phenonazines.
(9) In the compounds *cis*-**4**, CH_3CHPh groups are cis geometry for substituent Z; and the ratios cis/trans are determined from the peak areas of the NMR signals of the products. For determination of the geometry of the compound **5c**, we referred to the following literatures: C. A. Reilly and J. D. Swalen, *J. Chem. Phys.*, **32**, 1378 (1960); B. P. Dailey, A. Gawer, and W. C. Neikam, *Discuss. Faraday Soc.*, **34**, 18 (1962); G. Allen, D. J. Blears, and K. H. Welf, *J. Chem. Soc.*, 810 (1965). For determination of the geometry of the compound **5d**, we referred to the literature: L. M. Jackmann and S. Sternhell, "Applications of NMR Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, New York, N.Y., 1969, p 228.
(10) In the case of the isomeric mixture, the isomeric ratios are shown in Table I.
(11) In the report[2] by J. Hamelin et al., **5** (X = CH_3, R = H, Y = CN, Z = COOEt) was described as an oil, bp 169–171 °C (2 mmHg); we suppose it would be a mixture of **5** and the corresponding **7**.
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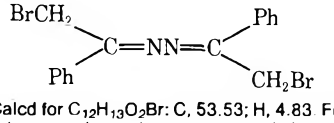
(23) Compound **15** has the structure:



(24) For **5d** Anal. Calcd for $C_{12}H_{13}O_2Br$: C, 53.53; H, 4.83. Found: C, 52.66; H, 4.87; the sample was column chromatographied six times, but these data are no good because **5d** is unstable.
(25) Mixed sample of **4e** and **5e** in the ratio 1:0.9.

Sensitized Photolyses of Methanesulfonyl Azide in Hydrocarbons

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The sensitized photolyses of methanesulfonyl azide (1) in hydrocarbons gave N-substituted methanesulfonamides (4) and methanesulfonamide, although the former had been formed via the singlet sulfonylnitrene and not via the triplet. These sensitized photolyses showed a tertiary/secondary ratio of 18.2 for the insertion regioselectivity toward C–H bonds in 2-methylbutane. The photolyses of 1 in *cis*- and *trans*-1,4-dimethylcyclohexanes led to nonstereospecific formation of 4, respectively, in contrast to the direct photolyses of 1. In the sensitized photolyses, 4 is formed not by a nitrene mechanism, but by a mechanism involving an intermediate, $CH_3SO_2\dot{N}_3H$.

There is much interest in the electronic multiplicities of nitrenes in relation to their insertion into C–H bonds of saturated hydrocarbons. Phenylnitrene inserted only via the triplet,[2] cyanonitrene inserted via both the singlet and the triplet,[3] and alkoxycarbonylnitrenes inserted only via the singlet.[4–7] For the ethers, however, it was found that insertion of ethoxycarbonylnitrene into their α C–H bonds proceeded via both the singlet and the triplet.[8–10]

Methanesulfonylnitrene, generated by the thermolysis or the photolysis of methanesulfonyl azide (1), was less regioselective than the other nitrenes for the insertion in primary, secondary, and tertiary C–H bonds of hydrocarbons.[11] The insertion has been shown to proceed with only the singlet from the stereochemical point of view: the sulfonylnitrene inserted stereospecifically into the tertiary C–H bonds of *cis*- and *trans*-1,4[12]- or 1,2[13]-dimethylcyclohexanes.

In these photolyses of 1 by earlier investigators, a low-pressure mercury lamp, which can excite the azide directly, has been employed. No report on the sensitized photolysis of 1 has been made except the photolysis in isopropyl alcohol, in which the hydrogen abstraction product was quantitatively obtained.[14] The triplet-sensitized photolyses of 1 in hydrocarbons gave the insertion products accompanied by the hydrogen abstraction product. This paper deals with the photosensitized decomposition of 1, describing the formation of the insertion and abstraction products which proceeds via a mechanism different from the nitrene mechanism advanced in the reaction with hydrocarbon C–H bonds.

Results and Discussion

A 1,2-dichloroethane solution of methanesulfonyl azide (1) and a hydrocarbon in the presence of acetophenone was irradiated by light from a high-pressure mercury lamp under an atmosphere of nitrogen (Scheme I). A circulating 1.5 M $CuSO_4$ aqueous solution was provided as a filter. The presence of the filter completely inhibited the direct excitation of 1. The yields of the products are listed in Table I.

$$\underset{1}{CH_3SO_2N_3} + R\text{–}H \xrightarrow[>3000\ \text{Å},\ -N_2]{\text{sensitization}} \underset{4}{CH_3SO_2NHR} + \underset{5}{CH_3SO_2NH_2}$$

R = hydrocarbon residue

Each of the reactions gave N-substituted mathanesulfonamides (4) and methanesulfonamide (5). Product 4 corresponds formally to that resulting from the insertion of singlet methanesulfonylnitrene into the C–H bonds. The formation of 4 under the present condition means that a reactive species other than the singlet nitrene should be involved in the insertion reaction. In the reaction with 2-methylbutane, the reaction products with the tertiary and the secondary C–H bonds ($4B_1$ and $4B_2$, see Table I) were isolated, but those with the primary ones were not detected. On the other hand, the direct photolysis of 1 gave four isomeric insertion products resulting from attack on all the primary, secondary, and tertiary C–H bonds.[11] The relative reactivities of reactive species 2 (Scheme I) toward C–H bonds were compared with those of singlet methanesulfonylnitrene, generated by direct photolysis[10] or thermolysis.[13] The data are displayed in Table II. Reactive species 2 was significantly a more selective intermediate than the singlet nitrene toward the C–H bonds of hydrocarbons. In the reactions with 2-methylbutane and 2,3-dimethylbutane, the lack of detection of the products with the primary C–H bonds is due to the high selectivity of 2. The highly selective insertion shows that 2 has a radical character. Then, different paths leading to 4 are considerable, as shown in eq 7–9 in Scheme I.

Scheme I

Excitation

$$CH_3COC_6h_5 \xrightarrow[>3000\ \text{Å}]{\text{photosensitization}} CH_3COC_6H_5^t \quad (1)$$

Energy transfer

$$\underset{1}{CH_3COC_6H_5^t} + CH_3SO_2N_3 \rightarrow CH_3COC_6H_5 + \underset{2}{CH_3SO_2N_3^t} \quad (2)$$

Abstraction

$$CH_3COC_6H_5^t + RH \rightarrow CH_3\dot{C}(OH)C_6H_5 + \cdot R \quad (3)$$

$$CH_3SO_2N_3^t \xrightarrow{-N_2} CH_3SO_2\dot{N}\cdot^t \xrightarrow{RH} \underset{6}{CH_3SO_2\dot{N}H} + \cdot R \quad (4)$$

$$2 \xrightarrow{RH} \underset{7}{CH_3SO_2NH\text{–}\dot{N}_2} + \cdot R \xrightarrow{-N_2} \underset{6}{CH_3SO_2\dot{N}H} + \cdot R \quad (5)$$

Path leading to 5

$$\underset{6}{CH_3SO_2\dot{N}H} + RH \rightarrow \underset{5}{CH_3SO_2NH_2} + \cdot R \quad (6)$$

Path leading to 4

$$\underset{6}{CH_3SO_2\dot{N}H} + \cdot R \rightarrow \underset{4}{CH_3SO_2NHR} \quad (7)$$

$$\left.\begin{aligned} \cdot R + CH_3SO_2N_3 &\rightarrow CH_3SO_2\dot{N}R + N_2 \\ CH_3SO_2\dot{N}R + RH &\rightarrow \underset{4}{CH_3SO_2NHR} + \cdot R \end{aligned}\right\} \quad (8)$$

$$\underset{7}{CH_3SO_2NH\text{–}\dot{N}_2} + \cdot R \rightarrow \underset{4}{CH_3SO_2NHR} + N_2 \quad (9)$$

First, a triplet sulfonylnitrene is the most probable intermediate (eq 4 followed by eq 7). The sensitized photolyses of 1 were carried out in *cis*- or *trans*-1,4-dimethylcyclohexane (*cis*-3 and *trans*-3, see Table III) diluted with 1,2-dichloroethane. The results are listed in Table III, compared with those of the direct photolyses of 1.[12]

The reaction of 1 with either *cis*-3 or *trans*-3 gave a mixture of *cis*-4 and *trans*-4 (stereoisomers); the reaction was completely nonstereospecific. On the contrary, the direct photolyses of 1 gave only one tertiary sulfonamide in spite of the presence of the triplet nitrene derived from the singlet.

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Table I. Sensitized Photolyses of 1 in Hydrocarbons

Hydrocarbon (3)	Product,[a] % 4		RNH_2 (5)
Cyclohexane	c-$C_6H_{11}NHR$[b] **A**, 17.8		14.5
$(CH_3)_2CHCH_2$-CH_3	$(CH_3)_2C(NHR)$-$CH(CH_3)_2$ **B_1**, 11.3	$(CH_3)_2CHCH$-$(NHR)CH_3$ **B_2**, 1.3	23.6
$(CH_3)_2CHCH$-$(CH_3)_2$	$(CH_3)_2C(NHR)$-$CH(CH_3)_2$ **C**, 12.2		26.3

[a] Calculated on the basis of the azide used. [b] R = SO_2CH_3.

Table II. Relative Reactivities of 2 and Methanesulfonylnitrene toward the C–H Bonds of 2-Methylbutane

	Product		
	$4B_1$	**$4B_2$**	C_4H_9–CH_2-NHR[a]
Type of C–H bond	3°	2°	1°
Relative reactivity:[b] sensitized	18.2	1	
direct[c]	2.3	1	0.24
thermolysis[d]	2.6	1	0.45

[a] R = SO_2CH_3. [b] Relative reactivities are given per secondary C–H bond. [c] Calculated from the data in ref 11. [d] Formed by decomposition at 150 °C in 1,4-dimethylpentane.[13]

Breslow et al. also reported that the insertion of the nitrene, generated by thermolysis, into the tertiary C–H bonds of *cis*- and *trans*-1,2-dimethylcyclohexanes proceeded stereospecifically.[13] Thus, it is concluded that the triplet nitrene does not insert into the C–H bonds of saturated hydrocarbons. Therefore, the nonstereospecific formation of *cis*-**4** or *trans*-**4** in the sensitized photolyses means that neither the singlet nitrene nor the triplet nitrene takes part in the formation of **4**. As an alternative, **4** may be formed via a mechanism shown in eq 8 from the facts that sulfonyl azides have a tendency to undergo induced decomposition by free radicals.[15] But the formation of **4** by such induced decomposition should be ruled out because the radical necessary to cause the induced decomposition is also produced concomitantly by the formation of **6** in the direct photolyses which lead to the formation of **4** stereospecifically. As a third alternative, the excited triplet azide leading to radical **7** is plausible as shown in eq 9. As for the triplet azide, Lwowski and Mattingly[16] reported the sensitized photolysis of ethyl azidoformate in cyclohexene; the excited triplet azide reacted with the solvent to give an abstraction product (urethane) without first decomposing to a triplet nitrene species because of the absence of the nitrene adduct in the cyclohexene. A tentative mechanism involving the triplet azide in the sensitized photolyses of methanesulfonyl azide may be as follows. Radical **6**, which is derived from the triplet nitrene and from radical **7**, gives only the abstraction product (**5**) without recombination with a hydrocarbon radical (·R). On the other hand, the amino radicals derived from triplet phenylnitrene[2] and triplet cyanonitrene[3] are able to recombine with hydrocarbon radicals to give the insertion products. Both amino radicals can be stabilized by resonance between the nitrogen atom and the phenyl or the cyano group, whereas no resonance stabilization, other than that involving d-orbital expansion on the sulfur atom, is available to radical **6**. However, radical **7**, derived from the triplet azide, would be stabilized by the nitrogen atoms in comparison with **6**. The long-lived radical **7**, stabilized by resonance, can thus recombine with the hydrocarbon radical to give **4** with evolution of nitrogen.

Experimental Section

IR spectra were recorded on Hitachi EP-S and Nippon Bunko (Jasco) Model A-3 photometers, and NMR spectra were taken on Hitachi R-20 and R-24 instruments, using tetramethylsilane as an internal standard. VPC was done on Shimdzu GC-2C and Nippon Denshi (JEOL) JGC 20K units, employing the following as absorbents: (A) 20% Apiezon M on Neopak 1A (60–80 mesh); (B) 20% Ucon Oil 5 HB 2000 on Celite (60–80 mesh); (C) 10% polyethylene glycol succinate on Neopak 1A (60–80 mesh). The products were separated by VPC, and the structures of the products were determined by means of elemental analyses and by measurements of the IR and NMR spectra. The structures of some of the products were determined by comparing their IR and NMR spectra with those of authentic samples. The quantitative analyses of the products by VPC and tests for the stability of each product during VPC analysis have been described in a previous paper.[17]

Materials. Methanesulfonyl azide (**1**) was prepared by the method of Reagan and Nickon.[14] Cyclohexane, 2-methylbutane, 2,3-dimethylbutane, and 1,2-dichloroethane were used after the commercial reagents had been purified according to the published directions.[18] Analytical grade acetophenone was used without further purification.

cis- and *trans*-1,4-Dimethylcyclohexanes (*cis*-**3** and *trans*-**3**) were prepared by the method of Feulgen.[19] A mixture of *p*-xylene (212 g, 2 mol) and acetic acid (180 g) was stirred in the presence of platinum black catalyst (2 g) and hydrogen at room temperature under ordinary pressure. The solution, separated from the catalyst by distillation at about 50 °C under reduced pressure, was washed with a 10% sodium carbonate solution and water and dried over potassium carbonate. A complete separation of the dimethylcyclohexanes into their geometric isomers was accomplished by repeated fractional distillation: *trans*-**3**, 119 °C; *cis*-**3**, 124 °C.[20] The purity of each isomer was checked on column A: column temperature, 90 °C; carrier gas, H_2, 30 mL/min; retention time, 10 min for *trans*-**3** and 12 min for *cis*-**3**. This separation gave a molar ratio of *cis*-**3** to *trans*-**3** of 3:1. No photochemical isomerization between *cis*-**3** and *trans*-**3** was observed under the conditions of these experiments.

N-Cyclohexylmethanesulfonamide (**4A**) was prepared from cyclohexylamine and methanesulfonyl chloride in a way similar to the preparation of cyclohexylurethane:[16] mp 103 °C; IR (Nujol) 3230 (NH), 1310 and 1150 cm^{-1} (SO_2); NMR ($CDCl_3$) τ 5.56 (brd s, 1, NH), 6.74 (brd s, 1, CH), 7.05 (s, 3, SCH_3), 7.6–9.0 (m, 10, ring 5 CH_2).

A mixture of *N*-(1.4-dimethylcyclohexyl)methansulfonamide stereoisomers (*cis*-**4** and *trans*-**4**) was prepared by mesylation of a 1,4-dimethylcyclohexylamine (cis–trans mixture), which had been prepared in a way similar to the preparation of 1-methylcyclohexylamine.[21] The sulfonamides were well separated into the cis and the trans isomers using column B. The assignment of each stereoisomer was assigned in comparison with the products obtained from the stereospecific insertions of singlet methanesulfonylnitrene into the tertiary C–H bonds of *cis*- and *trans*-1,4-dimethycyclohexanes.[12,13] *N*-(*trans*-1,4-Dimethylcyclohexyl)methanesulfonamide (*trans*-**4**): IR (neat) 3295 (NH), 1323 and 1153 cm^{-1} (SO_2); NMR ($CDCl_3$) τ 5.44 (brd, s, 1 NH), 7.00 (s, 3, SCH_3), 8.57 (s, 3, CH_3), 9.07 (d, 3, CH_3), 7.67–9.57 (m, 9, ring CH and 4 CH_2).

Anal. Calcd for $C_9H_{19}O_2NS$: C, 52.65; H, 9.32; N, 6.82. Found: C, 52.48; H, 9.29; N, 6.85.

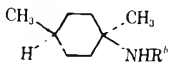
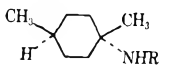
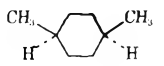
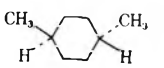
N-(*cis*-1,4-Dimethylcyclohexyl)methanesulfonamide (*cis*-**4**): IR (neat) 3285 (NH), 1325 and 1150 cm^{-1} (SO_2); NMR ($CDCl_3$) τ 5.35 (brd s, 1, NH), 6.97 (s, 3, SCH_3), 8.58 (s, 3, CH_3), 9.08 (d, 3, CH_3), 7.90–9.58 (m, 9, ring CH and 4 CH_2).

Anal. Found: C, 52.46; H, 9.33; N, 6.86.

Sensitized Photolyses of 1 in Hydrocarbons. A solution of 1.50 g (0.0124 mol) of methanesulfonyl azide (**1**) and 1.78 g (0.015 mol) of acetophenone in a mixture of hydrocarbon (0.15 mol) and 1,2-dichloroethane (0.3 mol) was stirred at 25 °C and irradiated by a high-pressure mercury lamp until the evolution of nitrogen was no longer observed. The nitrogen was produced in almost the theoretical amount, based on the azide used. The excess substrate was removed by distillation at 50–80 °C under 20–30 mmHg pressure. The residue was analyzed by VPC on columns B and C. Methanesulfonamide (**5**) had IR and NMR spectra and a VPC retention time identical with those of the authentic sample.

A. In Cyclohexane: *N*-Cyclohexylmethanesulfonamide (**4A**, 0.39 g) and bicyclohexyl (0.8 g) were isolated. Bicyclohexyl and **4A** had IR and NMR spectra and VPC retention times identical with those of authentic samples.

Table III. Reaction of 1 with *cis*- and *trans*-1,4-Dimethylcyclohexanes

Hydrocarbon (3)	Product,[a] %			
	 *trans*-4	 *cis*-4	*cis*-8 or *trans*-8	RNH_2 (5)
 *cis*-3	13.8 (0)[c]	4.3 (3.3)	8.7 (5.8)	21.9 (49.0)
 *trans*-3	12.9 (3.6)	2.8 (0)	4.0 (5.0)	21.2 (35.0)

[a] Calculated on the basis of the azide used. [b] R = SO_2CH_3. [c] Parentheses indicate the values from direct photolyses.

B. In 2-Methylbutane: *N*-(1,1-Dimethylpropyl)methanesulfonamide (**4B$_1$**, 0.24 g) and *N*-(1,2-dimethylpropyl)methanesulfonamide (**4B$_2$**, 0.027 g) were isolated. **4B$_1$**: IR (neat) 3320 (NH), 1325 and 1150 cm^{-1} (SO_2); NMR (CCl_4) τ 5.10 (brd s, 1, NH), 7.10 (s, 3, SCH_3), 8.38 (q, 2, CH_2), 8.70 (s, 6, 2 CH_3), 9.08 (t, 3, CH_3).

Anal. Calcd for $C_6H_{15}O_2NS$: C, 43.60; H, 9.15; N, 8.47. Found: C, 43.48; H, 9.20; N, 8.42.

4B$_2$: IR (neat) 3300 (NH), 1320 and 1140 cm^{-1} (SO_2); NMR (CCl_4) τ 4.94 (brd s, 1, NH), 6.30–7.00 (m, 1, NCH), 7.10 (s, 3, SCH_3), 8.05–8.60 (m, 1, CH), 8.80 (d, 3, CH_3), 9.03 (d, 6, $2CH_3$).

Anal. Found: C, 43.71; H, 9.10; N, 8.40.

C. In 2,3-Dimethylbutane: *N*-(1,1,2-Trimethylpropyl)methanesulfonamide (**4C**, 0.27 g) was isolated: IR (neat) 3310 (NH), 1315 and 1145 cm^{-1} (SO_2); NMR ($CDCl_3$) τ 5.59 (brd s, 1, NH), 6.98 (s, 3, SCH_3), 7.66–8.40 (m, 1, CH), 8.67 (s, 6, 2 CH_3), 9.07 (d, 6, 2 CH_3).

Anal. Calcd for $C_7H_{17}O_2NS$: C, 46.89; H, 9.55; N, 7.81. Found: C, 46.86; H, 9.50; N, 7.68.

D. In *cis*-3: *trans*-4 (0.35 g), *cis*-4 (0.11 g), and *N*-(*cis*-2,5-dimethylcyclohexyl)methanesulfonamide (*cis*-8, 0.22 g) were isolated. *cis*-8: IR (neat) 3250 (NH), 1320 and 1140 cm^{-1} (SO_2); NMR ($CDCl_3$) τ 5.48 (brd s, 1, NH), 7.20 (s, 3, SCH_3), 8.96 (d, 3, CH_3), 9.08 (d, 3, CH_3), 7.80–9.27 (m, 9, ring 3 H and 3 CH_2).

Anal. Calcd for $C_9H_{19}O_2NS$: C, 52,65; H, 9.32; N, 6.82. Found: C, 52.43; H, 9.27; N, 6.78.

E. In *trans*-3: *trans*-4 (0.33 g), *cis*-4 (0.07 g), and *N*-(*trans*-2,5-dimethylcyclohexyl)methanesulfonamide (*trans*-8, 0.1 g) were isolated. *trans*-8: IR (neat) 3270 (NH), 1320 and 1145 cm^{-1} (SO_2); NMR ($CDCl_3$) τ 5.50 (brd s, 1, NH), 7.06 (s, 3, SCH_3), 8.98 (d, 3, CH_3), 9.18 (d, 3, CH_3), 7.70–9.30 (m, 9, ring 3 CH and 3 CH_2).

Anal. Found: C, 52.51; H, 9.30; N, 6.80.

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Registry No.—**1**, 1516-70-7; cyclohexane, 110-82-7; 2-methylbutane, 78-78-4; 2,3-dimethylbutane, 79-29-8; **4A**, 19299-40-2; **4B$_1$**, 39653-34-4; **4C**, 64235-77-4; **4B$_2$**, 39653-33-3; *cis*-**3**, 624-29-3; *trans*-**3**, 2207-04-7; *trans*-**4**, 64235-76-3; *cis*-**4**, 64235-75-2; **8**, 64235-80-9; cyclohexylamine, 108-91-8; methanosulfonzl chloride, 124-63-0; *cis*-1,4-dimethylcyclohexylamine, 64235-79-6; *trans*-1,4-dimethylcyclohexylamine, 64235-78-5.

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Thermal Isomerization of Allylic Alcohols to Saturated Ketones

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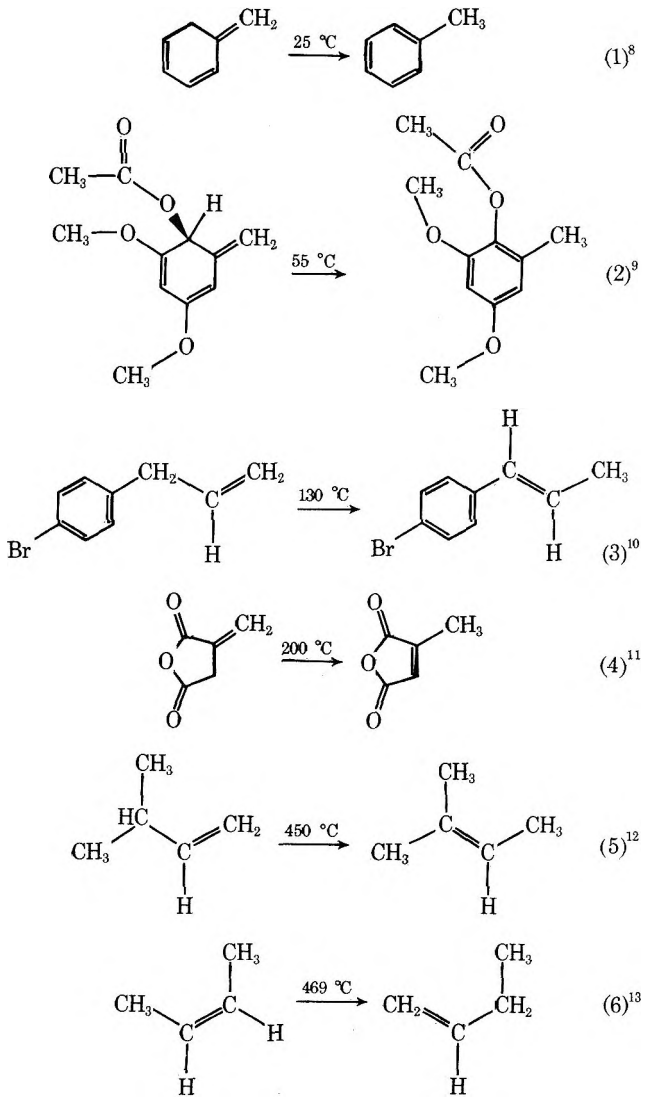
trans-Pent-3-en-2-ol and *trans*-1,3-diphenylprop-2-en-1-ol have been thermally isomerized to the saturated ketones 2-pentanone and 3-phenylpropiophenone. Rearrangements of mixtures of *trans*-2-deuterio- and *trans*-1,1,1-trideuteriopent-3-en-2-ol gave 2-pentanone and recovered starting material, indicative of extensive intermolecularity at some stage in the reaction. Rearrangement of undeuterated and *trans*-1-deuterio-1-pentadeuteriophenyl-3-phenylprop-2-en-1-ol, however, indicated intramolecular hydrogen transfer.

Sigmatropic migrations of hydrogen atoms must occur with retention of configuration;[1-3] they do not have the retention or inversion option available to a migrating carbon atom. The only stereochemical alternatives for a [1,*j*] sigmatropic hydrogen shift concern the system of *j* π electrons.

For thermally activated [1,5] hydrogen transfers,[4,5] the theoretically required suprafacial utilization of the pentadienyl fragment has been elegantly demonstrated.[6]

The theoretically predicted [1,3] thermal hydrogen migration with antarafacial allylic participation has not been uncovered; it has been considered unlikely by virtue of serious uncoupling within the π framework[1] and inaccessible by virtue of steric constraints.[7]

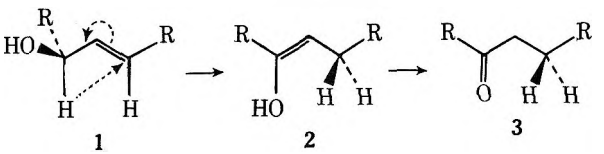
Yet reactions are known which, at least formally, correspond to such simple [1,3] hydrogen shifts (eq 1–6).



However, none of these reactions has been subjected to any sort of mechanistic appraisal. Without some appropriate experimentation, these and other such examples will contribute nothing toward a better understanding of the circumstances necessary for a thermal [1,3] hydrogen shift to occur intramolecularly with either suprafacial or antarafacial allylic participation.

Curiously, photochemical [1,3] sigmatropic shifts of hydrogen[14-17] are well-known, while one transition metal catalyzed [1,3] hydrogen migration is known to be intramolecular as well as stereospecific.[18]

As an initial approach to the study of thermal [1,3] hydrogen migrations we have studied the thermal reactions of two allylic alcohols. By analogy with substrates which undergo oxy-Cope isomerizations,[19,20] substituted allylic alcohols **1** might isomerize through a [1,3] hydrogen shift to give enols **2** able to isomerize readily to the more stable ketonic tautomers **3**.

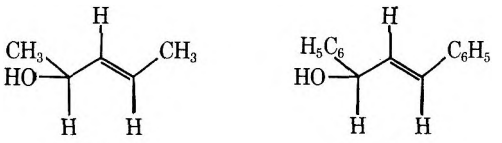


1 **2** **3**

Once the rearrangement had been established, and intramolecularity demonstrated, work with the optically active and deuterium-labeled substrates necessary for probing reaction stereochemistry would become justified.

Results and Discussion

The two systems chosen for study were *trans*-1,3-dimethyl- and *trans*-1,3-diphenylprop-2-en-1-ol (**4** and **5**). The first,



4 **5**

more systematically designated as *trans*-pent-3-en-2-ol, was prepared through an *Organic Syntheses* procedure[21] and the second through reduction of chalcone with sodium borohydride.[22,23]

The alcohols did indeed show the rearrangements sought. The pentenol **4**, when heated in a base-washed and degassed sealed tube for 30–180 min at 368 °C, gave a mixture of products including a 50–60% yield of 2-pentanone, identified through direct chromatographic and spectroscopic comparisons with authentic material. The diphenyl-substituted system **5**, when heated at 302 °C for 10–40 min in a similarly degassed and sealed tube, gave a complex mixture of products which included a 5–8% yield of 3-phenylpropiophenone, identified through chromatographic and spectroscopic comparisons with authentic material.[24]

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Table I. Mass Spectrometric Deuterium Analyses for 2-Pentanone from Thermolysis of 6 and 7[a,b]

Reaction time, min	Deuterium distribution				
	d_0	d_1	d_2	d_3	d_4
30	25	16	19	32	8
62	18	30	28	18	6
180	17	33	30	16	5

[a] 50% d_1, 50% d_3 by NMR and mass spectrometric analysis. [b] Temperature 368 °C.

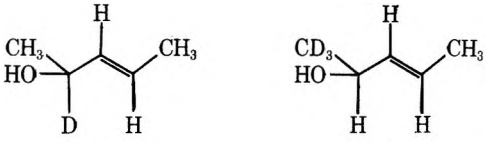
Table II. Mass Spectrometric Deuterium Analyses for 3-Phenylpropiophenone from Thermolysis of 5 and 8[a,b]

Reaction time, min	Deuterium distribution							
	d_0	d_1	d_2	d_3	d_4	d_5	d_6	d_7
10	45	4	1	0	1	11	37	1
20	44	6	2	0	1	14	30	3
30	51	7	1	0	1	13	25	2
40	49	8	0	1	2	14	23	3

[a] 54% d_0, 46% d_6 by mass spectrometric analysis. [b] Temperature 302 °C.

Having established that the rearrangement can be observed under reasonable conditions, the intra- or intermolecularity of the conversions was probed through the use of pairs of deuterium-labeled substrates.

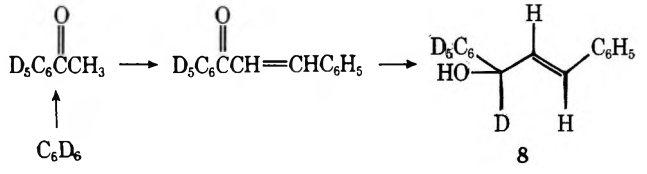
For the aliphatic case, *trans*-2-deuteriopent-3-en-2-ol (**6**) and *trans*-1,1,1-trideuteriopent-3-en-2-ol (**7**) were selected



6 **7**

and prepared: the first through reduction of *trans*-pent-3-en-2-one, the second by a Grignard reaction between crotonaldehyde and trideuteriomethylmagnesuim iodide.

For the chalcol analogue, the hexadeuterio substrate **8** was



8

prepared through a sequence beginning with the aluminum trichloride catalyzed reaction of acetyl chloride with perdeuteriobenzene. Aldol condensation with benzaldehyde and reduction with sodium borodeuteride completed the route.

For completely intramolecular [1,3] hydrogen or deuterium migration, the isotopic composition of starting material (**6** plus **7**, or **5** plus **8**) should be preserved in the ketonic products. For intermolecular mechanisms, such a result would be impossible. A free-radical chain process, the most probable intermolecular possibility, should lead to a nearly statistical distribution of labeled products.

In the event, thermal rearrangement of a mixture of **6** with **7** gave labeled 2-pentanone. The mass spectrometrically determined deuterium distributions in starting material and product, summarized in Table I, indicated extensive scrambling of label either prior to, during, or subsequent to the isomerization.

The results from a similar experiment with **5** plus **8** as

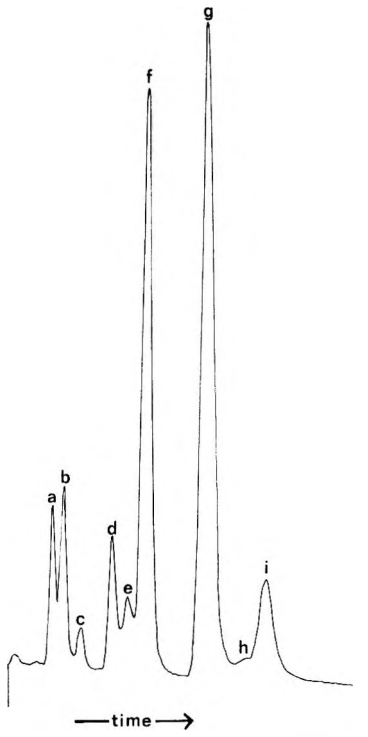


Figure 1. Total ion current vs. time from the MS/GC/COM analysis of the thermolysate (305 min at 175 °C) from **5** plus **8**. The products are identified as: a, *cis*-1,3-diphenylpropene; b, *trans*-1,3-diphenylpropene; c, *cis*-1,3-diphenylprop-2-en-1-ol; d, *cis*-1,3-diphenylprop-2-en-1-one; e, unknown; f, *trans*-1,3-diphenylprop-2-en-1-ol; g, 3-phenylpropiophenone; h, unknown; and i, *trans*-1,3-diphenylprop-2-en-1-one.

starting alcohol are given in Table II; they indicate a fair degree of intramolecularity. Were the process to involve the 1,3-diphenyl-1-hydroxyallyl radical as a chain-carrying species, an example of one intermolecular possibility, equal proportions of d_0 and d_6 substrates **5** and **8** should lead to equal proportions of d_0, d_1, d_5, and d_6 products. Instead, the distributions of label in starting alcohol are largely retained in the product ketone.

For the purposes of confirming this preliminary result as well as more fully characterizing the thermolysis products, a mass spectrometric/gas chromatographic/computer (MS/GC/COM) study was carried out. Instead of employing neat samples of the labeled chalcols, a highly dilute benzene solution (250 μg/mL) was prepared. Aliquots were placed into base-washed ampules, degassed, sealed, and heated at either 175 or 250 °C. MS/GC/COM analysis of the resulting thermolysate (see Figure 1) revealed a significantly increased yield (40%) of the desired product, 3-phenylpropiophenone, along with the cis and trans isomers of two previously unidentified products, 1,3-diphenylpropene and 1,3-diphenylprop-2-en-1-one (chalcone).[26] A typical gas chromatogram which has been computer generated from the total mass spectrometric ion current is shown in Figure 1. While small amounts of water were formed in the other thermolyses described above, it was not apparent in these gas-phase reactions which were conducted in the presence of a large excess of benzene vapor. The resulting deuterium distributions in the product 3-phenylpropiophenone from two such experiments are presented in Table III. Again, the ketone product is shown to arise from an intramolecular shift of hydrogen. The significant portion of d_5 ketone reflects the loss in isotopic integrity of the starting chalcol (**5** plus **8**), since unreacted starting material was found by mass spectral analysis to have the same concentration of d_5 species. This is most likely the result of a competing free-

Table III. Mass Spectrometric Deuterium Analyses for 3-Phenylpropiophenone from Thermolysis of 5 and 8[a]

Reaction temp, °C	Reaction time, min	Deuterium distribution							
		d_0	d_1	d_2	d_3	d_4	d_5	d_6	d_7
175	305	47	0	5	4	5	6	32	1
250	71	61	0	2	0	2	15	20	0

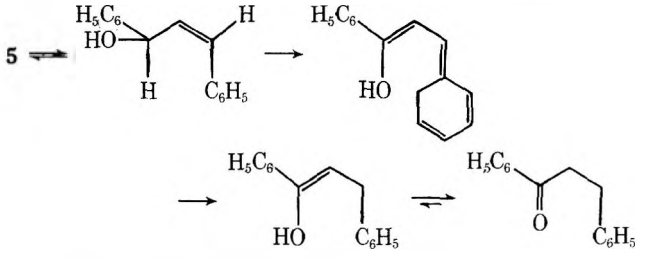
[a] 58% d_0, 42% d_6 by mass spectrometric analysis.

radical chain process which has been uncovered previously in the decomposition of the saturated secondary alcohols.[25]

The deuterium distributions for the alcohol are corrected for $[M - 1]^+$ fragmentation and, for this reason, contain relatively larger experimental errors (±8%) than do the distributions reported for the ketone (±4%). All of the data in Tables I–III come from electron impact mass spectra and are fully corroborated by the parallel, but redundant, methane chemical ionization results.

The variations in deuterium distributions for the two experiments reported in Table III are thought to be a result of the significantly different extents of reaction: the low-temperature reaction has been run to a much lower percent conversion.

With this demonstration of intramolecularity, further work toward defining mechanisms for such conversions seems in order. Such research efforts would need to test not merely for intramolecularity, but whether the hydrogen shift is really [1,3] or a [1,5] followed by [1,7] sequence (as illustrated in the scheme below), and to secure kinetic data as well as quantitative stereochemical information on the isomerization.



Experimental Section

Mass spectra were obtained on a Finnigan 1015D quadrupole mass spectrometer interfaced to a Texas Instruments 960A computer. Electron impact mass spectra were secured through helium charge exchange (ionization potential = 24 eV) at a source temperature of 70 °C, an electron energy of 100 eV, and a trap current of 400 μA. Chemical ionization spectra were taken using the same conditions as above along with a methane reagent gas (proton affinity = 126 kcal mol^{-1}) pressure of 1.0 ± 0.1 mm. The MS/GC/COM work was carried out with the following chromatographic conditions: a 1.5 m × 2 mm 3% OV-101 on 80/100 Chromosorb WHP glass column operated at 180 °C and a flow rate of 20 mL of methane or helium per minute.

Analytical and preparative GLC separations were carried out on Aerograph A90-P3 and 1520 instruments employing 1.5 m × 6 mm 20% SE-30 on 60/80 Chromosorb W columns. Analytical TLC was performed on 20 × 5 cm glass plates coated with a 0.25-mm layer of Brinkmann silica gel GF; preparative TLC was carried out on 20 × 20 cm glass plates coated with a 1.1-mm layer of Brinkmann silica gel PF-254.

***trans*-Pent-3-en-2-ol,** prepared according to Coburn,[21] had bp 119–121 °C (lit.[21] bp 119–121 °C).

***trans*-2-Deuteriopent-3-en-2-ol (6).** To a 100-mL three-neck round-bottom flask with mechanical stirrer, thermometer, and addition funnel was added 0.50 g (17.4 mmol, 4 equiv) of lithium aluminum deuteride (Ventron) and 10 mL of anhydrous ether. At 0 °C 1.45 g (17.3 mmol) of *trans*-pent-3-en-2-one (Pfaltz and Bauer; freshly distilled, bp 124–125 °C) in 35 mL of dry ether was added over 10 min with stirring. The reaction mixture was stirred an additional 35 min at 0 °C, warmed to room temperature for 30 min, and quenched by the addition of 0.5 mL of H_2O, 0.5 mL of 15% NaOH, and finally 1.5 mL of H_2O. The product was isolated by extraction with ether followed by washing with H_2O, drying ($MgSO_4$), filtering, and concentrating by distillation to give 0.967 g (65% yield). The structure of the product was clear from its characteristic infrared and mass spectra, and especially the NMR spectrum where the τ 5.7–6.2 1 H multiplet in **4** was completely absent and the τ 8.85 3 H doublet was now a singlet.

***trans*-1,1,1-Trideuteriopent-3-en-2-ol (7).** Treatment of crotonaldehyde (Matheson, Coleman and Bell; freshly distilled, bp 101–102 °C; 2.20 g, 31.4 mmol) with trideuteriomethylmagnesium iodide from trideuteriomethyl iodide (Stohler Isotopes; 5.00 g, 34.5 mmol) as previously described[21] gave 2.44 g (80% yield) of **7**. The structure of the product was confirmed by its characteristic infrared and mass spectra, and especially the NMR spectrum where the 3 H doublet at τ 8.85 in **4** was completely lacking.

***trans*-1,3-Diphenylprop-2-en-1-ol (5).** Chalcone, prepared by the procedure of Davey and Hearne,[22] was reduced with sodium borohydride;[23] the product alcohol had mp 54–56 °C (lit.[23] 55–56 °C).

Pentadeuteriophenyl Methyl Ketone. To a 100-mL three-neck round-bottom flask was added 5.60 g (59.5 mmol) of perdeuteriobenzene (Stohler Isotopes), 9.40 g (71 mmol) of $AlCl_3$, and 25 mL of CS_2. With cooling 5.60 g (72 mmol) of acetyl chloride was added by means of an addition funnel. A condenser was fitted to the flask and the reaction mixture was heated at reflux for 2 h. After quenching the reaction by the addition of 5 mL of D_2O, the aqueous phase was extracted with CS_2 (3 × 10 mL) and ether (3 × 10 mL). The combined organic phases were washed with 5% NaOH (3 × 10 mL) and H_2O (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated by distillation to give 6.10 g (82% yield) of acetophenone-d_5, whose NMR spectrum confirmed that the benzene ring was >97% deuterated.

***trans*-1-Pentadeuteriophenyl-3-phenylprop-2-en-1-one (Chalcone-d_5).** Chalcone-d_5 was prepared through the aldol condensation of acetophenone-d_5 with benzaldehyde as described previously.[22]

***trans*-1-Deuterio-1-pentadeuteriophenyl-3-phenylprop-2-en-1-ol (8).** Chalcol-d_6 (**8**) was obtained by sodium borodeuteride reduction of chalcone-d_5.[23]

3-Phenylpropiophenone, prepared by the method of Miyano and Sako,[24] had mp 69–72 °C (lit.[24] mp 70.5–71 °C).

Thermolyses. Neat samples of allylic alcohols in 18 cm × 8 mm ammonia-washed and oven-dried Pyrex ampules were thoroughly degassed through four freeze–pump–thaw cycles on a vacuum line and were sealed at 10^{-4} to 10^{-5} mm. Thermolyses were done by immersing the tubes in a potassium nitrate/sodium nitrite salt bath stirred with a Lightnin stirrer and maintained at constant temperature with two (450- and 125-W) heaters.

For the MS/GC/COM studies in the chalcol series, a dilute solution of d_0 and d_6 *trans*-1,3-diphenylprop-3-en-2-ol was made up in freshly distilled benzene (250 μg/mL of benzene). Pyrolyses were performed in ampules as above, but in the oven of a Varian A90-P3 gas chromatograph.

Products. 2-Pentanone was isolated from the thermolysis mixture by preparative GLC on the SE-30 column (vide supra) maintained at 125 °C. GLC-collected product was identical with authentic material (Eastman) both chromatographically and spectroscopically. 3-Phenylpropiophenone was isolated from the thermolysis mixture by preparative TLC on silica gel PF-254 (vide supra) eluting with 10:1 pentane/ether. The TLC-collected product was identical with authentic material[24] both chromatographically and spectroscopically. For the reactions employing deuterium-labeled substrates, 2-pentanone and 3-phenylpropiophenone were isolated and purified by preparative GLC or TLC, respectively, and analyzed mass spectrometrically.

In the MS/GC/COM study, products were delivered to the source of the mass spectrometer through the interfaced gas chromatograph (vide supra) using either helium (electron impact mode) or methane (chemical ionization mode) as the carrier gas.

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Registry No.—**4**, 3899-34-1; **5**, 62668-02-4; **6**, 64364-81-4; **7**, 64364-82-5; **8**, 64364-83-6; crotonaldehyde, 4170-30-3; 2-pentanone,

107-87-9; 3-phenylpropiophenone, 1083-30-3; *cis*-1,3-diphenylpropene, 1138-83-6; *trans*-1,3-diphenylpropene, 3412-44-0; *cis*-1,3-diphenylprop-2-en-1-ol, 62839-70-7; *cis*-1,3-diphenylprop-2-en-1-one, 614-46-0; *trans*-1,3-diphenylprop-2-en-1-one, 614-47-1; *trans*-pent-3-en-2-one, 3102-33-8.

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(26) Identified through chromatographic and mass spectrometric comparisons with authentic samples.

The α Effect in α-Chlorofluoro Ketones

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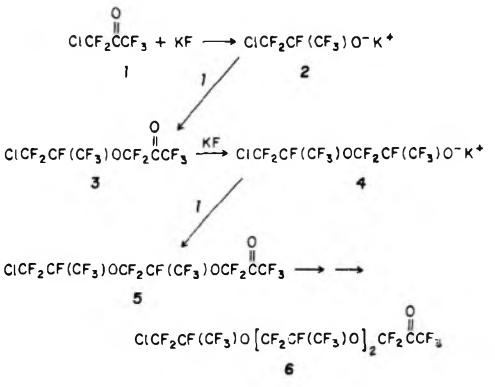
α-Chloropolyfluoro ketones are subject to displacement of chloride ion under mild conditions by relatively weak bases, notably fluoroalkoxide salts. The latter reagents react with α-chlorofluoro ketones to form fluorinated keto ethers; since these keto ethers add fluoride ion to give new, reactive fluoroalkoxides, a series of low oligomers is produced in each case. The new fluorinated keto ethers are shown to resemble hexafluoroacetone in their response to free radicals as well as to fluoride ion.

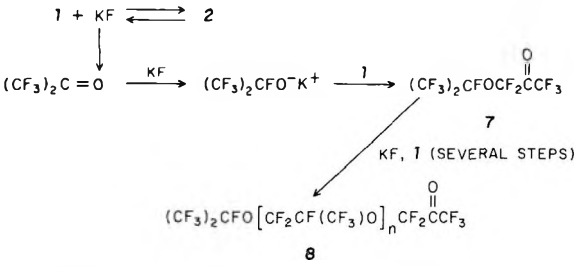
Anionic attack on saturated carbon with displacement of a substituent X^- is rarely encountered in highly fluorinated systems. If reaction with the fluorinated substrate does occur, the incoming base most frequently attacks a nonfluorine substituent with displacement of fluorocarbanion.[1] The known cases of intermolecular nucleophilic attack at sp^3 carbon in fluorinated compounds seem to be limited to those in which a carbonyl group is α to the leaving group X, and the nucleophile has usually been fluoride ion.[2] The results described below further define the conditions under which such reactions occur and demonstrate a wider scope for the reaction by the use of some other types of nucleophile.

Fluoroalkoxides. Chloropentafluoroacetone (1) in dimethylformamide reacts easily with 1 equiv of potassium fluoride to give the soluble adduct **2** which only slowly undergoes further change at 25 °C. In the presence of excess **1**, however, displacement of chloride ion by chlorohexafluoroisopropoxide ion **2** occurs to form the new ketone **3** (Scheme I). The reaction proceeds slowly at 25 °C and more rapidly at

Scheme I



Scheme II



temperatures up to 80 °C. Moreover, ketone **3** has a relatively unhindered carbonyl group and competes successfully with **1** for fluoride ion to form the fairly stable adduct fluoroalkoxide **4**. The latter also displaces chloride ion from **1** to form the higher fluoro ketone **5**. Ketone **5** and its higher analogues similarly form reactive alkoxides by addition of fluoride ion with the net result that a series of fluorinated keto polyethers is formed in diminishing yield as molecular weight increases. After the first displacement, each subsequent displacement will be seen to have the effect of introducing a unit of hexafluoropropene epoxide.[3]

Yields obtained with a 1:2 KF/1 mol ratio in dimethylformamide have been 30% for **3** and 14% for **5** with about 12% conversion to by-product hexafluoroacetone. In addition, a related series of by-products is formed in amounts that increase with increase in proportion of KF. These by-products contain no chlorine and result from formation of hexafluoroacetone and its subsequent reaction as indicated in Scheme II. Coreaction of both **1** and hexafluoroacetone with KF gave preparative yields of these by-products, and ketones **7** and **8** (n = 1, 2) were isolated.[4]

A reaction of **1** with KF carried out in triglyme proceeded very slowly at 40–80 °C, so the temperature was raised to 95

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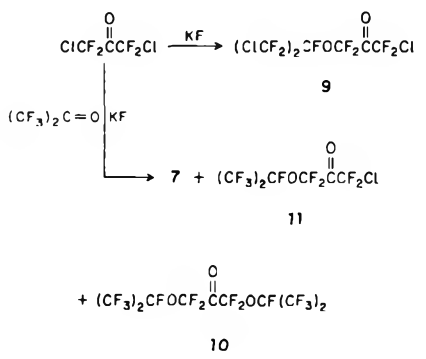
Scheme III

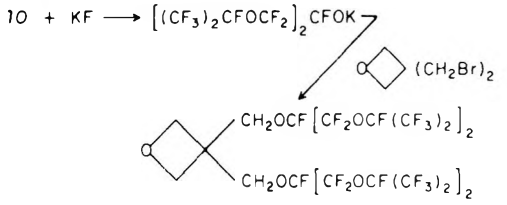


°C; reflux from a −80 °C condenser slowly lowered the temperature to 80 °C. Distillation gave a low yield of the cleavage product, trifluoroacetyl fluoride, and 39% of hexafluoroacetone along with 8% of **3** and 5% of **5.** Presumably, the higher temperatures led predominantly to displacement by fluoride ion because the fluoroalkoxides such as **2** were largely dissociated.[5]

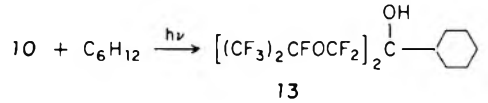
sym-Dichlorotetrafluoroacetone reacted with KF at 50 °C to give a low conversion to ketone **9.** Incorporation of hexafluoroacetone into the reaction mixture resulted in a preparative route to perfluoro ketone **10** along with monochloro ketone **11** (Scheme III) as well as ketone **7.**

As a test of the reversibility of the reaction by which **10** was formed, a mixture of KF and **10** in dimethylformamide was stirred at 25 °C until it became homogeneous and then was heated at 80–85 °C. No volatiles were detected, and **10** was recovered in 91% yield. Under conditions of synthesis, therefore, keto ethers such as **10** appear to be stable toward displacement of heptafluoroisopropoxide.

The fluorinated keto α-ethers resemble hexafluoroacetone in response to base in that substitution apparently does not occur and steric hindrance to attack at the electrophilic carbonyl carbon is low. The fluoroalkoxide from fluoride ion and **10** has good stability with respect to dissociation and is fairly nucleophilic, as was shown by its reaction with 3,3-bis(bromomethyl)oxetane to form oxetane **12** in 70% yield. Similar results have been obtained with hexafluoroacetone.[6]

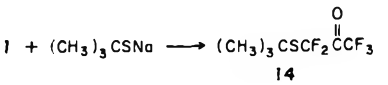


The reactivity of **10** toward alkyl radicals is also similar to that of hexafluoroacetone,[7] as exemplified by the radical chain reaction of **10** with cyclohexane to form carbinol **13** in 74% yield.

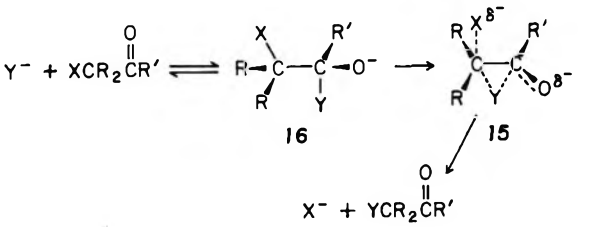


Discussion

The possibility that weak bases which add reversibly to the carbonyl carbon are required to successfully displace chloride from an α-chloropolyfluoro ketone was tested in a reaction with mercaptide. Chloropentafluoroacetone (**1**) reacted readily with sodium *tert*-butylmercaptide to give sulfide **14.** In contrast, sodium methoxide, which gives a stable adduct with **1** at −15 °C, led to a spectrum of decomposition products at 40 °C. These results support the idea that only weak bases and not strong ones give the reaction.



Although S_N2 attack at sp^3 carbon in highly fluorinated systems is unusual and perhaps unprecedented under such mild conditions, we appear to have here a special case of the well-recognized α effect in which a carbonyl group enhances the rate of replacement of an α substituent.[8] A commonly accepted picture involves triangular transition state **15.** The shielding effect by fluorine atoms on saturated carbon which resists direct penetration by a nucleophile could be mitigated in the presence of an adjacent carbonyl group, since the nucleophile could reversibly form adduct **16,** from which **15** would be readily accessible in the absence of side reactions such as haloform cleavage.

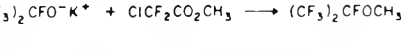


For the fluoro ketone case (in which R is F and R′ is fluoroalkyl) delocalization of negative charge onto oxygen in the transition state may reduce the noramlly high energy associated with unfavorable interactions with fluorine on sp^2 carbon. In a transition state resembling **15,** the bond to fluorine could even be more nearly sp^3 than sp^2. Thus, reversible addition of nucleophile to the carbonyl carbon apparently results in an appreciable fraction of occurrences in **15,** a pathway not available to completely saturated fluoroalkyl chlorides.

Loosening of the bond to leaving group X seems to be essential to a readily accessible transition state. Chloride ion is a sufficiently good leaving group, but fluoride and fluoroalkoxide are too strongly bonded to carbon to be readily displaced.

Another mechanistic possiblity after addition of nucleophile Y^- to the carbonyl group is bridging by carbonyl oxygen to form epoxide. Since such an epoxide intermediate would be expected to form readily after addition of fluoride ion, but does not, and since direction of subsequent ring opening would have to be highly specific to give ketone rather than acid fluoride, this mechanism is considered unlikely.

An attempted extension of the displacement of α-chlorines to an α-chloro ester,[9] methyl chlorodifluoroacetate, resulted in ready methylation of the anion in preference to either displacement of chloride or haloform cleavage.



Experimental Section

Infrared spectra were recorded on a Perkin Elmer 21 spectrophotometer with 20% solutions in CCl_4 unless otherwise specified. ^1H NMR spectra were taken on a Varian A-60 spectrometer in carbon tetrachloride with tetramethylsilane as internal standard; ^{19}F NMR spectra were taken on a Varian XL-100 spectrometer with the downfield direction from $CFCl_3$ as internal standard taken as positive. GLC purifications were carried out on 25% Fluorosilicone 1265 on Chromosorb W with a He flow rate of 400 mL/min.

Perfluoro-5-chloromethyl-4-oxahexanone-2 (3), Perfluoro-8-chloromethyl-5-methyl-4,7-dioxanonanone-2 (5), and Perfluoro-11-chloromethyl-5,8-dimethyl-4,7,10-trioxadodecanone-2 (6). A suspension of 10.5 g (0.18 mol) of anhydrous KF in 150 mL of dry dimethylformamide was stirred while 65.6 g (0.36 mol) of chloropentafluoroacetone was distilled in. The homogeneous reaction mixture was stirred at 50 °C for 2 h and then at 70 °C for 1 h, during

which time KCl precipated. A stillhead was attached, and the pot contents were raised slowly to 155 °C while 38.2 g of distillate was taken, bp 25–140 °C. Appreciably more KCl formed during this operation. Fractionation of volatiles collected in the cold trap and identification of the gases by IR showed 20% of chloropentafluoroacetone was recovered and 13% was converted to hexafluoroacetone. Fractionation of the liquid distillate from concentrated H_2SO_4 afforded 14.9 g (24% conversion) of **3**, bp 80–83 °C, and 6.8 g (11% conversion) of **5**, bp 64 °C (50 mmHg). Higher boiling oligomers were also present.

A similar reaction carried out at 25 °C for 6 days and 50 °C for 1 day, then worked up the same way, gave similar yields and conversions.

A ratio of KF/$ClCF_2COCF_3$ significantly greater than 0.5 led to an increased yield of oligomers derived from heptafluoroisopropoxide anion at the expense of chlorodifluoromethyl-terminated oligomers. An apparent increase in the relative amount of higher oligomers was also observed. Reaction of 16.8 g (0.29 mol) of KF and 65.6 g (0.36 mol) of chloropentafluoroacetone was carried out in 150 mL of dry dimethylformamide. After 3 days at 25 °C, only a minor amount of solid was deposited, in contrast to the reaction above. After 4 days at 40 °C, more KCl precipitated, and, after 2 days at 70 °C, considerable salt had precipitated. Distillation of the products followed by redistillation of the liquid products from H_2SO_4 gave ca. 1% of recovered $ClCF_2COCF_3$, 17% yield of hexafluoroacetone, 18% yield or 11.1 g of **3**, and 11% yield or 7.0 g of **5**. Intercut sizes and the presence of impurities detectable by GC indicated that hexafluoroacetone produced in the reaction had initiated the formation of a series of perfluorinated oligomers. This supposition was supported by the isolation of **7**, bp 55–56 °C, 2.7 g (5%) (see below for characterization). A higher boiling fraction, 4.5 g, bp 96–100 °C (50 mm), gave 2.3 g (4%) of **6** by GLC.

For **3**: IR (CCl_4) 5.54 μm (C=O); mass spectrum *m/e* 185 ($CF_3C^+FCF_2Cl$ with ^{37}Cl at 187), 147 ($CF_3COCF_2^+$), 97 (CF_3CO^+), 85 (CF_2Cl^+ with ^{37}Cl at 87), and 69 (CF_3^+); NMR (^{19}F) −68.8 (m, 2 F, CF_2Cl), −75.1 (t, J_{FF} = 4.5 Hz, atop broad m, 5 F, CF_3CO + OCF_2), −79.0 (m, 3 F, CF_3CF), and −140.3 ppm (t, J_{FF} = 21.5 Hz, of m, 1 F, CF). Anal. Calcd for $C_6ClF_{11}O_2$: C, 20.68; Cl, 10.17. Found: C, 20.57; Cl, 10.15.

For **5**: IR (CCl_4) 5.53 μm (C=O); mass spectrum *m/e* 313 ($M^+ - CF_3CFO(CF_2Cl)$), 185 ($CF_3CF^+CF_2Cl$ with ^{37}Cl at 187), 169 ($C_3F_7^+$), 147 ($CF_3COCF_2^+$), 97 (CF_3CO^+), 85 (CF_2Cl^+ with ^{37}Cl at 87), and 69 (CF_3^+); NMR (^{19}F) −69.0 (m, 2 F, CF_2Cl), −75.3 (rough t, J_{FF} = 4 Hz, atop broad m, 5 F, CF_3CO + OCF_2), −79.2 (m, 3 F, CF_3CCF_2Cl), −80.6 (m, 5 F, CF_3CFCF_2O), −141.1 (t, J_{FF} = 19 Hz, of m, 1 F, $CFCF_2Cl$), and −145.0 ppm (t, J_{FF} = 20 Hz of m, 1 F, $CFCF_2O$). Anal. Calcd for $C_9ClF_{17}O_3$: C, 21.01; Cl, 6.89. Found: C, 21.08; Cl, 6.31.

For **6**: IR (CCl_4) 5.54 μm (C=O); NMR (^{19}F) −69.0 (broad, 2 F, CF_2Cl), −75.3 (t, J_{FF} = 5 Hz, atop broad m, 5 F, CF_3COCF_2), −79.2 (m, 3 F, CF_3CCF_2Cl), −80.6 (m, 10 F, $2CF_3CFCF_2O$), −141.0 (broad, 1 F, $CFCF_2Cl$), 144.8 (broad, 1 F, $CFCF_2O$), and −145.4 ppm (broad, 1 F, $CFCF_2O$). Anal. Calcd for $C_{12}ClF_{23}O_4$: C, 21.18; Cl, 5.21. Found: C, 20.81; Cl, 5.23.

Perfluoro-5-methyl-4-oxahexanone-2 (7), Perfluoro-5,8-dimethyl-4,7-dioxanonanone-2 (8, *n* = 1), and Perfluoro-5,8,11-trimethyl-4,7,10-trioxadodecanone-2 (8, *n* = 2). Increased amounts of perfluoro ketone ethers can be obtained by replacing part of the chloropentafluoroacetone with hexafluoroacetone. With only equimolar amounts of hexafluoroacetone and KF present, sufficient products **7** and **8** (*n* = 1, 2) were formed for them to be isolated. A mixture of 10.5 g (0.18 mol) of KF, 150 mL of dry dimethylformamide, 29.9 g (0.18 mol) of hexafluoroacetone, and 33.7 g (0.18 mol) of chloropentafluoroacetone was stirred and refluxed at 35–40 °C for 2 days, then 45–50 °C for 3 days, and at 55 °C for 2 days. Distillation gave 43.2 g, bp 60–150 °C, along with 56% of recovered hexafluoroacetone. Fractionation of the liquid products by distillation gave 14.3 g (24% based on chloro ketone **1**), bp 56–59.5 °C: GC showed the product boiling near 59 °C to be pure **7**; IR (CCl_4) 5.54 μm (C=O); mass spectrum *m/e* 313 ($M^+ - F$), 263 ($M^+ - CF_3$), 235 ($(CF_3)_2CFOCF_2$), 169 ($C_3F_7^+$), 147 ($CF_3COCF_2^+$), 97 (CF_3CO^+), 69 (CF_3^+); mass calcd for $C_6F_{11}O_2$, 312.9722; found, 312.9763; NMR (^{19}F) −75.2 (t, J_{FF} = 5.6 Hz, 3 F, CF_3CO), −75.8 (d, J_{FF} = 21.2 Hz, of q, J_{FF} = 5.6 Hz, of septets, J_{FF} = 5.5 Hz, 2 F, OCF_2), −81.4 (t, J_{FF} = 5.5 Hz, of d, J_{FF} = 2.3 Hz, 6 F, CF_3), and −145.4 ppm (t, J_{FF} = 21.2 Hz, of septets, J_{FF} = 2.3 Hz, 1 F, CF). Anal. Calcd for $C_6F_{12}O_2$: C, 21.70; F, 68.66. Found: C, 21.42; F, 68.85.

Fractions with bp 115–117 °C were 6.0 g (13% based on **1**) of crude **8** (*n* = 1). An analytical sample was obtained by GLC: IR (CCl_4) 5.52 μm (C=O); NMR (^{19}F) −75.3 (t, J_{FF} = 5 Hz, atop m, 5 F, CF_3COCF_2), −80.7 (m, 3 F, CF_3CFCF_2), −81.2 (broad, 2 F, OCF_2CF), −81.5 (m, 6 F, $(CF_3)_2CF$)), −145.0 (t, J_{FF} = 21 Hz, 1 F, $(CF_3)_2CF$), and −146.0 ppm (t, J_{FF} = 20 Hz, 1 F, CF_3CFCF_2). Anal. Calcd for $C_9F_{18}O_3$: C, 21.70; F, 68.66. Found: C, 21.30; F, 68.38.

A fraction with bp 92–93 °C (50 mmHg) was 1.5 g (based on **1**) of crude **8** (*n* = 2). An analytical sample was obtained by GLC: IR (CCl_4) 5.54 μm (C=O); NMR (^{19}F) −75.6 (t, J_{FF} = 5.5 Hz, atop broad m, 5 F, CF_3COCF_2), −80.7 (m, 6 F, 2 CF_3CFCF_2), −81.2, (broad, 4 F, 2 OCF_2CF), −81.5 (m, 6 F, $(CF_3)_2CF$), −144.9 (broad m, 1 F, $(CF_3)_2CF$), and −145.8 ppm (broad m, 2 F, CF_3CFCF_2).

Perfluoro-1,6-dichloro-5-chloromethyl-4-oxahexanone-2 (9). A mixture of 10.5 g (0.18 mol) of KF and 150 mL of dry dimethylformamide was stirred at 15 °C while 71.6 g (0.36 mol) of dichlorotetrafluoroacetone was added rapidly. After 1 day at 45–50 °C, the mixture was distilled to give 64% of crude recovered ketone and 10.8 g of a liquid which was redistilled from H_2SO_4. There was thus obtained 3.1 g (5% conversion and 13% yield) of **9**: bp 73–75 °C (80 mmHg); IR (CCl_4) 5.53 μm (C=O); NMR (^{19}F) −65.9 (m, 6 F, CF_2Cl), −72.2 (d, J_{FF} = 21.3 Hz, of t, J_{FF} ~ 6.5 Hz, of overlapping pentets, J_{FF} ~ 6.5 Hz, 2 F, OCF_2), and −135.4 ppm (t, J_{FF} = 21.3 Hz, of overlapping pentets, J_{FF} = 5.4 Hz, 1 F, CF). Anal. Calcd for $C_6Cl_3F_9O_2$: C, 18.89; Cl, 27.89. Found: C, 18.84; Cl, 27.66.

Perfluoro-1-chloro-5-methyl-4-oxahexanone-2 (11) and Perfluoro-2,8-dimethyl-3,7-dioxanonanone-5 (10). A mixture of 21.0 g (0.36 mol) of dry KF, 150 mL of dry dimethylformamide, 59.8 g (0.36 mol) of hexafluoroacetone, and 35.8 g (0.18 mol) of dichlorotetrafluoroacetone was heated at reflux (40–60 °C) for 3 days. Distillation afforded 63 g of liquid, bp 30–145 °C, along with 16.5 mL at −80 °C (46%) of recovered hexafluoroacetone. Redistillation from H_2SO_4 gave 18.7 g (21% conversion and 39% yield from hexafluoroacetone) of **10**, bp 117–118 °C. A center-cut, single component by GC, was analyzed: IR (CCl_4) 5.51 μm (C=O); mass spectrum *m/e* 479 ($M^+ - F$), 313 ($M^+ - F - HFA$), 263 ($M^+ - F - HFA - CF_2$), 235 ($(CF_3)_2CFOCF_2^+$), 169 ($C_3F_7^+$), 147 ($CF_3COCF_2^+$), 97 (CF_3CO^+); NMR (^{19}F) −75.0 (d, J_{FF} = 21.5 Hz, of septets, J_{FF} = 5.5 Hz, 2 F, OCF_2), −81.4 (m, 6 F, CF_3), and −145.3 ppm (t, J_{FF} = 21.5 Hz, of septets, J_{FF} = 2.1 Hz, 1 F, CF). Anal. Calcd for $C_9F_{18}O_3$: C, 21.70; F, 68.66. Found: C, 21.60; F, 68.59.

Many coproducts form along with **10**, including the expected intermediate **11** and its fluoride ion displacement product **7**. These compounds were obtained from a larger scale reaction along with substantial amounts of mixed high-boiling products. A reaction of 87.1 g (1.5 mol) of KF, 500 mL of dimethylformamide, 250 g (1.5 mol) of hexafluoroacetone, and 149.5 g (0.75 mol) of dichlorotetrafluoroacetone was stirred and heated at 45–60 °C for 1 week. Distillation gave 78 mL at −80 °C (52% recovery) of crude hexafluoroacetone and 244 g of liquid, bp 45–140 °C. Distillation from H_2SO_4 gave 20.5 g (8% conversion based on dichloro ketone) of **7**, bp 58–60 °C, identified by ^{19}F NMR; 17.5 g (7% yield based on dichloro ketone) of **11**, bp 84–86 °C; 81.5 g (22% conversion and 45% yield from hexafluoroacetone) of **10**; and 68.2 g of mixed fluorinated higher boilers. A sample of **11**, one component by GC, was analyzed: IR (neat) 5.54 μm (C=O); NMR (^{19}F) −66.2 (t, J_{FF} = 7.5 Hz, 2 F, CF_2Cl), −73.5 (d, J_{FF} = 21.5 Hz, of m, 2 F, OCF_2), −81.3 (t, J_{FF} = 5.7 Hz, of d, J_{FF} = 1.2 Hz, 6 F, CF_3), and −145.6 ppm (t, J_{FF} = 21.5 Hz, of septets, J_{FF} = 1.2 Hz, 1 F, CF). Anal. Calcd for $C_6ClF_{11}O_2$: C, 20.68; Cl, 10.17; F, 59.97. Found: C, 20.90; Cl, 10.01; F, 59.68.

Cyclohexylbis(perfluoroisopropoxymethyl)carbinol (13). A solution of 20.0 g (0.04 mol) of **10** and 33.6 g (0.40 mol) of cyclohexane in 50 mL of trichlorotrifluoroethane was stirred and irradiated under nitrogen with a low-pressure helical mercury lamp placed around the quartz reaction tube. Irradiation was continued for 5 h with the temperature at 40–50 °C. Distillation gave 17.3 g (74%) of adduct **13**: bp 99–100 °C (10 mmHg); $n^{24}D$ 1.3388; IR (neat) 2.74 (OH), 3.37 and 3.46 (satd CH), 8–9 μm (CF, C–O); NMR (^1H) 2.82 (s, 1 H, OH) and 1–2.3 ppm (m, 11 H, CH); NMR (^{19}F) −73.2 (m, 2 F, OCF_2), −80.8 (m, 6 F, CF_3), and −145.6 ppm (t, J_{FF} = 23 Hz, of septets, J_{FF} = 2 Hz, 1 F, CF). Anal. Calcd for $C_{15}H_{12}F_{18}O_3$: C, 30.94; H, 2.08; F, 58.73. Found: C, 31.10; H, 2.13; F, 58.62.

***tert*-Butylthiopentafluoroacetone (14).** A suspension of 9.6 g (0.2 mol) of 50% NaH/mineral oil in 150 mL of dry dimethylformamide was stirred at 10–15 °C while 23.4 g (0.26 mol) of *tert*-butylmercaptan was added dropwise. When H_2 evolution was complete, 36.5 g (0.20 mol) of chloropentafluoroacetone was distilled into the cooled mixture. The mixture was then stirred and warmed from 15 to 40 °C, where solid precipitated and a mild exotherm occurred. The mixture was heated at 55–60 °C for 2.5 h and then distilled to give 35 g of crude products, bp 50–85 °C (100 mmHg). Redistillation afforded 12.6 g (27%) of **14**, bp 61–68 °C (100 mmHg), purified further by GLC for analysis: IR (neat) 3.33, 3.42, and 3.46 (saturated CH), 5.59 (C=O), 7.14 and 7.28 ($(CH_3)_3C$), and 8–9 μm (CF); NMR (^1H) 1.56 ppm (s, CH_3); NMR (^{19}F) 73.6 (t, J_{FF} = 7.9 Hz, 3 F, CF_3), −83.4 ppm (q, J_{FF}

= 7.9 Hz, 2 F, CF_2). Anal. Calcd for $C_7H_9F_5OS$: C, 35.60; H, 3.84; S, 13.57. Found: C, 35.33; H, 3.76; S, 13.38.

3,3-Di[bis(perfluoroisopropoxymethyl)fluoromethoxymethyl]oxetane (12). A mixture of 3.9 g (0.067 mol) of KF, 33.4 g (0.067 mol) of ketone **10**, 7.8 g (0.032 mol) of 3,3-bis(bromomethyl)oxetane, and 75 mL of dry dimethylformamide was stirred until homogeneous and then heated at 65–70 °C for 2 days and at 80 °C for 6 h. Dilution with 500 mL of water gave a lower layer which was washed with water, dried, and distilled to afford 24.9 g (70%) of oxetane **12**: bp 85 °C (0.05 mmHg); IR 3.35 and 3.45 (saturated CH), 7.5–9 (CF, C–O), and 10.10 μm (oxetane ring); NMR (^1H) 4.37 (s, 1, oxetane CH_2) and 4.30 (broad s, 1, CH_2OCF); NMR (^{19}F) −78.8 (broad m, 4, CF_2O), −81.4 (m, 12, CF_3), −142.6 (m, 1, CH_2OCF), and −146.0 ppm (t of m, J_{FF} = 21.8 Hz, 2, CF_2OCF). Anal. Calcd for $C_{23}H_8F_{38}O_7$: C, 24.71; H, 0.72; F, 64.56. Found: C, 24.74; H, 0.85; F, 64.35.

Registry No.—1, 79-53-8; **3**, 64457-48-3; **5**, 64457-49-4; **6**, 64457-50-7; **7**, 64457-51-8; 8 (n = 1), 64457-52-9; 8 (n = 2), 64457-53-0; **9**, 64457-54-1; **10**, 64457-55-2; **11**, 64457-56-3; **12**, 64457-57-4; **13**, 64457-58-5; **14**, 64457-59-6; hexafluoroacetone, 684-16-2; 1,3-dichlorotetrafluoroacetone, 127-21-9; cyclohexane, 110-82-7; *tert*-butylmercaptan, 75-66-1; 3,3-bis(bromomethyl)oxetane, 2402-83-7.

References and Notes

(1) An often quoted example is the attack of hydroxide on trifluoromethyl iodide to give fluoroform, as described by J. Banus, H. J. Emeleus, and R. N. Haszeldine, *J. Chem. Soc.*, 60 (1951). For reactions of this type, formation of a charge-transfer complex has not been ruled out as an initial step.
(2) L. G. Anello, A. K. Price, and R. F. Sweeney, *J. Org. Chem.*, **33**, 2692 (1968); U. S. Patent 3 379 765 (Apr I 23, 1968).
(3) P. Tarrant, C. G. Allison, K. P. Barthold, and E. C. Stump, Jr., "Fluorine Chemistry Reviews", Vol. 5, P. Tarrant, Ed., Marcel Dekker, New York, N.Y., 1971, p 96 ff, discuss oligomerization of hexafluoropropene epoxide to polyether acid fluorides.
(4) D. Sianesi, R. Fontanelli, and G. Caporiccio, U. S. Patent 3 513 203 (May 19, 1970), prepared the closely related ketoethers $CF_3O[CF_2CF(CF_3)O]_n$-CF_2COCF_3 by a different route.
(5) F. W. Evans, M. H. Litt, A.-M. Weidler-Kubanek, and F. P. Avonda, *J. Org. Chem.*, **33**, 1837 (1968).
(6) German Patent 2 116 105 (Sept. 7, 1972).
(7) E. G. Howard, P. B. Sargeant, and C. G. Krespan, *J. Am. Chem. Soc.*, **89**, 1422 (1967).
(8) E. L. Eliel, "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, pp 103–106.
(9) M. H. Maguire and G. Shaw, *J. Chem. Soc.*, 2713 (1957), report the only successful reaction of this type to come to our attention. Sodium 2,4-dichlorophenoxide gave a low yield of the chloride displacement product with ethyl chlorodifluoroacetate.

Hydroformylation Catalyzed by Cis-Chelated Rhodium Complexes. Extension to Polymer-Anchored Cis-Chelated Rhodium Catalysts

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The chelating phosphine ligands $Ph_2PCH_2CH_2PPh_2$, $Ph_2PCH_2CH_2CH_2PPh_2$, and $Ph_2P(CH_2)_4PPh_2$ have been examined as ligands in the rhodium catalyzed hydroformylation of 1-pentene and 2-pentene. 1,2-Bis(diphenylphosphino)ethane causes a large decrease in the normal/branched (n/b) selectivity of 1-pentene hydroformylations at 60–120 °C and 100–800 psi. Increasing addition of PPh_3 causes increased n/b ratios. Hydroformylations of 2-pentene with $Ph_2PCH_2CH_2PPh_2$ exhibited low n/b selectivities which increased as pressure was lowered and temperature was raised. Using a polymer-anchored version of the catalyst (i.e., Ⓟ-$C_6H_4P(Ph)CH_2CH_2P(Ph_2)RhH(CO)L$) selectivities of 40–42% hexanal could be obtained from 2-pentene at 140 °C and 100–400 psi. The inherent propensity toward anti-Markownikoff rhodium hydride addition to a terminal double bond is lower for *cis*-phosphine chelated rhodium hydrides than for *trans*-bisphosphine–rhodium hydride complexes. This is attributed to differences in steric effects.

Phosphines and arsines have long been investigated as ligands for rhodium in the hydroformylation of olefins.[1] Detailed mechanistic investigations of hydroformylation were reported by Wilkinson et al.[2–4] using $RhH(CO)(PPh_3)_3$ as the catalyst. It has been found that rhodium complexes are more active "oxo" catalysts than cobalt compounds, permitting their use at low temperatures to give a minimum of by-products.[5] In general, rhodium-catalyzed hydroformylations are performed at temperatures from 40 to 140 °C and pressures from 50 to 1500 psi.[6] Under these conditions the selectivity to aldehydes is often greater than 99%.

Addition of tertiary phosphine ligands to rhodium-catalyzed hydroformylations greatly reduces the tendency for double bond isomerization. For example, 1-pentene was converted to 72% *n*-hexanal and 28% 2-methylpentanal in the presence of $RhH(CO)(PPh_3)_3$.[7] Similar selectivities were reported by Osborn, Wilkinson, and Yang[2] using $Rh(CO)Cl(PPh_3)_2$ and by Pruett and Smith[8] using a triphenyl phosphite–rhodium complex. Roth et al.[7] demonstrated that increasing additions of triphenylphosphine to $Rh(CO)Cl(PPh_3)_2$ resulted in a higher selectivity to *n*-heptanal from 1-hexene, while Pruett and Smith[8] observed a similar effect upon addition of excess triphenyl phosphite to $RhH(CO)(P(OPh)_3)_3$. High rates and very high terminal selectivities were observed by Brown and Wilkinson[9] when $RhH(CO)(PPh_3)_3$ was used in molten triphenylphosphine at 85–150 °C.

Recently, increased attention has been given to attaching homogeneous catalysts to polymer supports.[10–14] It is now well established that polymer-anchored $RhH(CO)(PPh_3)_3$ exhibits considerably higher selectivities than its homogeneous analogue, when the resin to which it is anchored has high P/Rh ratios and high loadings of phosphine.[12,14] At 1:1 H_2/CO, normal to branched (n/b) selectivities as high as 20:1 have been observed,[15] and by varying the H_2:CO ratios n/b selectivities up to 64:1 were achieved.[14]

Despite the extensive selectivity studies already reported, very little work describes the effect that cis-chelating phosphines exert in hydroformylation reactions. The n/b selectivity using $RhH(CO)(PPh_3)_3$ is strongly dependent on the position of equilibrium between $RhH(CO)_2(PPh_3)_2$ and $RhH(CO)_2PPh_3$.[2–4,16] This is summarized in Scheme I. The associative pathway, which leads to higher n/b selectivities,[2–4,16] proceeds mainly by anti-Markownikoff rhodium hydride addition of $RhH(CO)_2(PPh_3)_2$ to the terminal carbon. When two phosphine ligands are bound to rhodium, selectivity is higher. This suggested that a chelating ligand, such as bis(diphenylphosphino)ethane (see complex **1**, Scheme II), might give high n/b selectivities because this ligand would keep two

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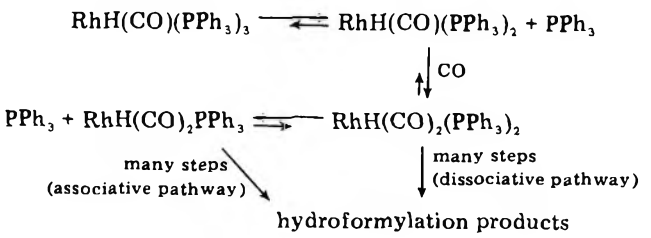
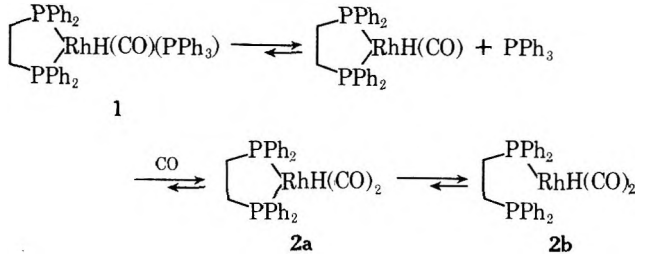
Scheme I



Scheme II



phosphines chelated to the metal. The position of equilibrium between **2a** and **2b** would greatly favor **2a.**

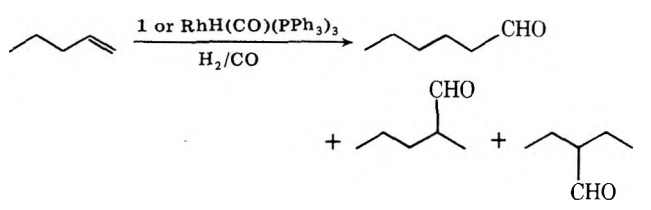
To the degree that the hydroformylation mechanisms, using $RhH(CO)(PPh_3)_3$ and **1** as catalysts, are mechanistically the same, one might postulate that **1** might be highly selective. However, the phosphine ligands in intermediate **2a** are always cis while the phosphines in $RhH(CO)_2(PPh_3)_2$ are trans. This difference in cis and trans ligand geometries may change the observed oxo chemistry. Therefore, hydroformylation studies were undertaken on both 1- and 2-pentene substrates using cis-chelating phosphines. Furthermore, polymer-anchored 1,2-diphenylphosphinoethane was prepared and used in rhodium-catalyzed hydroformylations.

Results and Discussions

Hydroformylation of 1-Pentene Catalyzed by $RhH(CO)(PPh_3)(PPh_2CH_2CH_2PPh_2)$, 1, vs. $RhH(CO)(PPh_3)_3$. Complex **1** was prepared by simple ligand exchange in benzene. Alternatively, bis(diphenylphosphino)ethane was simply added to hydroformylation reactions along with $RhH(CO)(PPh_3)_3$.

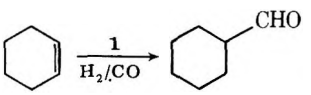
$$RhH(CO)(PPh_3)_3 + PPh_2CH_2CH_2PPh_3 \rightarrow 1 + 2PPh_3$$

Upon dissolution, 2 mol of triphenylphosphine dissociated and, under hydroformylation conditions, the equilibria shown in Scheme II were assumed. Then **1** was used to catalyze the hydroformylation of 1-pentene at temperatures from 60 to 120 °C and pressures from 100 to 800 psi using 1:1 H_2/CO. The results are summarized in Table I. The n/b selectivity varied from 1.0 to 2.0 showing conclusively that catalysis by **1** is *far less selective* than catalysis using $RhH(CO)(PPh_3)_3$ (which



under the same conditions gives n/b ratios of 3.0 to 3.5). Also, the change in selectivity with temperature was stronger at 100 psi than at either 400 or 800 psi using **1** (Table I).

The lower selectivity of **1** is partially due to the ability of this cis complex to promote double bond isomerization. Significant quantities of 2-pentene were detected during the reaction. This stands in sharp contrast to the behavior of $RhH(CO)(PPh_3)_3$ where isomerization of terminal olefins is not observed under normal hydroformylation conditions.[17] Second, the n/b ratio resulting from terminal double bond hydroformylation was inherently lower using **1**. Complex **1** is also a more active catalyst than $RhH(CO)(PPh_3)_3$. For example, cyclohexene was quantitatively converted to cyclohexanecarboxaldehyde at 85 °C, 400 psi, 1:1 H_2CO, in 20 h using complex **1**, but no aldehyde was obtained employing $RhH(CO)(PPh_3)_3$.



We verified that the n/b selectivity is increased by increasing the P/Rh ratio when using $RhH(CO)(PPh_3)_3$ and excess PPh_3. This phenomenon is shown in Table II for 1-pentene reactions at 100 psi, 1:1 H_2/CO, at 80 °C. These data are presented to serve as a comparison with the effect that adding excess $PPh_2CH_2CH_2PPh_2$ to $RhH(CO)(PPh_3)_3$ has on the selectivity of 1-pentene hydroformylations (summarized in Table III). The effects of adding this cis ligand are striking. With a 9 mol excess of $PPh_2CH_2CH_2PPh_2$ (i.e., P/Rh = 21), the highest n/b ratio was only 1.2. Furthermore, over the entire matrix of conditions used, the selectivity was almost constant (0.9 to 1.2). In contrast, the selectivity climbs from 3.0 to 7.6 as excess triphenylphosphine is added (Table II). Clearly, $PPh_2CH_2CH_2PPh_2$ reduces n/b selectivity. Furthermore, by raising the $PPh_2CH_2CH_2PPh_2$/Rh ratio from 1 (Table I) to 9 (Table III) the selectivity was further de-

Table I. Hydroformylation of 1-Pentene Catalyzed by $RhH(CO)(PPh_3)(PPh_2CH_2CH_2PPh_2)$[a]

	Yield, % (n/b), selectivity (normal), %			
psi	60 °C	80 °C	100 °C	120 °C
100	93 (2.0) 67	95 (1.9) 65	99 (1.7) 61	95 (1.0) 50
400	96 (1.9) 65	93 (2.0) 67	89 (1.8) 65	92 (2.0) 67
800	88 (1.8) 65	99 (1.8) 65	97 (1.9) 65	100 (1.8) 65

[a] 1-Pentene (1.0 mL, 9.1 mmol), rhodium (0.09 mmol), benzene (8.0 mL), 21 h, H_2/CO = 1:1.

Table II. Effect of P/Rh Ratio on Selectivity in Hydroformylations of 1-Pentene at 100 psi and 80 °C Catalyzed by $RhH(CO)(PPh_3)_3 + PPh_3$

P:Rh	Conversion, %	n/b ratio	Selectivity, %
5:1	97.1	3.0	75
10:1	96.6	3.5	78
15:1	96.0	4.9	83
30:1	96.6	5.6	85
50:1	93.2	7.6	88

[a] 1-Pentene (1.0 mL, 9.1 mmol), rhodium (0.09 mmol), benzene (8.0 mL), 21 h, H_2/CO = 1:1.

Table III. Hydroformylation of 1-Pentene Catalyzed by $RhH(CO)(PPh_3)_3$ in the Presence of Excess $PPh_2CH_2CH_2PPh_2$[a]

	Yield, n/b, selectivity (normal)			
psi	60 °C	80 °C	100 °C	120 °C
100	89%, 1.2, 55%	92%, 1.1, 52%	93%, 1.0, 50%	96%, 0.9, 47%
400	68%, 1.1, 52%	97%, 1.0, 50%	97%, 1.0, 50%	99%, 1.0, 50%
800	39%, 1.0, 50%	96%, 1.0, 50%	98%, 1.0, 50%	97%, 1.0, 50%

[a] 1-Pentene (1.0 mL, 9.1 mmol), rhodium (0.09 mmol), benzene (8.0 mL), P/Rh = 21:1, 21 h, H_2/CO = 1:1.

Table IV. The Influence of Added Bisphosphines on Selectivity in Hydroformlations of 1-Pentene with $RhH(CO)(PPh_3)_3$[a]

Phosphine	Conversion, %	n/b ratio	Normal selectivity, %
None	99	3.5	78
PPh_3	98	6.7	87
$PPh_2(CH_2)_2PPh_2$	92	1.1	52
$PPh_2(CH_2)_3PPh_2$	89	0.9	47
$PPh_2(CH_2)_4PPh_2$	93	1.2	55

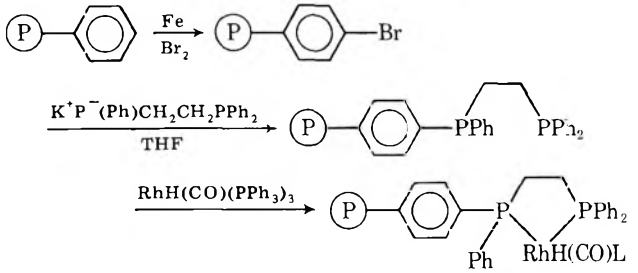
[a] 1-Pentene (1.0 mL, 9.1 mmol), rhodium (0.09 mmol), benzene (8.0 mL), P/Rh = 21:1, 100 psi (H_2/CO = 1:1), 80 °C, H_2/CO = 1:1.

Table V. Hydroformylation of 1-Pentene Catalyzed by Polymer-Anchored Catalyst 3a[a]

psi	Yield, n/b, selectivity (normal) 60 °C	80 °C	100 °C	120 °C
100	25%, 2.7, 73%	22%, 0.8, 47%	59%, 1.2, 55%	91%, 1.0, 50%
200	89%, 2.7, 73%	68%, 1.0, 50%	92%, 1.0, 50%	97%, 1.0, 50%
400	97%, 2.2, 69%	91%, 1.0, 50%	96%, 1.0, 50%	86%, 0.9, 47%
800	100%, 1.2, 55%	100%, 1.0, 50%	100%, 1.1, 52%	100%, 1.0, 50%

[a] 1-Pentene (1.0 mL, 9.1 mmol), catalyst (0.09 mmol of Rh), benzene (8.0 mL), P/Rh = 2.1:1, phosphine loading 5.7%, 21 h, H_2/CO = 1:1.

Scheme III



3a, PL = 5.7; P/Rh = 2.1
3b, PL = 22.2; P/Rh = 21

creased. This trend is just the opposite of that found upon adding excess triphenylphosphine (Table II).

To see if other chelating ligands exhibited a similar effect on hydroformylation selectivity, 1,3-bis(diphenylphosphino)propane and 1,4-bis(diphenylphosphino)butane were also studied. Representative results, summarized in Table IV, clearly establish that both of these ligands also lower the n/b selectivity.

Hydroformylations of 1-Pentene Catalyzed by Polymer-Anchored 1,2-Bis(diphenylphosphino)ethane Rhodium Complexes. Reaction of brominated styrene–divinylbenzene (1%) resins with $[PPh_2CH_2CH_2PPh]^-K^+$ followed by ligand exchange with $RhH(CO)(PPh_3)_3$ gave polymer-anchored catalyst 3 (Scheme III). These resin-anchored catalysts are unique since they should exhibit greater resistance to the leaching of rhodium or migration of rhodium along a catalyst bed than previous resin-anchored rhodium catalysts.[12,14,15,19] Two resins were prepared. Catalyst **3a** had a ligand loading (i.e., PL, the percentage of resin phenyl rings substituted with the ligand) of 5.7% and a P/Rh = 2.1 (almost all resin-attached ligands are chelating a rhodium). In contrast, catalyst **3b** had a ligand loading of 22.2% and P/Rh = 21. Thus, a higher density of ligand sites was available and about 9 out of 10 of these ligands did not chelate rhodium.

Table VI. Hydroformylation of 1-Pentene by Polymer-Anchored Catalyst 3b[a]

psi	Yield, n/b, selectivity (normal) 60 °C	80 °C	100 °C	120 °C
100	61%, 2.0, 67%	96%, 2.0, 67%	95%, 2.1, 68%	100%, 1.2, 55%
200	72%, 2.0, 67%	100%, 2.0, 67%	98%, 2.1, 68%	100%, 1.0, 50%
400	100%, 2.2, 69%	100%, 2.1, 68%	100%, 2.1, 68%	99%, 1.0, 50%
800	99%, 1.0, 50%	100%, 1.0, 50%	100%, 1.0, 50%	100%, 1.0, 50%

[a] 1-Pentene (1.0 mL, 9.1 mmol), catalyst (0.09 mmol of Rh), benzene (8.0 mL), P/Rh = 21:1, phosphine loading 22.2%, 21 h, H_2/CO = 1:1.

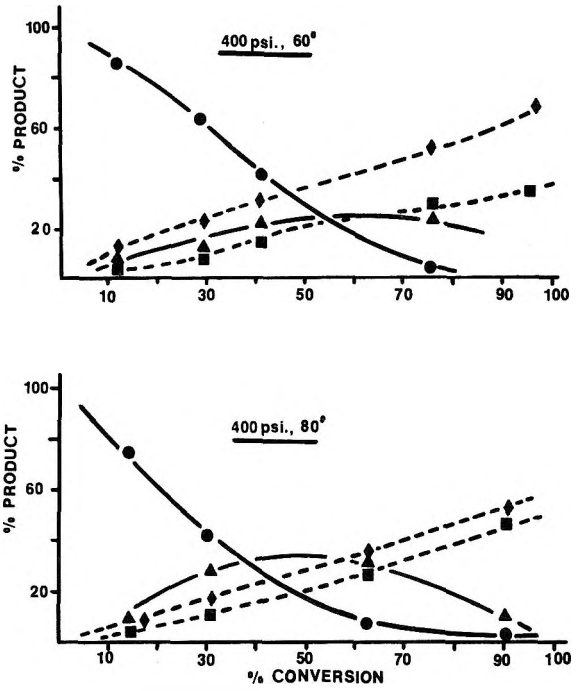


Figure 1. The product distribution as a function of conversion in hydroformylations of 1-pentene catalyzed by resin **3a**: (●) 1-pentene, (▲) 2-pentene, (◆) hexanal, (■) 2-methylpentanal.

Hydroformylations of 1-pentene were carried out using both **3a** and **3b** at 60–120 °C and 100–800 psi (summarized in Tables V and VI). As expected, based on the results with complex **1**, the n/b selectivities were low using both **3a** and **3b** over all conditions employed. For both **3a** and **3b** the selectivity decreased as either the temperature or the pressure was raised. The product distributions using **3a** are shown as a function of conversion in Table VII and Figure 1. Significant isomerization to 2-pentene occurred at both 60 and 80 °C (400 psi).

Despite the fact that a build up of 2-pentene occurs in these reactions, the n/b ratio remains constant as conversion increases. The fact that the n/b ratio does not depend on conversion implies that hydroformylation occurs mainly at the terminal double bond even when large amounts of 2-pentene are present. Thus, hydroformylation of the terminal isomer is faster than that of the internal isomers. Also, the n/b selectivity is low in terminal hydroformylation.

While other explanations may be advanced,[20] one can attribute this result to a lower propensity for anti-Markownikoff

Table VII. Product Distribution (%) as a Function of Conversion in Hydroformylations of 1-Pentene Using Catalyst 3a[a]

Cond	Conv, %	n/b	1-Pentene/ 2-pentene	1-Pentene	2-Pentene	Normal aldehyde[b]	Branched aldehyde[c]
400 psi, 60 °C	12	2.2	93/7	82.0	6.0	8.15	3.77
	29	2.2	86/14	61.8	9.8	19.73	8.76
	41	2.2	59/41	35.0	22.1	29.42	13.48
	76	2.0	7/93	1.7	22.4	50.20	25.70
	97	2.2				66.26	30.10
400 psi, 80 °C	15	1.2	90/10	76.5	8.5	8.19	6.82
	31	1.2	59/41	40.6	28.0	17.10	14.25
	63	1.2	16/84	5.9	30.8	34.53	28.77
	91	1.0	8/92	0.7	7.9	46.05	45.12

[a] 1-Pentene (1.0 mL, 9.1 mmol) catalyst (0.09 mequiv of Rh), benzene (8.0 mL), P/Rh = 2.1:1, H_2/CO = 1:1. [b] *n*-Hexanal. [c] 2-Methylpentanal.

Table VIII. Hydroformylation of 2-Pentene Catalyzed by $RhH(CO)(PPh_3)(PPh_2CH_2CH_2PPh_2)$[a]

psi	Yield (%), n/b 60 °C	80 °C	100 °C	120 °C
100	68, 0.12	79, 0.14	73, 0.39	90, 0.57
400	95, 0.06	92, 0.13	96, 0.17	98, 0.30
800	89, 0.06	90, 0.08	89, 0.07	95, 0.12

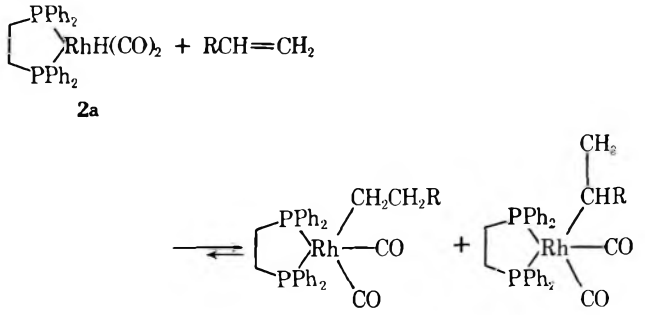
[a] 1-Pentene (1.0 mL, 9.1 mmol), rhodium (0.08 mmol), benzene (8.0 mL), 21 h, H_2/CO = 1:1.

Table IX. Hydroformylation of 2-Pentene Catalyzed by $RhH(CO)(PPh_3)_3$[a]

psi	Yield (%), n/b 60 °C	80 °C	100 °C	120 °C
100	87, 0.10	90, 0.23	91, 0.38	79, 0.49
400	98, 0.04	97, 0.10	93, 0.13	94, 0.27
800	94, 0.03	99, 0.04	100, 0.05	100, 0.06

[a] 1-Pentene (1.0 mL, 9.1 mmol), rhodium (0.09 mmol), benzene (8.0 mL), 21 h, H_2/CO = 1:1.

rhodium hydride addition of **2a** relative to $RhH(CO)_2(PPh_3)_2$. Since anti-Markownikoff addition of $RhH(CO)_2(PPh_3)_2$ to olefins is due largely to a steric effect,[16] we suggest that **2a** is less sterically hindered than its trans counterpart $RhH(CO)_2(PPh_3)_2$.



Resin **3a** catalyzed the isomerization of 1-pentene to 2-pentene in the presence of high CO pressures. Thus, after 20 h at 80 °C and 400 psi of carbon monoxide, 40% of 1-pentene was converted to 2-pentene. This contrasts with $RhH(CO)(PPh_3)_3$ where isomerization is inhibited by the presence of carbon monoxide.[4,21]

Resins **3a** and **3b** were readily filtered from product solutions and recycled, often with little loss of activity. For example, catalyst **3a** proved to be very active even after 20 recycles at 600 psi and 80 °C. Remarkably, the filtrations used to separate the resin catalyst from the products were performed in air! At high temperatures, however, the activities of both **3a** and **3b** dropped after each cycle. For example, the yields of aldehydes obtained from reactions conducted at 120 °C, 400 psi, and 21 h with resin **3a** were 86, 73, 50, and then 15% (at 72 h) on successive recycles. The n/b selectivity remained constant.

Hydroformylation of 2-Pentene Catalyzed by $RhH(CO)(PPh_3)(PPh_2CH_2CH_2PPh_2)$, 1, and by $RhH(CO)(PPh_3)_3$. Published kinetic data on the hydroformylation of internal olefins with phosphine-substituted rhodium complexes is skimpy. The most detailed information available is for $RhH(CO)(PPh_3)_3$ at 25 °C and 1 atm[22] where 2-pentene hydroformylation was about 25 times slower than that of 1-pentene. When internal olefins were hydroformylated at 70–100 °C, terminal aldehydes were not obtained from phosphine–rhodium catalysts.[22,23] Thus, isomerization using phosphine–rhodium catalysts is markedly repressed below 100 °C.[23–26] Using $RhCl(CO)(PPh_3)_2$, Roth et al.[7] observed no terminal product in 2-pentene hydroformylations at 70 °C, but upon increasing the temperature to 150 °C the amount of *n*-hexanal increased to 36.8%. Excess triphenylphosphine reduced the amount of normal isomer to 16.1% at 150 °C. Excess triphenylphosphine caused the same effect in *cis*-2-butene hydroformylations catalyzed by Rh_2O_3.[23]

Since 1 exhibited a high isomerization activity (relative to $RhH(CO)(PPh_3)_3$), we though it might be a superior catalyst for the terminal hydroformylation of internal olefins. This would require (1) a rapid internal to terminal isomerization rate relative to internal hydroformylation, (2) significantly faster reaction at the terminal (versus internal) double bond, and (3) a high inherent n/b selectivity when the terminal double bond was hydroformylated. We felt that the first two criteria might hold. Thus, hydroformylations of 2-pentene were carried out employing $RhH(CO)(PPh_3)(PPh_2CH_2CH_2PPh_2)$, **1**, at 60–120 °C and 100–800 psi (results in Table VIII).

The n/b selectivities using 1 were low. However, the yield of *n*-hexanal increased as the temperature was raised from 60 to 120 °C at each pressure. In fact, 36% normal product was obtained at 120 °C and 100 psi. Raising the temperature increased the isomerization rate faster than the rate of internal hydroformylation. At temperatures from 60 to 120 °C, the selectivity to *n*-hexanal decreased as the pressure was increased. Either the rate of isomerization decreased as carbon monoxide pressure increased[21] or the rate of internal olefin hydroformylation increased relative to isomerization.

To compare the effect of the 1,2-bis(diphenylphosphino)-ethane to that of triphenylphosphine, the selectivities in rhodium-catalyzed 2-pentene hydroformylations were obtained at the same conditions (see Table IX). The trends are similar. The amount of terminal product increases as temperature is raised, but the amount of terminal product is less with $RhH(CO)(PPh_3)_3$. At 100 °C and 100 psi a n/b selectivity

Table X. Hydroformylation of 2-Pentene Catalyzed by $RhH(CO)(PPh_3)_3$ in the Presence of Excess PPh_3[a]

psi	Yield (%), n/b		
	60 °C	100 °C	120 °C
100	40, 0.06	85, 0.03	74, 0.10
400	49, 0.05	100, 0.03	99, 0.09
800	66, 0.03	100, 0.05	100, 0.08

[a] 2-Pentene (1.0 mL, 9 mmol), rhodium (0.09 mmol), benzene (8 mL), P/Rh = 21:1, 21 h, H_2/CO = 1:1.

Table XI. Hydroformylation of 2-Pentene Catalyzed by $RhH(CO)(PPh_3)_3$ in the Presence of $PPh_2CH_2CH_2PPh_2$[a]

psi	Yield (%), n/b			
	60 °C	80 °C	100 °C	120 °C
100	28, 0.00	55, 0.00	72, 0.00	62, 0.10
400	9, 0.00	36, 0.00	61, 0.00	78, 0.02
800	7, 0.00	12, 0.00	65, 0.00	90, 0.00

[a] 2-Pentene (1.0 mL, 9.1 mmol), rhodium (0.09 mmol), benzene (8.0 mL), P/Rh = 21:1, 21 h, H_2/CO = 1:1.

Table XII. Hydroformylation of 2-Pentene by Polymer-Anchored Catalyst 3a[a]

psi	Yield (%), n/b				
	60 °C	80 °C	100 °C	120 °C	140 °C
100	28, 0.45	56, 0.48	71, 0.66	78, 0.68	91, 0.72
200	15, 0.39	74, 0.46	62, 0.65	51, 0.66	98, 0.69
400	63, 0.15	91, 0.14	97, 0.43	95, 0.64	100, 0.69
800	100, 0.05	100, 0.20	96, 0.29	100, 0.43	100, 0.66

[a] 2-Pentene (1.0 mL, 9.1 mmol), catalyst (0.09 mmol of rhodium), benzene (8.0 mL), P/Rh = 21:1, phosphine loading 5.7%, 21 h, H_2/CO = 1:1.

Table XIII. Hydroformylation of 2-Pentene by Polymer-Anchored Catalyst 3b[a]

psi	Yield (%), n/b			
	60 °C	80 °C	100 °C	120 °C
100	22, 0.11	44, 0.11	63, 0.16	88, 0.29
200	53, 0.08	74, 0.08	95, 0.12	86, 0.28
400	80, 0.06	99, 0.08	100, 0.10	93, 0.29
800	100, 0.03	93, 0.06	98, 0.13	95, 0.22

[a] 2-Pentene (1.0 mL, 9.1 mmol), catalyst (0.09 mmol of Rh), benzene (8.0 mL), P/Rh = 21:1, phosphine loading 22.2%, 21 h, H_2/CO = 1:1.

of 0.38 was achieved. Thus, at mild conditions, isomerization does become competitive with internal hydroformylation.

The addition of excess triphenylphosphine (Table X) or excess 1,2-bis(diphenylphosphino)ethane (Table XI) inhibits isomerization in 2-pentene hydroformations. Only branched products were obtained when $Ph_2PCH_2CH_2PPh_2$ was used at 60–100 °C and 100 to 800 psi. Traces of *n*-hexanal were found at 120 °C and 100 or 400 psi. Excess triphenylphosphine reduced the amount of normal product but did not eliminate it, as was the case using the chelating ligand.

Hydroformylations of 2-Pentene Catalyzed by Polymer-Anchored 1,2-Bis(diphenylphosphino)ethane rhodium Complexes. Resin catalysts **3a** and **3b** were employed in 2-pentene hydroformylations at 60–140 °C and 100–800 psi. High aldehyde yields were obtained in all cases except at 100–200 psi and 60–80 °C where partial conversion occurred at 21 h. Surprisingly, the n/b selectivities for resin **3a** (Table XII) were higher than those of **1** (Table VIII), although the trends were the same. The selectivity increased with increasing temperature using **3a** and **3b** (Tables XII and XIII)

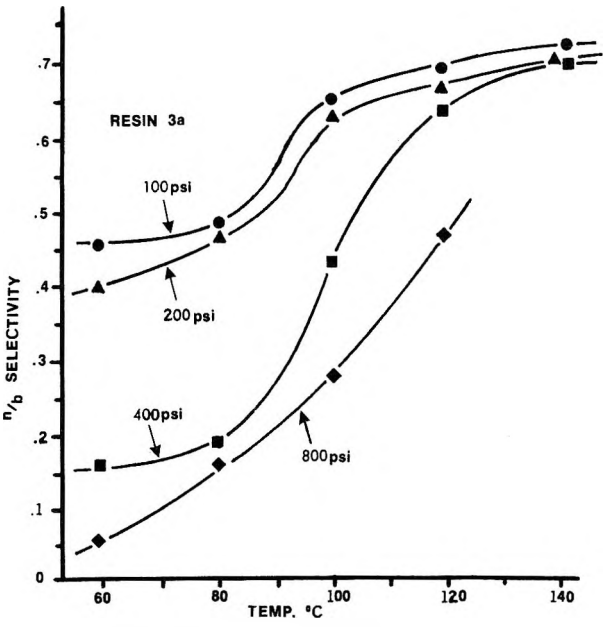


Figure 2. The normal to branched product selectivity as a function of temperature in 2-pentene hydroformylations catalyzed by resin **3a**.

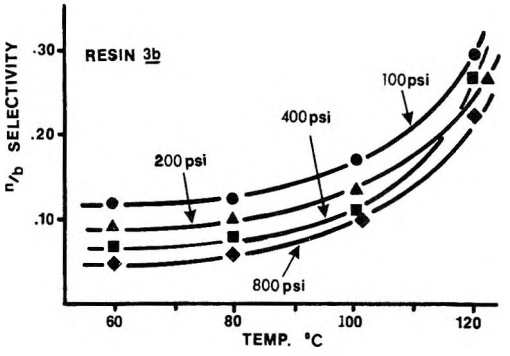


Figure 3. The normal to branched product selectivity as a function of temperature in 2-pentene hydroformylations catalyzed by resin **3b**.

and decreased as the pressure was raised with resin **3a**. Figures 2 and 3 plot selectivity vs. temperature for resins **3a** and **3b** at different pressures. The highest selectivity achieved was n/b = 0.72 using **3a** at 100 psi and 140 °C. This corresponds to a 42% yield of *n*-hexanal from 2-pentene. *Thus, the selectivity to normal product was greater at 140 °C than that reported for $Rh(CO)Cl(PPh_3)_2$ at 200 °C.* Unfortunately, the temperature dependence of selectivity levels off above 120 °C suggesting that further temperature increases will have only a modest effect at raising the n/b ratio.

The terminal selectivity of **3b** in 2-pentene hydroformylations (Table XIII) was lower than that of **3a**. Since excess $Ph_2PCH_2CH_2PPh_2$ suppresses isomerization, the low selectivity of **3b** with its 22% ligand loading and P/Rh = 21 is not surprising. Thus, more internal hydroformylation is expected with **3b**. This agrees with the observation (Table V and VI) that resin **3a** is less selective than **3b** in 1-pentene hydroformylations (i.e., isomerization to 2-pentene plays a larger role when **3a** is the catalyst).

The selectivity of **3b** (Table XIII) is higher than that of its soluble analogue, **1** (Table XI), at the same P/Rh ratio (21:1). For example, 10–20% normal product was obtained using **3b** at 100–120 °C and 100–800 psi despite its excess of ligand (P/Rh = 21). Linear product formation was more effectively suppressed with **1**. This may be attributed to the restricted

Table XIV. Product Distribution (%) as a Function of Conversion in Hydroformylations of 2-Pentene Using Catalyst 3a[a]

Cond	Conv, %	n/b	1-Pentene/ 2-pentene	1-Pentene	2-Pentene	Normal aldehyde[b]	Branched aldehyde[c]
200 psi, 80 °C	7.3	0.59	6/94	5.3	87.4	2.71	4.61
	26	0.52	4/96	3.2	70.5	8.98	17.35
	51	0.47	7/93	3.4	46.0	16.18	34.42
	74	0.46	10/90	2.5	23.6	23.41	50.43
	94	0.51	11/89	0.7	5.4	31.08	62.20
400 psi, 80 °C	35	0.15	0.1/99.9	0.06	64.9	4.46	30.58
	52	0.20	0.5/99.5	0.2	47.4	9.00	43.41
	76	0.16	3/97	0.8	23.6	10.43	65.17
	91	0.14	10/90	0.8	8.0	11.29	79.84

[a] 1-Pentene (1.0 mL, 9.1 mmol), catalyst (0.09 mmol of Rh), benzene (8.0 mL), P/Rh = 21:1, H_2/CO = 1:1. [b] *n*-Hexanal. [c] 2-Methylpentanal and 2-ethylbutanal.

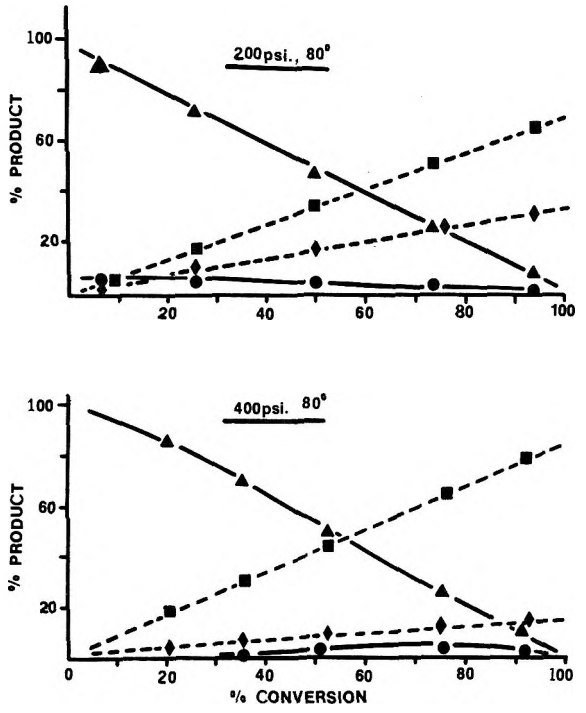


Figure 4. The product distribution as a function of conversion in hydroformylations of 2-pentene catalyzed by resin 3a: (●) 1-pentene, (▲) 2-pentene, (◆) hexanal, (■) 2-methylpentanal.

ligand mobility within the **3b** polymer matrix. At 22% ligand loading, the ligand concentration available to rhodium is lower than that available to the same P/Rh in the homogeneous solutions. This is an example of partial matrix isolation.[27,28]

The rate of 2-pentene hydroformylations decreased as excess 1,2-bis(diphenylphosphino)ethane was added. The rates were often greater using **3b** than using **1** (homogeneous) at P/Rh = 21. Again, this is a manifestation of ligand matrix isolation.

Product distributions as a function of conversion for 2-pentene reactions at 200 and 400 psi are summarized in Table XIV and Figure 4. At 400 psi and 80 °C, the amount of 1-pentene observed never reached 1%. When the pressure was reduced to 200 psi at 80 °C, as much as 5% 1-pentene was detected early in the reaction. However, this level decreased steadily as conversion increased. The n/b ratio was independent of conversion.

Conclusions

Using chelating phosphine ligands in rhodium-catalyzed 1-pentene hydroformylations sharply decreases the n/b selectivity. The isomerization activity is greater with 1,2-bis(diphenylphosphino)ethane (relative to PPh_3). The n/b selectivity is reduced during reaction at the terminal double bond. The hydroformylation activity for internal double bonds is greater using complex **1** than with $RhH(CO)(PPh_3)_3$. Yields of terminal product from 40 to 45% may be obtained from 2-pentene at temperatures from 120 to 140 °C using a polymer-anchored 1,2-bis(diphenylphosphino)ethane complex. However, this system cannot match the high n/b ratios for internal olefins, given by modified cobalt catalysts. For example, $Co_2(CO)_5(PBu_3)_2$ gives as much *n*-heptanal from 2-hexene as from 1-hexene.[29] Slaugh and Millineaux[1] have noted good yields for terminal products with cobalt systems, and Asinger, Fell, and Rupilius[30] found 76% terminal product could be obtained from *trans*-4-octene. Finally, phosphine modified cobalt catalysts, at 190 °C, gave >80% nonanol from 2-octene.[31] The high selectivity of phosphine-modified cobalt catalysts results in part from the higher steric hindrance encountered in the production of branched isomers.

Rhodium complexes of cis-chelating phosphines have a lower regioselectivity for anti-Markownikoff rhodium hydride addition than either phosphine modified cobalt catalysts or $RhH(CO)(PPh_3)_3$. This probably results from the lower steric demand of the cis ligand during rhodium hydride addition.

Experimental Section

Benzene and toluene were dried over CaH_2 for at least 24 h and distilled under nitrogen. Similar care was taken to dry all solvents. Nitrogen, hydrogen, and carbon monoxide were obtained commercially (99 + %) and used as received. $RhH(CO)(PPh_3)_3$ and the bisphosphine ligands ($PPh_2(CH_2)_nPPh_2$, n = 2, 3, and 4) were obtained from Strem or Pressure Chemical Co.

Preparation of $C_6H_5P(H)CH_2CH_2P(C_6H_5)_2$. The title compound was prepared from phenylphosphine and diphenylvinylphosphine sulfide by base-catalyzed addition of $C_6H_5PH_2$ across the vinyl group, followed by $LiAlH_4$ reduction of the sulfide according to the method of King.[32] A 40% yield, bp 210–215 °C (0.2 mmHg), was obtained. The product had an NMR spectrum identical with that reported.[33]

Preparation of Cis-Chelated Resin Catalyst 3. A dry THF solution (100 mL) containing $C_6H_5P(H)CH_2CH_2P(C_6H_5)_2$ (15.7 g, 49 mmol) was added slowly to a suspension of potassium metal (14 g, 359 mmol) in dry THF (100 mL) under nitrogen. A yellow precipitate appeared immediately. Stirring was continued 2 days at 22 °C under nitrogen and unreacted potassium was then removed. The solution was transferred, under nitrogen, to a rapidly stirred THF slurry of brominated styrene–1% divinylbenzene resin beads (6.4 g, 20.78% Br, 34% of rings brominated, 16.6 mg-atoms of bromine per g). This reaction was stirred under nitrogen 72 h and unreacted $KP(C_6H_5)CH_2CH_2P(C_6H_5)_2$ was hydrolyzed in deoxygenated acetone–water (3:1, 1 L). The resin beads were washed successively in 1-L each of the following nitrogen-purged solvents: acetone, water, benzene, and methanol. The beads were dried at 22 °C (0.1 mmHg) for several days. Analysis found 7.71% P which corresponded to 22.2% of the phenyl rings containing a bound $P(C_6H_5)CH_2CH_2P(C_6H_5)_2$ group. Aliquotes of the polymer were then swollen in benzene and reacted with the desired amount of $RhH(CO)(PPh_3)_3$ to effect phosphine exchange. Using various ratios of polymer to $RhH(CO)(PPh_3)_3$, the P/Rh of the resin could be varied. The resulting polymers (i.e., **3a** and **3b**) were

then extracted (soxhlett) with benzene and dried under vacuum. Hydroformylations of 1-pentene or 2-pentene using **3a** or **3b** were carried out as described below.

Hydroformylations of 1-Pentene by Resin-Anchored Catalysts. Hydroformylations were carried out in 150 cm^3 stainless steel pressures bombs (dried at 120 °C overnight and purged with nitrogen while cooling). The resin catalyst (0.09 mmol of Rh) was added with benzene (8 mL) and 1-pentene (1.0 ml, 9.1 mmol). The bomb was cooled (ice bath), pressurized with carbon monoxide (400 psi), and allowed to equilibrate 5 min before venting to atmospheric pressure. This procedure was repeated twice. The bomb was raised to the desired pressure with equal amounts of hydrogen and carbon monoxide (or the appropriate amounts of each in cases where a 1:1 ratio was not used). The bomb was placed in a preequilibrated oil bath and vigorously shaken for the desired reaction time. The reactions were conducted at a constant pressure by connecting the reaction bomb to a gas reservoir via stainless steel tubing (coiled to permit shaking) and a pressure control valve. Thus, the pressure to the bomb remained constant while the pressure in the gas reservoir dropped. Kinetics were easily monitored by measuring the pressure change in the reservoir (known volume) by means of a pressure transducer connected to a recorder. Thus, pressure vs. time plots were directly obtained during the reaction. This system is described elsewhere in detail.[18]

Upon completion, the bomb was cooled and gases were then vented. The reaction solution was quantitatively analyzed by VPC. The resin was recovered (filtration), washed (extracted), and dried under vacuum before being recycled. The products, hexanal and 2-methylpentanal, were isolated by preparative VPC and analyzed by NMR and IR. They were identical with authentic samples. Product yields were routinely obtained by analytical GLC using electronic integration.

Comparison of Homogeneous and Resin-Anchored Catalysts. The polymer-anchored and homogeneously catalyzed reactions were compared using equal solution volumes, equivalent amounts of rhodium, equal 1-pentene/Rh ratios, and the same 1-pentene/benzene ratios. The reactions were always compared at equal temperatures, pressures, P/Rh ratios, and H_2/CO ratios. However, even when conducted this way, they are not completely analogous because the swollen volume of the resin does not fill the entire solution volume. Thus, rhodium and phosphorus are confined to the swollen polymer's volume using anchored-catalysts as opposed to the entire solution volume in homogeneous runs. For this reason, selectivity was directly compared at equivalent "concentrations" in several cases. In one case, where resin **3a** occupied 20% of the reaction solution's volume, the concentration of rhodium in the homogeneous reaction was increased by a factor of five (to 5.0×10^{-2} M HpRh). Now the local concentration of phosphine and rhodium in the resin was quite close to that in the homogeneous reaction. Selectivities did not depend upon the concentration of catalyst at the conditions studied in this paper.

Preparation of $RhH(CO)(PPh_3)(PPh_2CH_2CH_2PPh_2)$, 1. To a 300 mL Schlenk flask (under nitrogen) was added 1.836 g (2 mmol) of $RhH(CO)(PPh_3)_3$, 0.796 g (2 mmol) of $PPh_2CH_2CH_2PPh_2$, and 200 mL of benzene. The reaction mixture was heated to reflux with stirring for 3 days. Then, benzene was evaporated in vacuo and the residue was extracted with hot *n*-hexane followed by drying to give a yellow-grey solid. Anal. Calcd: Rh, 12.98; C, 68.19. Found: Rh, 12.82; C, 68.63.

Acknowledgments. This research was supported in part by the Office of Naval Research and by National Science Foundation Grant No. DMR-73-07545-A01.

Registry No.—1, 64611-33-2; $C_6H_5P(H)CH_2CH_2P(C_6H_5)_2$, 33355-58-7; $BhH(CO)(PPh_3)_3$, 64665-44-7; PPh_3, 603-35-0; $PPh_2(CH_2)_2PPh_2$, 1663-45-2; $PPh_2(CH_2)_3PPh_2$, 6737-42-4; $PPh_2(CH_2)_4PPh_2$, 7688-25-7; $KP(C_6H_5)CH_2CH_2P(C_6H_5)_2$, 64611-28-5; styrenedivinylbenzene polymer, 9003-70-7; 1-pentene, 109-67-1; 2-pentene, 109-68-2.

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(16) Wilkinson[3] demonstrated that $(PPh_3)_3RhH(CO)$ was converted to an equilibrium mixture of $(PPh_3)_2RhH(CO)_2$, $(PPh_3)RhH(CO)_2$, and $[Rh(CO)_2(PPh_3)_2]_2$ in solution in the presence of CO. He then postulated that hydroformylation proceeded through one of two paths, depending on the conditions.[4] In the associative pathway, olefin first coordinates to $(PPh_3)_2RhH(CO)_2$ followed by rapid metal hydride addition across >C=C<. In the dissociative pathway, PPh_3 is lost from $(PPh_3)_2RhH(CO)_2$ giving $(PPh_3)RhH(CO)_2$ which coordinates with olefin fo lowed by fast metal hydride addition. The selectivity is determined in the metal hydride addition step. For both electronic and steric reasons,[4] the dissociative pathway, where $(PPh_3)RhH(CO)_2$ adds across the olefin, is less selective than the associative path where $(PPh_3)_2RhH(CO)_2$ adds across the olefin. At higher phosphine concentrations, Wilkinson[4] postulated (because the equilibrium would favor formation of $(PPh_3)_2RhH(CO)_2$) that the associative pathway was increasingly favored, thus accounting for the increased selectivity at high phosphine concentrations. The associative pathway may be criticized for requiring a 20-electron intermediate unless it is viewed as a direct rhodium hydride addition to an uncoordinated olefin.
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Neighboring Group Participation in the Conversion of β-Substituted Ethanesulfonate Salts to β-Substituted Ethanesulfonyl Chlorides

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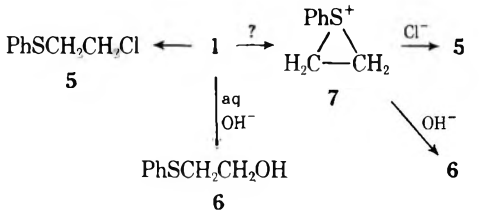
Reaction of the sulfonate **1** with either PCl_5, $POCl_3$, or $SOCl_2$ proceeds with desulfonation to give chloride **5** rather than the expected sulfonyl chloride **2**. This is in contrast to the results from similar reactions with the analogous β-substituted sulfonates containing neighboring bromine, oxygen, and sulfone groups which give the sulfonyl chlorides, e.g., **3**, **4**, and **9**, respectively. When **10** is reacted with $SOCl_2$, desulfonation occurs and a 60% distilled yield of a 41:59 mixture of the isomeric chlorides **15** and **16**, respectively, is obtained. One may infer that the sulfonium ion **11** is the intermediate which leads to **15** and **16**. Desulfonation of **1** also occurs in poor yield upon prolonged boiling in aqueous sodium hydroxide.

In connection with other studies, we attempted to convert the sulfonate **1** to the sulfonyl chloride **2** using reactions and conditions previously employed to successfully prepare similar β-substituted ethanesulfonyl chlorides, e.g., **3** and **4**.[2,3] However, the only product obtained upon treatment of **1** with either phosphorus pentachloride, phosphorus oxychloride, or thionyl chloride was **5**, the product of desulfonation.[4] Furthermore, upon heating **1** to reflux in aqueous sodium hydroxide, desulfonation occurred, giving the alcohol **6** in poor yield.

$PhSCH_2CH_2SO_3^-Na^+$ (**1**) $PhSCH_2CH_2SO_2Cl$ (**2**)

$BrCH_2CH_2SO_2Cl$ (**3**) $PhOCH_2CH_2SO_2Cl$ (**4**)



Since the driving force for neighboring-group participation is known to be greater for sulfur than for oxygen or bromine,[5,6] we suspected involvement by the β-phenylthio group and intermediacy of the sulfonium ion **7** in the desulfonation reactions of **1**.

If nucleophilic participation by sulfur is occurring during the chlorination reaction of **1**, this participation should be absent in the chlorination of the corresponding sulfone. When **8** was subjected to the chlorination procedure, no abnormality in its conversion to **9** was observed.

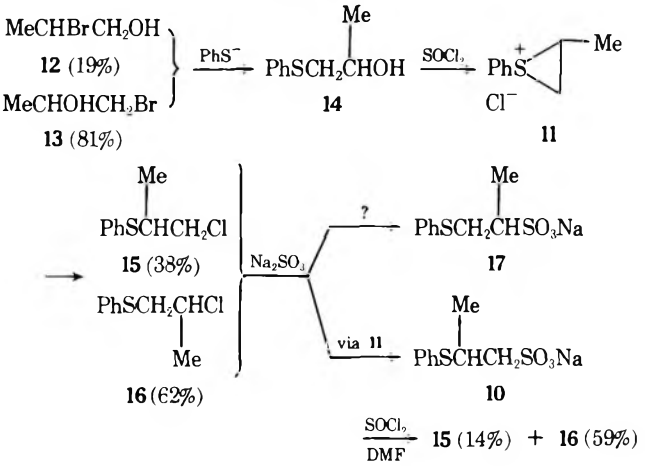
$$PhSO_2CH_2CH_2SO_3^-Na^+ \xrightarrow{SOCl_2} PhSO_2CH_2CH_2SO_2Cl$$

8 **9**

To ascertain whether or not the sulfonium ion **7** is an intermediate in the reactions of **1** discussed above, it was decided to subject the sulfonate **10** to the chlorination reaction. The sulfonate **10**, which would provide an unsymmetrical cyclic sulfonium ion, i.e., **11**, was prepared according to the sequence of reactions shown in Scheme I.[7]

Reaction of thiophenoxide with the commercially available mixture of bromohydrins **12** and **13** afforded a single β-phenylthio alcohol **14** (see Experimental Section) owing to the greater relative reactivity of the primary bromide **13**.[8,9]

Scheme I



Chlorination of the secondary alcohol **14** proceeded, not unexpectedly,[6,10] with sulfur participation and gave a mixture of the chlorides **15** and **16** from ring opening of the sulfonium ion **11**.

Mueller and Butler[11] have shown that in methylene chloride at −75 °C the sulfonium ion **11** undergoes attack by chloride ion to give a 68:32 mixture of **15** and **16**, respectively. On standing at ambient temperature, the mixture of **15** and **16** equilibrated, presumably via **11**, giving a **15**/**16** ratio of 15:85. Thus, **15** is favored kinetically, while **16** is thermodynamically the more stable. Although the mixture of **15** and **16** which formed from **14** cannot be directly compared to the Mueller–Butler results, it seems reasonable to assume that the **15**:**16** ratio is approaching the thermodynamic composition for the conditions employed.

Reaction of the mixture of chlorides **15** and **16** with sodium sulfite allowed the isolation of the sodium sulfonate salt, which is assigned structure **10** on the assumption that it is formed in a kinetically controlled process from **11**.[12–14] Analysis of the sodium sulfonate salt by TLC on silica gel and on neutral alumina revealed a single spot, although a shoulder on the methyl doublet in the NMR spectrum suggests the possibility of 10–15% of the isomer **17**. Upon refluxing a dry benzene suspension of **10** with an excess of thionyl chloride and a catalytic amount of dimethylformamide,[15] concentrating in vacuo, and distilling the residue, a 60% yield of a 41:59 mixture of the chlorides **15** and **16**, respectively, was obtained. This ratio of the chlorides is similar to that obtained on conversion of **14** to **15** and **16**, further suggesting the approach to equilibrium.

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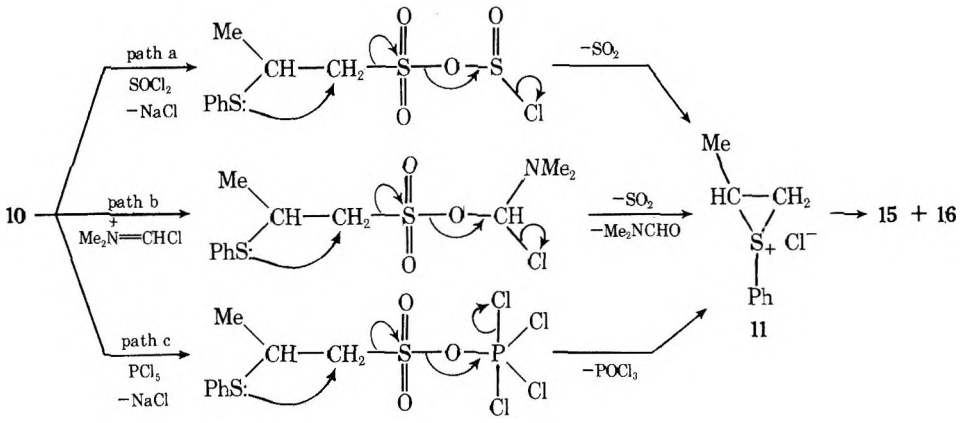
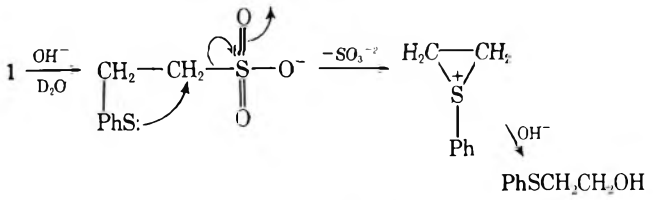
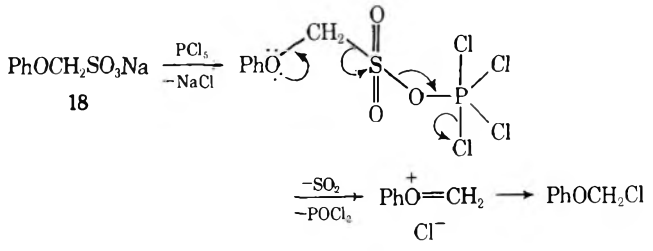
Scheme II



Scheme III



Scheme IV



It is interesting to consider possible mechanisms for the sulfite group-displacement reactions. The sulfonate group is known to be an excellent nucleophile,[16] but neither it nor the chlorosulfonyl group is generally treated among common leaving groups.[17] Since the sulfite group would presumably need activation for displacement in benzene, path a in Scheme II represents a mechanism which is consistent with the experimental data and is similar to the mechanism for other displacement reactions involving thionyl chloride.[18] Paths b and c are similar pathways for the Zollinger reagent[15] and phosphorus pentachloride.[19]

Because of the greatly different reaction conditions, the sluggish displacement of the sulfite group from **1** by hydroxide ion most likely involves the loss of the solvated sulfite group with no SO_2 evolution, Scheme III. The forcing conditions and the aqueous medium make loss of sulfite a relatively more facile process than the loss of sulfite ion (as SO_3^{-2}) from **10** with thionyl chloride in benzene.

Although there is no other known example of β participation in a desulfonation reaction, an apparently analogous reaction occurs on attempted chlorination of aryloxymethanesulfonic acids or their salts.[20] The parent salt **18**, for example, reacts readily with phosphorus pentachloride or thionyl chloride at room temperature and sulfur dioxide is eliminated. The probable driving force for this reaction is formation of the resonance-stabilized intermediate (Scheme IV).

Participation by the thioether group in these desulfonation reactions is, thus, additional evidence of this group's superiority relative to other similar neighboring groups when three-membered ring formation is involved.[5,6] Although we did not explore the conversion of the nitrogen derivative analogous to **1**, it seems likely, based on the relatively high tendency for nitrogen participation,[5,6] that it might undergo desulfonation upon chlorination.

Experimental Section

Melting points are uncorrected. Infrared spectra were determined on a Beckman Acculab I spectrometer, the NMR spectra on a Bruker HFX-10 90-MHz spectrometer using tetramethylsilane as an internal standard, and the refractive indexes on a Bausch and Lomb Abbe 3L refractometer. Elemental analyses were determined either by the Analytical Services Laboratory of the Department of Chemistry, The University of Alabama, Tuscaloosa, or by Galbraith Laboratories, Inc., Knoxville, Tenn.

Sodium 2-Phenylthioethanesulfonate (1). 2-Phenylthioethyl chloride[21] (100 g, 0.579 mol) was added to anhydrous sodium sulfite (100 g, 1.26 mol) in water (750 mL). The solution was boiled under reflux for 48 h and then cooled to room temperature to yield white platelets of the salt (125 g, 90.0%): mp >260 °C; IR (KBr) 1180 (γ_{as} SO_2), 1045 cm^{-1} (γ_{sym} SO_2); NMR (D_2O), δ 7.56 (m, 5 H, ArH), 3.52 (m, 4 H, SCH_2CH_2)

Anal. Calcd for $C_8H_9NaO_3S_2$: C, 40.00; H, 3.78. Found: C, 40.13; H, 3.90.

Reaction of Sodium 2-Phenylthioethanesulfonate (1) with Phosphorus Pentachloride. Phosphorus pentachloride (15 g, 72 mmol) was ground with **1** (22.5 g, 93.7 mmol) in a mortar. The solid reacted after a few seconds with gas evolution to yield a pasty liquid, which was poured into water (400 mL) and extracted with chloroform (3 × 70 mL). The organic layer was washed with sodium bicarbonate (5%, 3 × 100 mL) and water (2 × 150 mL), dried ($MgSO_4$), and concentrated in vacuo to leave a yellow oil that was distilled to yield 2-phenylthioethyl chloride (**5**) (12.5 g, 77.3%) which was identical with a sample prepared by the method of Ford-Moore et al.:[21] bp 95–97 °C (2 mm); $n^{21}D$ 1.5837; IR (film) 3060, 3010, 2970, 1580, 1475, 1435, 1370, 1295, 1270, 1205, 1160, 1115, 1080, 1060, 1020, 990, 850, 725, and 675 cm^{-1}; NMR ($CDCl_3$) δ 7.43 (m, 5 H, ArH), 3.67 (m, 2 H, CH_2Cl), 3.21 (m, 2 H, SCH_2).

In a separate experiment the phosphorus pentachloride was replaced by thionyl chloride in benzene with dimethylformamide as a catalyst;[15c] after a 24-h reflux period, **1** was converted to **5** in 13% yield.

Phenyl 2-Chloroethyl Sulfone. 2-Phenylthioethyl chloride[21] (8.50 g, 49.2 mmol) was added in one portion to glacial acetic acid (35 mL) containing 30% hydrogen peroxide (15 mL) and boiled under reflux for 0.5 h. Cold water (150 mL) was added to the reaction mixture to yield white platelets of the sulfone (6.00 g, 59.6%): mp 52 °C (from ethanol) (lit.[21] mp 52 °C); IR (KBr) 1315 (γ_{as} SO_2), 1140 cm^{-1} (γ_{sym} SO_2).

Sodium 2-Phenylsulfonylethanesulfonate (8). Phenyl 2-chloroethyl sulfone (5.00 g, 24.4 mmol) was boiled under reflux for 12 h with anhydrous sodium sulfite (6.20 g, 48.8 mmol) in water (40 mL). The reaction mixture was filtered and cooled to yield white crystals of the salt (6.60 g, 99.2%): mp >250 °C; IR (KBr) 1285 (γ_{as} SO_2), 1175 (γ_{as} SO_3Na), 1140 (γ_{sym} SO_2), 1030 cm^{-1} (γ_{sym} SO_3Na); NMR (D_2O) δ 7.56 (m, 5 H, ArH), 3.52 (m, 4 H, $CH_2CH_2SO_3Na$). The salt was used to prepare **9** without further purification.

2-Phenylsulfonylethanesulfonyl Chloride (9). Thionyl chloride (19.9 g, 167 mmol) was added dropwise to sodium 2-phenylsulfonylethanesulfonate (5.00 g, 18.4 mmol) in benzene (100 mL) containing dimethylformamide (10 drops) over a 1-h period. The solution was boiled under reflux for 14 h and then evaporated to dryness in vacuo.

The crude product was recrystallized three times from chloroform to yield white needles of the sulfonyl chloride (2.76 g, 55.8%): mp 173 °C; IR (KBr) 1405 (γ_{as} SO_2Cl), 1350 (γ_{as} SO_2), 1215 (γ_{sym} SO_2Cl), 1135 cm^{-1} (γ_{sym} SO_2); NMR ($CDCl_3$) δ 7.87 (m, 5 H, ArH), 4.07 (m, 2 H, $CH_2CH_2SO_2Cl$), 3.72 (m, 2 H, $CH_2CH_2SO_2Cl$).

Anal. Calcd for $C_8H_9ClO_4S_2$ C, 35.76; H, 3.38. Found: C, 35.99; H, 3.33.

Hydrolysis of (1). Compound 1 (10.0 g, 41.7 mmol) was added to sodium hydroxide (2.50 g, 62.5 mmol) in water (20 mL) at 90 °C and stirred at that temperature for 48 h. The reaction mixture was cooled to 5 °C and the white precipitate was recrystallized from acetone to give 1 (1.08 g) identical (IR spectrum) with starting material. Water (150 mL) was added to the above liquor, and the solution was acidified (6 N HCl) and extracted with ether (7 × 50 mL). The extract was dried ($MgSO_4$) and concentrated in vacuo to yield an oil, identified by comparison of its IR and GLC retention time (6 ft × 0.25 in. column of 10% OV-17 on Gas Chrom Q, 225 °C) with an authentic sample, as 2-phenylthioethanol (1.25 g, 19.5%).

1-Phenylthio-2-propanol (14). A 19:81 mixture of 2-bromo-1-propanol **12** and 1-bromo-2-propanol **13**, respectively (Eastman Yellow Label) (65.3 g, 470 mmol), was added dropwise to a solution of thiophenol (51.7 g, 470 mmol) and sodium hydroxide (19.0 g, 475 mmol) in water (180 mL). The solution was boiled under reflux for 48 h, the organic layer was then separated, and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic and ether layers were concentrated in vacuo and the crude product was distilled to yield **14** (59.0 g, 74.5%) which proved to be a single isomer (>99%) by GLC: bp 105–106 °C (0.6 mm); n^{25}_D 1.5700; IR (film) 3360, 3080, 2980, 2920, 1580, 1480, 1440, 1120, 1060, 1010, 930, 730, 680 cm^{-1}; NMR ($CDCl_3$) δ 7.33 (m, 5 H, ArH), 1.28 (d, J = 6.5 Hz, 3 H, $CHCH_3$), 3.87 (br m, 1 H, $CH_2CHOHCH_3$), 3.11 (d, J = 13 Hz, of d, J = 4 Hz, 1 H, $HCHCHOHCH_3$), 2.84 (d, J = 13 Hz, of d, J = 8 Hz, 1 H, $HCHCHOHCH_3$), 2.58 (s, 1 H, OH).

Anal. Calcd for $C_9H_{12}OS$: C, 64.25; H, 7.19. Found: C, 64.40; H, 7.19.

1-Chloro-2- (15) and 2-Chloro-1-phenylthiopropane (16). Thionyl chloride (124 g, 1.04 mol) was added dropwise to **14** (51.7 g, 308 mmol) in benzene (250 mL) and then the mixture was boiled under reflux for 14 h. The solvent was removed in vacuo and the crude product distilled to yield a 38:62 mixture (as determined by NMR) of **15** and **16**, respectively (46.0 g, 80.2%): bp 98 °C (1.0 mm); n^{25}_D 1.5645; IR (film) 3080, 2980, 2940, 2860, 1580, 1480, 1440, 1380, 1270, 1180, 1090, 1030, 1010, 730, 690 cm^{-1}; NMR ($CDCl_3$) δ 1.66 (d, relative area 62, $CH_2CHClCH_3$), 1.48 (d, relative area 38, $CHCH_3CH_2Cl$), 2.95–3.90 (m, 2 H, CH_2 from **15** and **16**), 3.90–4.20 (m, 1 H, CH from **15** and **16**), 7,33 (m, 5 H, ArH from **15** and **16**).

Anal. Calcd for $C_9H_{11}ClS$: C, 57.90; H, 5.94. Found: C, 58.04; H, 5.96.

Sodium 2-Phenylthiopropanesulfonate (10). A 38:62 mixture of **15** and **16**, respectively (43.0 g, 231 mmol), was added to a solution of anhydrous sodium sulfite (62.0 g, 492 mmol) in water (150 mL) and boiled under reflux for 64 h. The reaction mixture was filtered hot and cooled to 0 °C to deposit white platelets, which were dried in vacuo to yield mainly **10** (21.6 g, 36.9%): mp > 260 °C; IR (KBr) 1180 (γ_{as} SO_3Na), 1060 cm^{-1} (γ_{sym} SO_3Na); NMR (D_2O) δ 7.78 (m, 5 H, ArH), 4.06 (br m, 1 H, CH_3CHCH_2), 3.69 (d, J = 14 Hz, of d, J = 5 Hz, 1 H, HCHCHMeSPh), 3.36 (d, J = 14 Hz, of d, J = 5 Hz, 1 H, HCHCHMeSPh), 1.83 (d, J = 6.5 Hz, 3 H, $CHCH_3$), 1.79 (shoulder).

Anal. Calcd for $C_9H_{11}O_3S_2Na$: C, 42.51; H, 4.36. Found: C, 42.49; H, 4.44.

Reaction of Sodium 2-Phenylthio-1-propanesulfonate (10) with Thionyl Chloride. Thionyl chloride (66.2 g, 556 mmol) was added dropwise to a stirred mixture of **10** (18.5 g, 72.8 mmol) in dry benzene (200 mL) containing dimethylformamide (10 drops). The mixture was boiled under reflux for 24 h, concentrated in vacuo, and distilled to yield a 41:59 mixture of **15** and **16**, respectively (8.2 g, 60%): bp 100–102 °C (3 mm); n^{25}_D 1.5645; IR (film) 3080, 2980, 2940, 1585, 1480, 1440, 1375, 1270, 1180, 1090, 1060, 1025, 1010, 750 and 680 cm^{-1}; NMR ($CDCl_3$) δ 1.66 (d, relative area 59, $CH_2CHClCH_3$), 1.47 (d, relative area 41, $CHCH_3CH_2Cl$).

Anal. Calcd for $C_9H_{11}ClS$: C, 57.90; H, 5.94. Found: C, 58.04; H, 5.77.

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Registry No.—**1**, 64440-79-5; **5**, 5535-49-9; **8**, 64440-80-8; **9**, 64440-81-9; **10**, 64440-82-0; **12**, 598-18-5; **13**, 19686-73-8; **14**, 937-56-4; **15**, 19826-03-0; **16**, 5877-11-2; PCl_5, 10026-13-8; $SOCl_2$, 7719-09-7; phenyl 2-chloroethyl sulfone, 938-09-0.

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The Phenylseleno Neighboring Group. Solvolysis of 2-Phenylselenoethyl Chloride

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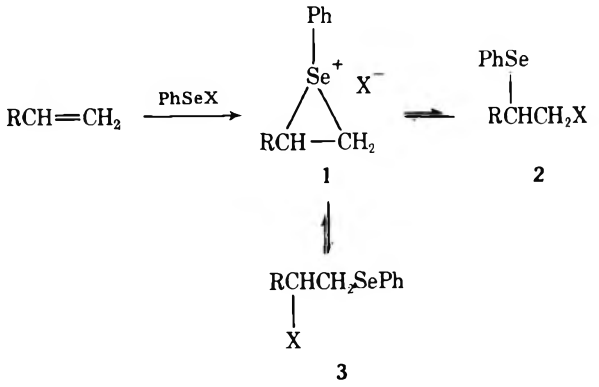
Solvolysis of 2-phenylselenoethyl chloride is an anchimerically assisted reaction in methanol and in aqueous ethanol. While the selenium compound is only some five times faster than the analogous sulfur derivative in methanol, selenium participation is extraordinarily efficient in aqueous ethanol. The Grunwald–Winstein *m* value for the aqueous ethanolysis of 2-phenylselenoethyl chloride was found to be 0.40, which is typical of nucleophilically assisted reactions. Furthermore, with decreasing solvent ionizing power the calculated enthalpy and entropy of activation become less positive and more negative, respectively. This is discussed.

The ease of formation[2-8] of β-phenylselenoalkyl halides, esters, alcohols, and ethers and the synthetic utility[6-13] of the intermediate selenides have attracted considerable recent interest. A semiquantitative study[13] of the ease of rearrangement of the kinetic addition products **2** to the thermodynamic products **3**, presumably via the seleniranium ions **1**,



R = H or alkyl
X = Cl, Br, acetate, or trifluoroacetate

has appeared, and the thermal and solvolytic instability of secondary β-phenylselenoalkyl halides has been noted.[7] We now present the results of the first quantitative study of the reactivity of such compounds and compare the neighboring group effects of sulfur and selenium.

First-order rate constants were measured conductometrically for the solvolysis in aqueous ethanol and in methanol of phenylselenoethyl chloride (**2**, R = H, X = Cl). The results of these studies are summarized in Table I and comparisons with analogous studies with sulfur compounds[14,15] are shown in Table II.[16,17]

Divalent sulfur groups are well known for their tendency to nucleophilically participate in solvolysis reactions.[18] Furthermore, sulfur neighboring group participation is especially facile when three-membered rings result.[18,19] Since intramolecular nucleophilicity parallels intermolecular nucleophilicity (e.g., I > Br > Cl and RS > RO[18,20,21]) one would predict that the phenylseleno group should be superior to the highly efficient phenylthio neighboring group.[23] In fact, this trend does indeed occur, and phenylselenoethyl chloride is found to be the most reactive primary chloride known when those which ionize with resonance stabilization are excluded. Obviously, this high degree of reactivity is the result of nucleophilic participation by selenium.

The solvolyses of **2** (R = H, X = Cl) are found to be mildly dependent on solvent. A plot of log *k* vs. Grunwald–Winstein *Y* values for the aqueous ethanolyses (25 °C) gives an *m* value of 0.40 (see Figure 1), which is typical of nucleophilically assisted reactions.[18] We also note that the enthalpy and entropy of activation are becoming less positive and more negative, respectively, with decreasing ionizing power. Thus, in poorly ionizing solvents, such as methanol, solvolysis rates are not greatly affected by a temperature change. Furthermore, since the same trend does not occur with the sulfur compounds,[24] there is a great difference in relative reactivities as the solvent is changed (see Table II).

Although strongly anchimerically assisted reactions are generally assumed not be nucleophilically solvent assisted,[25] a recent theory by McEwen et al.[22,25] explaining enhanced nucleophilicity of certain organophosphorus and organoarsenic compounds suggests a possible explanation for the observed trends in these solvolyses. According to the McEwen theory, solvent could nucleophilically assist the neighboring group as shown in Figure 2. If this type of solvent participation occurs, the reactions would be sensitive to solvent ionizing

Table I. Solvolysis Data for 2-Phenylselenoethyl Chloride

Solvent	$k \times 10^4$, s^{-1}	Temp., °C	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
50E[a]	22.1 (±0.8)	25.6		
70E[a]	1.12 (±0.05)	0.0		
	8.13[b]	25.0	12.3	−31.4
	8.55 (±0.77)	25.6		
80E[a]	0.880 (±0.098)	0.0		
	5.52[b]	25.0	11.3	−35.6
	5.80[c]	25.0		
	7.14[c]	27.7		
	10.2 (±1.4)	35.0		
90E[a]	2.25 (±0.06)	25.2		
MeOH	0.670 (±0.011)	0.0		
	2.94[b]	25.0	8.98	−44.6
	4.54 (±0.11)	32.8		
	6.32 (±0.43)	40.3		

[a] Percent (v/v) aqueous ethanol; 80E = 80% EtOH. [b] Calculated using the experimentally determined $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. [c] Only one kinetic determination at this temperature.

Table II. Relative Rates of Solvolysis at 25 °C

Substrate	Solvent	Relative rate
$PhSCH_2CH_2Cl$	MeOH	1.00[a,b]
$PhSeCH_2CH_2Cl$	MeOH	4.98[a]
p-$MeC_6H_4SCH_2CH_2Cl$	80% EtOH (w/w)	1.00[a,c]
$PhSeCH_2CH_2Cl$	80% EtOH (w/w)	216[d]

[a] Calculated using extrapolated rates. [b] Using $\Delta H^{\ddagger}$ = 17.29 kcal mol^{-1} and $\Delta S^{\ddagger}$ = −19.90 eu, see ref 16; rate data from ref 14. [c] Using $\Delta H^{\ddagger}$ = 17.83 kcal mol^{-1} and $\Delta S^{\ddagger}$ = −24.31 eu, see ref 16; rate data from ref 15. [d] Rate data extrapolated from *mY* plot assuming 80% EtOH (w/w) = 83.4% EtOH (v/v).

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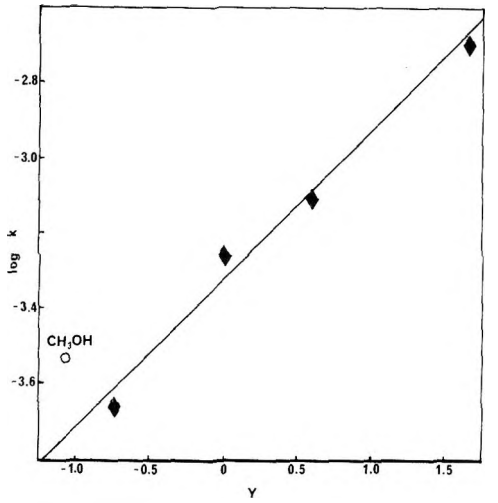

Figure 1. Grunwald–Winstein plot for the aqueous ethanolysis of 2-phenylselenoethyl chloride at 25 °C. The open circle (O), for the methanolysis reaction, is not included in the least-squares plot.

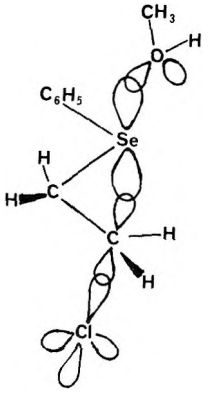

Figure 2. A possible transition state for the anchimerically assisted methanolysis of 2-phenylselenoethyl chloride with nucleophilic solvent assistance. Other geometries are possible.

power *and* solvent nucleophilicity instead of ionizing power alone.[27] That the methanol rate is significantly faster than that which is predicted from the Grunwald–Winstein plot (see Figure 1) seems to suggest that some factor other than ionizing power may be important. Furthermore, one would expect that the involvement of solvent as shown in Figure 2 would be accompanied by a substantial negative entropy of activation. As the solvent is changed toward the highly nucleophilic and poorly ionizing end of the spectrum, one would expect a trend toward more negative $\Delta S^{\ddagger}$ values; this is observed in the solvolyses of phenylselenoethyl chloride. The interesting proposal of solvent assistance of the type shown in Figure 2 is a subject on which we hope to comment at a later date.

Because the measured rates and the comparisons reported in Table II are probably affected by ion pairing phenomena, we have initiated studies of derivatives which will allow for the measurement of ionization rates corrected for ion pair return.

Experimental Section

Preparation and Purification of Chemicals. Methanol. Absolute methanol was distilled from magnesium methoxide as described by Lund and Bjerrum.[28]

Ethanol. Absolute ethanol was distilled from magnesium ethoxide as described by Lund and Bjerrum.[28] Aqueous ethanol for the kinetic measurements was prepared by mixing volume quantities of freshly distilled absolute ethanol with deionized water.

2-Phenylselenoethyl Chloride. Phenylselenenyl chloride (Aldrich) was reacted with ethylene according to the procedure of Kataev et al.[2] giving a quantitative yield of 2-phenylselenoethyl chloride which, after distillation, had physical properties and spectral properties consistent with those reported.[2]

Kinetic Method. Rates were determined conductometrically with a Beckman Model PC-18A impedence bridge capable of 0.1% accuracy. The conductivity cells had platinized electrodes, cell constants of 0.2–0.4, and a solution capacity of approximately 25 mL. Typically, solutions of 10^{-3} M were used for kinetic measurements. When temperatures other than ambient were employed, the solvent was preconditioned to the desired temperature for at least 0.1 h and, after addition of the substrate, the solutions were conditioned at the desired temperature for at least 5 min prior to recording the conductance. The raw conductance data, consisting of approximately 12 readings at intervals, were fitted to the first-order rate equation by means of the least-squares computer program (LSKIN) developed by Professor D. F. DeTar.

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Registry No.—2-Phenylselenoethyl chloride, 50630-24-5.

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(17) Rate data for the analogous sulfur compounds were also available for solvolysis in 20 mol % dioxane. Unfortunately, the selenium derivative was not soluble enough in this solvent to allow reliable kinetic runs.
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(19) C. J. M. Stirling, *J. Chem. Educ.*, **50**, 844 (1973).
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(22) W. E. McEwen, J. E. Fountaine, D. N. Schulz, and W.-I. Shiau, *J. Org. Chem.*, **41**, 1684 (1976).
(23) S. P. McManus, M. R. Smith, F. T. Herrmann, and R. A. Abramovitch, *J. Org. Chem.*, **43**, preceding paper in this issue (1978).
(24) There is no established trend, e.g., see footnotes *b* and *c* in Table II.
(25) See ref 18, chapters 1 and 3.
(26) W. E. McEwen, W.-I. Shiau, Y.-I. Yeh, D. N. Schulz, R. U. Pagilagen, J. B. Levy, C. Symmes, Jr., G. O. Nelson, and I. Granoth, *J. Am. Chem. Soc.*, **97**, 1787 (1975).
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Syntheses of Diaza-, Azaoxa-, Diazaoxa-, and Triazasulfonium Ions

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Methods for synthesizing diaza-, azaoxa-, diazaoxa-, and triazasulfonium tetraphenylborates were described, and some of their reactivities were discussed.

Sulfonium ions substituted by heteroatoms are of considerable interest, and aza-, oxa-, and thiasulfonium ions have been studied to a great extent.[1] Only a few studies, however, have been carried out on diaza-, azaoxa-, diazaoxa-, and triazasulfonium ions. Syntheses of these sulfonium ions have been investigated in our laboratories, and the results are described in this paper.

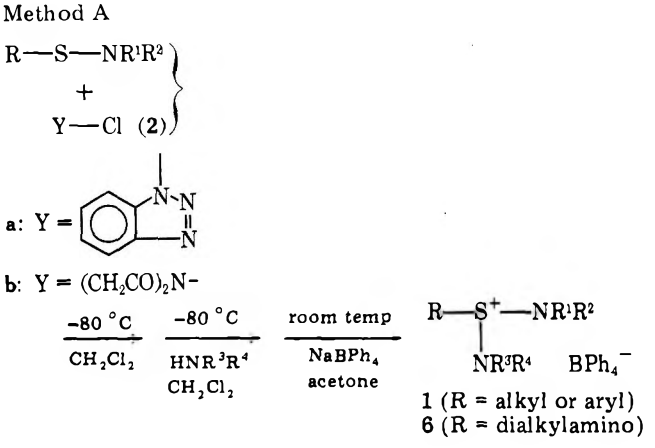
Results and Discussion

Diazasulfonium Ions. Richards and Tarbell prepared ethyldimorpholinosulfonium tetrafluoroborate by the reaction of dimorpholino sulfide and triethyloxonium tetrafluoroborate.[2] They stated, however, that "numerous other alkylation reactions of amine sulfides with a variety of alkylating agents did not yield isolable products". We also examined reactions of various alkylating agents and various diamino sulfides, but none of our attempts yielded diazasulfonium salts. Thus, alkylations of diamino sulfides cannot be a general method for preparing diazasulfonium salts.

Johnson, Bacon, and Kingsbury prepared azasulfonium salts by the treatment of sulfides with 1-chlorobenzotriazole followed by the addition of amines and silver tetrafluoroborate.[3] Vilsmaier and Sprügel synthesized azasulfonium salts from sulfides, *N*-chlorosuccinimide, and amines.[4] In view of these reactions, treatments of sulfenamides with *N*-halo compounds and then with amines were investigated as a possible method for the synthesis of diazasulfonium salts.

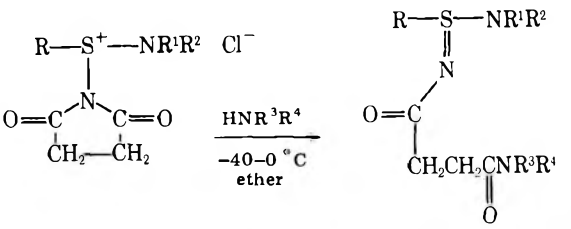
It was found that diazasulfonium salts **1a–f** summarized in Table I were successfully prepared by the treatment of an alkane or arene sulfenamide with 1-chlorobenzotriazole (**2a**) or *N*-chlorosuccinimide (**2b**) in dichloromethane followed by the addition of a secondary amine at −80 °C and the addition of sodium tetraphenylborate (**3**) at room temperature.

Method A



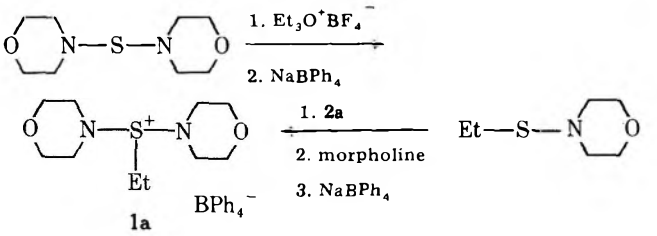
Although both **2a** and **2b** are effective for oxidation of sulfides, yields are higher when **2a** is used (yields of **1b** with **2a**, 65%; with **2b**, 51%).

After our work was completed, Haake and Benack reported in a communication that, when a suspension of an adduct formed from a sulfenamide and **2b** was treated in ether between −40 and 0 °C with 2 equiv of a secondary amine (morpholine or diethylamine), no displacement of succinimide was detected and the succinimide ring was always opened, forming sulfinamidine derivatives in 67–89% yields.[5]



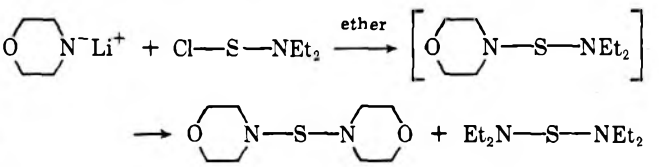
It is of interest that a slight difference in the reaction conditions results in the formation of different product. It is possible that the lower yields of **1** observed by use of **2b** in our system are due to concurrent occurrence of the ring opening, but only the crystalline products were isolated and products of side reactions were not determined.

In order to compare **1a** prepared by method A with the salt prepared by Richards and Tarbell,[2] we treated dimorpholino sulfide with triethyloxonium tetrafluoroborate and exchanged the anion of the salt with BPh_4^-. The ^1H NMR spectra and the melting points showed that these two salts were identical.



When diphenylamine was allowed to react with a mixture of *N*-methanesulfenylpiperidine and **2a** at −80 °C and then **3** was added, the product isolated was a diaminosulfonium ion containing no diphenylamine moiety and was found to be **1c** (25% yield). Apparently, the weakly nucleophilic diphenylamino group cannot react with the intermediate, which decomposed upon warming and yielded **1c**.

When two dialkylamino groups of **1** are different, such sulfonium ions are chiral. If chiral **1** is to be prepared by alkylation of diamino sulfides, one must have diamino sulfides possessing two different amino groups. Harpp and Back[6] attempted to prepare such sulfides from the reaction of a dialkylamino phthalimido sulfide and another dialkylamine, but they obtained two kinds of symmetric diamino sulfides, presumably formed by disproportionation of the expected product. We attempted to prepared diethylamino morpholino sulfide from the reaction of diethylaminosulfenyl chloride and lithium morpholide in ether. However, during the process of



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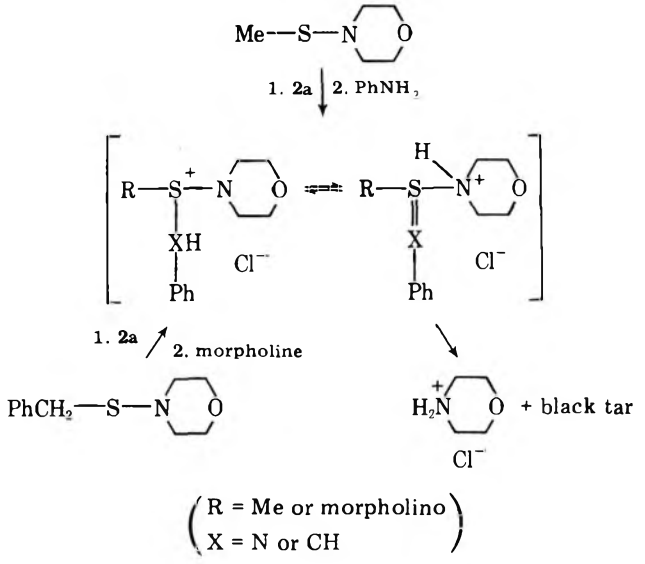
purification, disproportionation proceeded, and it was not possible to isolate the pure sulfide.

However, when one uses method A for the preparation of 1 from sulfenamides, **2**, and secondary amines, diazasulfonium ions possessing two different amino groups (such as **1d–f**) can readily be prepared. By use of optically active anions, it would be possible to resolve them.

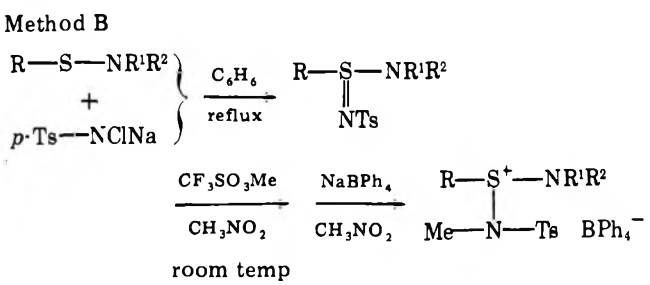
In an attempt to prepare an aminosulfilimine, aniline was added to a mixture of *N*-methanesulfenylmorpholine and **2a** at −80 °C. The color of the solution changed from pale yellow to orange, to deep red, and finally to black, and morpholinium chloride precipitated almost quantitatively. The anilino proton in the anilinomorpholinosulfonium ion appears to be quite labile.

In an attempt to prepare a diazasulfonium ylide, the synthesis of benzyldimorpholinosulfonium ion was investigated. However, as soon as morpholine was added to a mixture of *N*-(phenylmethanesulfenyl)morpholine and **2a** at −80 °C, morpholinium chloride precipitated. The benzyl protons in the benzylmorpholinosulfonium ion formed appear to be quite labile. These results show that diazasulfonium ions tend to decompose when they have labile α protons.



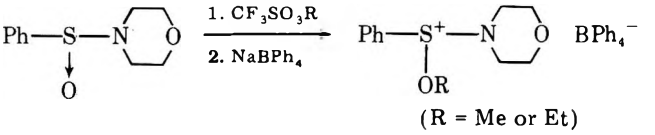
The reactivities of diazasulfonium ions were investigated by allowing an equimolar mixture of **1b**, dimsyl sodium, and benzophenone to react in dimethyl sulfoxide for 1 h at 50 °C. The product formed was *N*-methanesulfenylmorpholine, and no products indicative of the formation of a ylide were found. Richards and Tarbell[2] reported similar results in the reaction of ethyldimorpholinosulfonium tetrafluoroborate with butyllithium. When 1 was mixed with sodium methoxide in methanol at −40 °C and warmed up to room temperature, no reaction took place.

Another possible route for the preparation of a diazasulfonium ion is the methylation of an aminosulfilimine. Johnson et al. prepared an azasulfonium ion by methylation of a sulfilimine.[7] When an equimolar mixture of *N*-*p*-toluenesulfenylmorpholine and chloramine-T was refluxed in benzene,

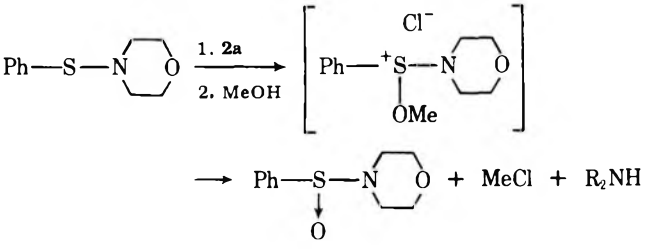


the corresponding sulfilimine was produced, which was treated with methyl trifluoromethanesulfonate and **3**. The corresponding diazasulfonium salt (**1g**) was obtained.

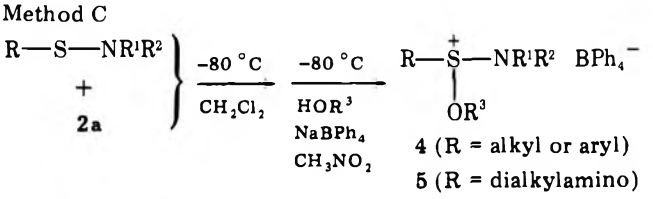
Azaoxasulfonium Ions. The azaoxasulfonium salt formed by the reaction of *N*-*p*-toluenesulfinylpyrrolidine and methyl triflate was stable only in methyl triflate, but those prepared by the treatment of *N*-benzenesulfinylmorpholine with methyl or ethyl triflate and **3** were isolable as stable high-melting crystals.[8] However, this alkylation method worked only when the amine group in sulfinamides was a cyclic secondary amine (morpholine or pyrrolidine) and R was methyl or ethyl. Thus, it is desirable to find a method which is generally applicable.



When methanol was added to a mixture of *N*-*p*-toluenesulfenylmorpholine and **2a** at −80 °C and then the solution was warmed up to room temperature, the following products were found. Since the reactions of alkoxymorpholinosulfonium ions with nucleophiles (methyl sulfide and tertiary amines) were exclusively the dealkylation from the alkoxy groups,[8] the above results are most reasonably explained by assuming the formation of methoxymorpholino-*p*-tolylsulfonium ion, which is attacked by chloride ion at the methyl carbon.



However, when **3** was added together with ROH to a mixture of a sulfenamide and **2a** at −80 °C, the anion was exchanged *at −80 °C* with tetraphenylborate ion which possesses no nucleophilicity, and the corresponding azaoxasulfonium salt was successfully isolated. The azaoxasulfonium salts (**4**) prepared are listed in Table I. This method appears to be applicable to various alcohols. It was possible to prepare **4d** from menthyl alcohol. This method was also applicable to phenols, and aryl salts (**4a,b,f**) were prepared.



Vilsmaier and Sprügel showed that the reaction of *S*-(*N*-succinimido)dimethylsulfonium ion with an amine yielded an azasulfonium ion, but its reaction with α-naphthol was different from that with an amine and yielded a naphthylsulfonium ion.[4] It is of interest to compare their findings with ours; the treatment of *N*-(2-propanesulfenyl)morpholine with **2a**, *p*-cresol, and **3** yielded **4b**. The use of **2b** in place of **2a** yielded no isolable products except amine salts.

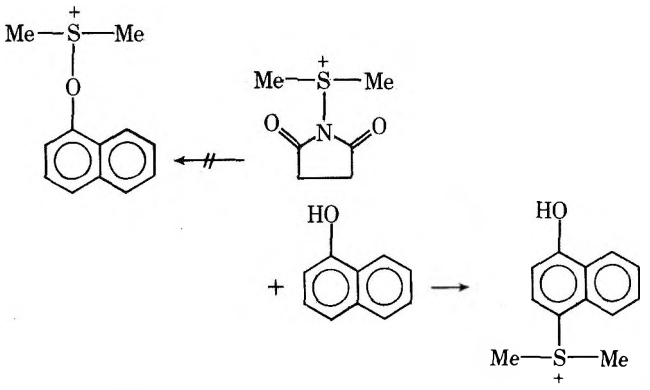
So far as we are aware, **4a,b,f** are the first examples of aryloxysulfonium ions; diarylaryloxysulfonium ions are unknown, and dialkylaryloxysulfonium ions cannot be isolated since they readily undergo a Sommelet-type rearrange-

Table I. Yields of Hetero-Substituted Sulfonium Salts

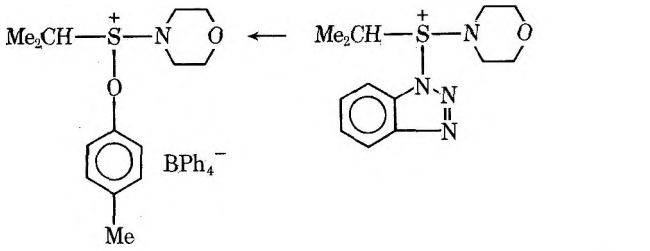
Method	Reactants	Registry no.			Registry no.		Products	Registry no.	Yield, %
A	$EtSN(CH_2CH_2)_2O$	24378-12-9	2a[b]	$HN(CH_2CH_2)_2O$	110-91-8	3[d]	$EtS^+N(CH_2CH_2)_2O$, BPh_4^- $N(CH_2CH_2)_2O$ (1a)	64520-81-6	60
A	$MeSN(CH_2CH_2)_2O$	4837-30-3	2a	$HN(CH_2CH_2)_2O$		3	$MeS^+N(CH_2CH_2)_2O$, BPh_4^- $N(CH_2CH_2)_2O$ (1b)	64520-83-8	65
A	$MeSN(CH_2CH_2)_2O$		2b[c]	$HN(CH_2CH_2)_2O$			1b		51
A	$MeSN(CH_2)_5$	7257-48-9	2a	$HN(CH_2)_5$	110-89-4	3	$MeS^+N(CH_2)_5$, BPh_4^- $N(CH_2)_5$ (1c)	64520-85-0	76
A	$MeSN(CH_2)_5$		2a	$HNEt_2$	109-89-7	3	$MeS^+N(CH_2)_5$, BPh_4^- NEt_2 (1d)	64520-87-2	70
A	$PhSNMe_2$	24380-79-8	2a	$HN(CH_2CH_2)_2O$		3	PhS^+NMe_2, BPh_4^- $N(CH_2CH_2)_2O$ (1e)	64508-82-3	91
A	p-$O_2NC_6H_4SN(CH_2CH_2)_2O$	40208-36-4	2a	$HNEt_2$		3	p-$O_2NC_6H_4S^+N(CH_2CH_2)_2O$, BPh_4^- NEt_2 (1f)	64520-89-4	63
A	$MeSN(CH_2)_5$		2a	$HNPh_2$	122-39-4	3	1c		25
B	p-TolS(=NTs)$N(CH_2CH_2)_2O$	64520-78-1		CF_3SO_3Me	333-27-7	3	p-$TolS^+N(CH_2CH_2)_2O$, BPh_4^- MeNTs (1g)	64520-91-8	62
C	$Me_2CHSN(CH_2CH_2)_2O$	64520-79-2	2a	HOPh	108-95-2	3	$Me_2CHS^+N(CH_2CH_2)_2O$, BPh_4^- OPh (4a)	64520-93-0	33
C	$Me_2CHSN(CH_2CH_2)_2O$		2a	HOC_6H_4Me-p	106-44-5	3	$Me_2CHS^+N(CH_2CH_2)_2O$, BPh_4^- OC_6H_4Me-p (4b)	64520-95-2	14
C	p-$TolSN(CH_2CH_2)_2O$	35390-53-5	2a	HOMe	67-56-1	3	p-$TolS^+N(CH_2CH_2)_2O$, BPh_4^- OMe (4c)	64520-97-4	82
C	p-$TolSN(CH_2CH_2)_2O$		2a	1-Menthol	2216-51-5	3	p-$TolS^+N(CH_2CH_2)_2O$, BPh_4^- O-menthyl (4d)	64535-88-2	47
C	p-$TolSNMeCH_2Ph$	64520-80-5	2a	HOMe		3	p-$TolS^+NMeCH_2Ph$, BPh_4^-	64520-99-6	10

C	p-TolSN(CH_2CH_2)$_2$O		2a	HOC_6H_4Me-p		3	p-TolS$^+$N(CH_2CH_2)$_2$O, BPh_4^- (OMe (4e))	64508-65-2	38
C	O(CH_2CH_2)$_2$NSN(CH_2CH_2)$_2$O	5038-11-9	2a	$HOCH_2C(CH_3)_3$	75-84-3	3	O(CH_2CH_2)$_2$NS$^+$N(CH_2CH_2)$_2$O, BPh_4^- (OC_6H_4Me-p (4c))	64508-67-4	60
C	O(CH_2CH_2)$_2$NSN(CH_2CH_2)$_2$O		2a	$HOCH_2CH_2OH$	107-21-1	3	O(CH_2CH_2)$_2$NS$^+$N(CH_2CH_2)$_2$O, BPh_4^- ($OCH_2C(CH_3)_3$ (5a))	64508-69-6	51
C	O(CH_2CH_2)$_2$NSN(CH_2CH_2)$_2$O		2a	HOC_6H_4Me-p		3	O(CH_2CH_2)$_2$NS$^+$N(CH_2CH_2)$_2$O, BPh_4^- (OCH_2CH_2OH (5b))	64508-71-0	45
C	O(CH_2CH_2)$_2$NSN(CH_2CH_2)$_2$O		2a	$HOCHMe_2$	67-63-0	3	O(CH_2CH_2)$_2$NS$^+$N(CH_2CH_2)$_2$O, BPh_4^- (OC_6H_4Me-p (5c))	64508-73-2	37
C	Et_2NSNEt_2	3768-61-4	2a	$HOCHMe_2$		3	$Et_2NS^+NEt_2$, BPh_4^- ($OCHMe_2$ (5d))	64521-06-8	38
A	$(CH_2)_5NSN(CH_2)_5$	25116-80-7	2a	$HN(CH_2)_5$		3	$(CH_2)_5NS^+N(CH_2)_5$, BPh_4^- ($OCHMe_2$ (5e))	58357-09-8	82
A	O(CH_2CH_2)$_2$NSN(CH_2CH_2)$_2$O		2a	$HN(CH_2CH_2)_2O$		3	O(CH_2CH_2)$_2$NS$^+$N(CH_2CH_2)$_2$O, BPh_4^- ($N(CH_2)_5$ (6a))	58357-03-2	71
D	O(CH_2CH_2)$_2$NSN(CH_2CH_2)$_2$O		2a	$ClN(CH_2CH_2)_2O$	23328-69-0	3	6b ($N(CH_2CH_2)_2O$ (6b))		52
A	O(CH_2CH_2)$_2$NSN(CH_2CH_2)$_2$O		2a	$HN(CH_2)_5$		3	O(CH_2CH_2)$_2$NS$^+$N(CH_2CH_2)$_2$O, BPh_4^- ($N(CH_2)_5$ (6c))	58357-05-4	50
A	Et_2NSNEt_2		2a	$HN(CH_2CH_2)_2O$		3	$Et_2NS^+NEt_2$, BPh_4^- ($N(CH_2CH_2)_2O$ (6d))	64508-75-4	88
A	O(CH_2CH_2)$_2$NSN(CH_2CH_2)$_2$O		2a	HNMePh		3	O(CH_2CH_2)$_2$NS$^+$N(CH_2CH_2)$_2$O, BPh_4^- (NMePh (6e))	58357-01-0	62
A	O(CH_2CH_2)$_2$NSN(CH_2CH_2)$_2$O		2a	$HNEt_2$		3	O(CH_2CH_2)$_2$NS$^+$N(CH_2CH_2)$_2$O, BPh_4^- (NEt_2 (6f))	64508-77-6	51
A	Et_2NSNEt_2		2a	$HNEt_2$		3	$Et_2NS^+NEt_2$, BPh_4^- (NEt_2 (6g))	65408-78-7	35
B	O(CH_2CH_2)$_2$NS(=NTs)N(CH_2CH_2)$_2$O 3249-59-0			CF_3SO_3Me		3	O(CH_2CH_2)$_2$NS$^+$N(CH_2CH_2)$_2$O, BPh_4^- (MeNTs (6h))	64508-80-1	63

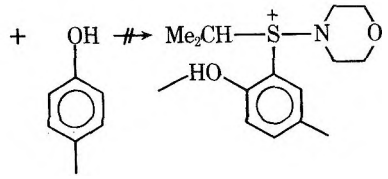
[a] Reactants were added in the order listed. Solvents used were CH_2Cl_2 for 1a–f and 6a–g, CH_2Cl_2–CH_3NO_2 for 4a–f and 5a–e and CH_3NO_2 for 1g and 6h. Reactants were mixed at −80 °C, except those for methods B and D, which were mixed at room temperature. [b] Registry no.: 21050-95-3. [c] Registry no.: 128-09-6. [d] Registry no.: 143-66-8.



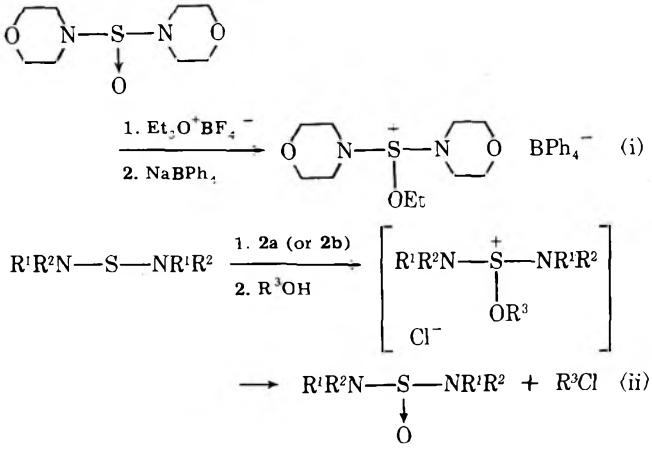
ment.[9,10] We attempted to prepare diphenylphenoxysulfonium salt by the reaction of phenyl sulfide with **2a** and *p*-cresol, but the desired sulfonium ion was not obtained.



4b



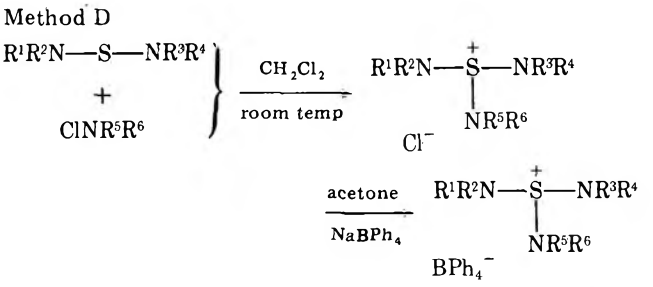
Diazaoxasulfonium Ions. The methods previously described for the preparation of diazaoxasulfonium ions were (i) alkylation of diamino sulfoxide[11] and (ii) reactions of diamino sulfides with **2a** and ROH.[12] Method i is not a general method for the preparation of diazaoxasulfonium ions, since it worked only with triethyloxonium tetrafluoroborate as the alkylating agent. Method ii was applicable to methanol, 2-propanol, and 2-methyl-2-propanol, but the diazaoxasulfonium ions formed could not be isolated.



In an attempt to find a method generally applicable to the preparation of various diazaoxasulfonium ions, method C was applied to this system; diazaoxasulfonium tetraphenylborates, **5a–e**, were successfully prepared.

It is of interest to note that method C is applicable to ethylene glycol, neopentyl alcohol, and *p*-cresol. **5c** is an example of the aryloxysulfonium salts which have not been described in the literature (except **4a,b,f** reported on in this paper).

Triazasulfonium Ions. Three methods have been found to be useful for the preparation of triazasulfonium salts (**6**): method A, reaction of a diamino sulfide with **2a** (or **2b**) followed by the treatment with a secondary amine and then with **3**[11] (preparation of **6a–g**); method B, alkylation of a diaminosulfilimine[13] followed by the treatment with **3** (preparation of **6h**); and method D, reaction of a diamino sulfide with an *N*-chloroamine (preparation of **6b**).



These triazasulfonium salts are very stable toward nucleophiles. For instance, when a CD_3NO_2 solution of **6b** and triphenylphosphine was heated at 100 °C for 1 day or when **6b** was refluxed in methanol for 1 day, no change was observed in its NMR spectrum. **6h** is an exception and decomposed to amine salts when heated with triphenylphosphine in CD_3NO_2 at 80 °C for 1 h.

Recently, Dawson and Swern reported the preparation of iminosulfonium salts from the reaction of a sulfide with **2a** (or **2b**) and a *primary* amine.[14] However, when syntheses of **4** or **6** containing a hydrogen atom on their nitrogen atoms were attempted using a primary amine, decomposition alway took place and amine salts were the main products. The instability of such azaoxa- and triazasulfonium ions is probably ascribable to the elimination of an alcohol or an amine from the sulfonium ion because of the presence of a labile hydrogen on its nitrogen atom and a labile alkoxy or amino group on the adjacent sulfur atom.

Experimental Section

Materials. *N*-Methanesulfenylmorpholine was prepared from methyl disulfide, chlorine gas, and morpholine[15] [bp 52–54 °C (6.5 mm); lit.[16] 48–49 °C (5 mm)]. Other sulfenamides were prepared in a similar manner:[15] *N*-ethanesulfenylmorpholine [bp 42.5–45 °C (2 mm)], *N*-methanesulfenylpiperidine [bp 59–61 °C (13 mm)], *N*-*p*-toluenesulfenylmorpholine [bp 80 °C (4.5 mm), mp 39–42 °C], *N*-benzenesulfenylmorpholine [bp 65 °C (4.0 mm), mp 32–35 °C, lit.[16] mp 33–36 °C], *N,N*-dimethylbenzenesulfenamide [bp 80 °C (8.0 mm)], *N*-*p*-nitrobenzenesulfenylmorpholine [mp 87.5–89.0 °C, lit.[16] 89–91 °C), *N*-benzyl-*N*-methyl-*p*-toluenesulfenamide (mp 45–47.5 °C); *N*-(2-propanesulfenyl) morpholine [bp 77–80 °C (5 mm)].

N-(Phenylmethanesulfenyl)morpholine was prepared by refluxing a benzene solution (15 mL) of *N*-(phenylmethanesulfenyl)succinimide (10 mmol) and morpholine (10 mmol) for 12 h. After the succinimide formed was removed by washing with water, the benzene was evaporated off and the residue obtained was recrystallized from ethanol: yield 69%; mp 73.5–75 °C (lit.[17] 72–74 °C). Harpp and Back prepared this compound by the reaction of *N*-(phenylmethanesulfenyl)-phthalimide and morpholine.[17] Although their method and ours are equally effective, ours has one advantage; *N*-(phenylmethanesulfenyl)succinimide is readily prepared by refluxing an equimolar mixture of benzyl disulfide and *N*-bromosuccinimide in benzene for 40 min (90% yield),[18] whereas *N*-(phenylmethanesulfenyl)phthalimide must be prepared by a two-step synthesis from benzyl disulfide via phenylmethanesulfenyl chloride.

Diamino sulfides were prepared according to Blake's method:[19] Dimorpholino sulfide (mp 125–126 °C, lit.[19] 125–126 °C), bis(diethylamino) sulfide [bp 58 °C (5.5 mm), lit.[20] 85 °C (12 mm)], dipiperidino sulfide (mp 72–74 °C, lit.[19] 74 °C).

Attempt for Preparing Diethylamino Morpholino Sulfide. An ethereal solution (40 mL) of morpholine (0.1 mol) was added to an ethereal solution (70 mL) of phenyllithium (0.1 mol). To this solution was added an ethereal solution (40 mL) of diethylaminosulfenyl chloride[21] (0.078 mol) at 20 °C in 30 min. After the mixture was al-

lowed to stand for 2 h, lithium chloride was filtered off and the solvent removed. The NMR spectrum of the brown oil obtained showed that it contained diethylamino morpholino sulfide in about 80% yield. However, when the oil was distilled at 67–82 °C (1 mm), the contents of dimorpholino sulfide and bis(diethylamino) sulfide increased. When the oil was kept in a freezer, crystals of dimorpholino sulfide gradually appeared and disproportionation slowly proceeded. It was not possible to isolate pure diethylamino morpholino sulfide.

Preparation of 1e (Method A). A CH_2Cl_2 solution (5 mL) of *N,N*-dimethylbenzenesulfenamide (5 mmol), a CH_2Cl_2 solution (5 mL) of **2a** (5 mmol), and a CH_2Cl_2 solution (3 mL) of morpholine (5 mmol) were placed separately in a glass vessel composed of three compartments connected to a vacuum line. After a freeze–thaw cycle was repeated twice, the first two solutions were mixed at −80 °C. The mixture was pale yellow, but when the amine solution was added to the mixture it became colorless. After the solution was allowed to warm up to room temperature, it was added to an acetone solution (20 mL) of $NaBPh_4$ (5 mmol). White precipitates which formed (NaCl) were filtered, and the addition of ether gave white crystals, which were found to be a 1:1 complex of **1e** and acetone: yield 91%; IR (KBr) 1720 cm^{-1}; NMR (CD_3SOCD_3) δ 2.10 [s, 6, $(CH_3)_2CO$], 3.06 [s, 6, $(CH_3)_2N$], 3.35–3.58 (m, 4, NCH_2CH_2O), 3.66–3.90 (m, 4, NCH_2CH_2O), 6.70–7.30 (m, 20, BPh_4), and 7.74 ppm (s, 5, PhS). Anal. Calcd for $C_{39}H_{45}BN_2O_2S$: C, 75.96; H, 7.36; N, 4.54. Found: C, 75.72, 75.77; H, 7.49, 7.52; N, 4.40, 4.42. This 1:1 complex formation was observed only when R is an aryl group, and no such complex was formed when R is an electron-releasing alkyl group (Me or Et). The complex did not lose the acetone under vacuum (10^{-4} mm, 25 °C, 6 h), but when the complex was heated up to 185 °C it melted at 182.5–183.6 °C; NMR the same as that of the complex except the loss of the δ 2.10 singlet; IR no 1720-cm^{-1} band. Anal. Calcd for $C_{36}H_{39}BN_2OS$: C, 77.41; H, 7.04; N, 5.02. Found: C, 77.35; H, 7.12; N, 4.90.

Other diazasulfonium salts were prepared in a similar manner. **1a:** yield 60%; mp 220–221 °C; Anal. Calcd for $C_{34}H_{41}BN_2O_2S$: C, 73.90; H, 7.48; N, 5.03. Found: C, 74.32; H, 7.70; N, 5.03. **1b:** yield 65%; mp 220–222 °C; Anal. Calcd for $C_{33}H_{39}BN_2O_2S$: C, 73.59; H, 7.30; N, 5.20. Found: C, 74.37; H, 7.44; N, 5.19. **1c:** yield 76%; mp 208–209 °C; Anal. Calcd for $C_{35}H_{43}BN_2S$: C, 78.64; H, 8.10; N, 5.24. Found: C, 78.56; H, 8.27; N, 5.21. **1d:** yield 70%; mp 217–218 °C; Anal. Calcd for $C_{34}H_{43}BN_2S$: C, 78.14; H, 8.29; N, 5.36. Found: C, 78.15; H, 8.58; N, 5.30. **1f:** yield 63%; mp 181–184 °C (dec).

Elemental Analyses. The results of C, H, N analyses of **1f, 4d–f, 5d,e,** and **6g** were somewhat removed from the theoretical values, but their NMR spectra were consistent with their structures.

Preparation of 1a by Exchange of the Anion of the Salt Prepared by Richards and Tarbell. An aqueous solution (10 mL) of ethyldimorpholinosulfonium tetrafluoroborate[2] (0.26 mmol) was added drop by drop to an aqueous solution (10 mL) of $NaBPh_4$ (0.25 mmol), and the white precipitates formed were filtered and dried, yield 83%. It NMR spectrum and melting point were the same as those of **1a** prepared by method A.

Preparation of 1g by Methylation of a Sulfilimine (Method B). A mixture of *N*-*p*-toluenesulfenylmorpholine (10 mmol), chloramine-T (10 mmol), pyridine (0.5 mL), and benzene (50 mL) was refluxed for 5 h, and the sodium chloride formed was filtered off. Concentration of the filtrate yielded the corresponding sulfilimine (81%). The sulfilimine (2.28 mmol) was stirred with methyl triflate (2.13 mmol) in nitromethane (30 mL) for 1 day at room temperature, and then a nitromethane solution (15 mL) of **3** (2.1 mmol) was added. After the solution was stirred for 0.5 h, ether was added. The crystals obtained were purified by recrystallization from acetone–ether (62%), mp 117–118 °C. Anal. Calcd for $C_{43}H_{45}BN_2O_3S_2$: C, 72.46; H, 6.37; N, 3.93. Found: C, 72.34; H, 6.87; N, 3.95.

Reaction of *N*-Benzenesulfenylmorpholine with 2a and Methanol. A CH_2Cl_2 solution (10 mL) of *N*-benzenesulfenylmorpholine (3.2 mmol) and a CH_2Cl_2 solution (15 mL) of **2a** (3.2 mmol) were mixed at −80 °C. When a CH_2Cl_2 solution (10 mL) of methanol (3.75 mmol) was added to this yellow solution at −80 °C it became colorless. After the solution was warmed up to room temperature its NMR spectrum was determined, which showed that the sulfenylmorpholine and methanol were quantitatively converted to *N*-benzenesulfinylmorpholine [δ 2.95–3.22 (m, 4, NCH_2), 3.60–3.90 (m, 4, OCH_2), 7.45–7.70 (m, 5, C_6H_5)] and methyl chloride (δ 2.96, s, 3), respectively.

Preparation of 4a (Method C). A cooled (−80 °C) CH_2Cl_2 solution (15 mL) of **2a** (6.2 mmol) was added to a CH_2Cl_2 solution (15 mL) of *N*-(2-propanesulfenyl)morpholine (6.2 mmol) at −80 °C. To this pale-yellow solution of a cooled CH_3NO_2 solution (20 mL) of phenol (6.2 mmol) and **3** (6.2 mmol) was added. After the mixture was stirred for 1 h it was allowed to warm up to room temperature. Addition of ether precipitated a mixture of **4a** and NaCl, which was separated and dissolved in acetone for removal of NaCl. Recrystallization from acetone–ether gave white crystals of **4a:** yield 33%; mp 131–132 °C; NMR (CD_3COCD_3) δ 1.60, 1.78 [d, 6, $(CH_3)_2CH$–], 3.74 (s, 8, NCH_2CH_2O), 4.35–5.00 [m, 1, $(CH_3)_2CH$–], 6.75–7.60 (m, 20, BPh_4, and 7.50–7.52 (s, 5, OPh). Anal. Calcd for $C_{37}H_{40}BNO_2S$: C, 77.47; H, 7.03; N, 2.44. Found: C, 77.53; H, 7.18; N, 2.54.

Other azaoxasulfonium salts were prepared in a similar manner. **4b:** yield 14%; mp 117–118 °C (dec). Anal. Calcd for $C_{38}H_{42}BNO_2S$: C, 77.67; H, 7.21; N, 2.38. Found: C, 77.59; H, 7.21; N, 2.37. **4c:** yield 82%; mp 149–150 °C. Anal. Calcd for $C_{36}H_{38}BNO_2S$: C, 77.27; H, 6.84; N, 2.56. Found: C, 77.37; H, 7.06; N, 2.74. **4d:** yield 47%; mp 118–120 °C; $[\alpha]^{24}_D$ −36.0 [c 2, acetone]. **4e:** yield 10%; mp 186–188 °C (dec). **4f:** yield 38%; mp 236–237 °C.

Preparation of 5a (Method C). A CH_2Cl_2 solution (15 mL) of **2a** (3.0 mmol), a CH_2Cl_2 solution (15 mL) of dimorpholino sulfide (3.0 mmol), and a CH_3NO_2 solution (15 mL) of neopentyl alcohol (3.0 mmol) and **3** (3.0 mmol) were treated in a manner similar to that described above for the preparation of **4a.** Recrystallization from acetone–ether–hexane gave white crystals of **5a:** yield 60%; mp 125–127 °C (dec). Anal. Calcd for $C_{37}H_{47}BN_2O_3S$: C, 72.77; H, 7.76; N, 4.59. Found: C, 72.60; H, 7.80; N, 4.57. **5b–e** were prepared in a similar manner. **5b:** yield 51%; mp 108.5–110.0 °C (dec). Anal. Calcd for $C_{34}H_{41}BN_2O_4S$: C, 69.85; H, 7.07; N, 4.71. Found: C, 69.39; H, 7.00; N, 4.69. **5c:** yield 45%; mp 236–237 °C. Anal. Calcd for $C_{39}H_{43}N_2O_3SB$: C, 74.28; H, 6.87; N, 4.44. Found: C, 74.10; H, 7.39; N 4.25. **5d:** yield 37%; mp 118 °C (dec). **5e:** yield 38%; mp 196–199 °C (dec).

Preparation of 6a (Method A). In a manner similar to that described for the preparation of **1e,** a CH_2Cl_2 solution (10 mL) of dipiperidino sulfide (2.5 mmol) and a CH_2Cl_2 solution (10 mL) of **2a** (2.5 mmol) were mixed at −80 °C, and then a CH_2Cl_2 solution (10 mL) of piperidine (2.6 mmol) was added. After the mixture was warmed up to room temperature, an acetone solution (10 mL) of sodium tetraphenylborate (2.5 mmol) was added to the mixture and then the sodium chloride which precipitated was filtered. Upon addition of ether, crystals of **6a** precipitated, which were recrystallized from acetone–ether: yield 82%; mp 224.5–225.0 °C. Anal. Calcd for $C_{39}H_{50}BN_3S$: C, 77.59; H, 8.35; N, 6.96. Found: C, 77.38; H, 8.49; N, 6.62. **6c–f** were prepared in a similar manner. **6c:** yield 50%; mp 212.5–213.5 °C. Anal. Calcd for $C_{37}H_{46}BN_3O_2S$: C, 73.13; H, 7.63; N, 6.92. Found: C, 72.83; H, 7.64; N, 6.65. **6d:** yield 88%; mp 209.5–210.5 °C. Anal. Calcd for $C_{36}H_{48}BN_3OS$: C, 74.33; H, 8.32; N, 7.23. Found: C, 74.15; H, 8.53; N, 7.20. **6e:** yield 62%; mp 186.5–187.5 °C. Anal. Calcd for $C_{39}H_{44}BN_3O_2S$: C, 74.39; H, 7.04; N, 6.67. Found: C, 74.48; H, 7.39; N 6.83. **6f:** yield 51%; mp 195–196 °C. Anal. Calcd for $C_{36}H_{46}BN_3O_2S$: C, 72.59; H, 7.78; N, 7.06. Found: C, 71.99; H, 7.58; N, 6.79. **6g:** yield 35%; mp 193.5–194.5 °C.

Preparation of 6b from *N*-Chloromorpholine (Method D). A CH_2Cl_2 solution (20 mL) of *N*-chloromorpholine (12 mmol) was added to a CH_2Cl_2 solution (20 mL) of dimorpholino sulfide (10 mmol) at room temperature, and the mixture was stirred for 1 day. Upon addition of carbon tetrachloride, white crystals of trimorpholinosulfonium chloride precipitated, which were recrystallized from dichloromethane: yield 52%; mp 131–132 °C.

An acetone solution (15 mL) of trimorpholinosulfonium chloride (2.37 mmol) was mixed with an acetone solution (15 mL) of $NaBPh_4$ (2.37 mmol). Upon addition of ether, a mixture of **6b** and NaCl precipitated, which was added to acetone and filtered. Ether was added to the filtrate, and crystals of **6b** precipitated: yield 69%; mp 210–211 °C. Anal. Calcd for $C_{36}H_{44}BN_3O_3S$: C, 70.92; H, 7.28; N, 6.89. Found: C, 71.31; H, 7.53; N, 6.84.

Preparation of 6h (Method B). *N*-*p*-Toluenesulfonyldimorpholinosulfilimine was prepared by the reaction of dimorpholino sulfide (10 mmol) with chloramine-T (10 mmol) in refluxing benzene (40 mL) in the presence of pyridine (0.2 mL);[13] recrystallization from $CHCl_3$–ether gave white crystals: yield 60%; mp 146–148 °C.

This sulfilimine (2.0 mmol) was stirred with methyl triflate (2 mmol) in nitromethane (15 mL) for 5 h at room temperature, and then a nitromethane solution (15 mL) of **3** (2.0 mmol) was added. After the mixture was stirred for 0.5 h ether was added. White precipitates which formed (**6h** and CF_3SO_3Na) were filtered and extracted with acetone. Addition of ether to the acetone extracts gave white needles of **6h:** yield 63%; mp 123–124 °C. Anal. Calcd for $C_{40}H_{46}BN_3O_4S_2$: C, 67.88; H, 6.57; N, 5.94. Found: C, 67.40; H, 7.06; N, 5.53.

Registry No.—*N*-Benzenesulfenylmorpholine, 4837-31-4; *N*-(phenylmethanesulfenyl)morpholine, 7257-55-8; *N*-(phenylmethanesulfenyl)succinimide, 14204-23-0; **1e** acetone complex, 64508-83-4; ethyldimorpholinosulfonium tetrafluoroborate, 24407-43-0; *N*-ben-

zenesulfinylmorpholine, 16066-32-3; trimorpholinosulfonium chloride, 64508-84-5.

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Imidazo[1,2-*a*]pyridine 1-Oxide. Synthesis and Chemistry of a Novel Type of *N*-Oxide

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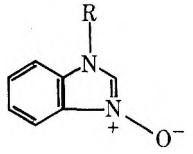
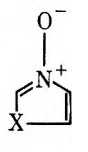
2-Phenylimidazo[1,2-*a*]pyridine 1-oxide, the first *N*-oxide of the polyazaindenes with the oxide function in the π-excessive five-membered ring, has been prepared. In contrast to the π-deficient *N*-oxides, back-bonding of the oxygen appears to be minimal. Some transformations of this compound are described.

The chemistry of π-deficient heterocyclic *N*-oxides has been the subject of numerous studies for many years. In contrast, much less is known about π-excessive heterocyclic *N*-oxides. Among the few representatives of this class of *N*-oxides are compounds of the general types A and B.[1,2] No *N*-oxides

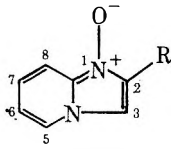


A



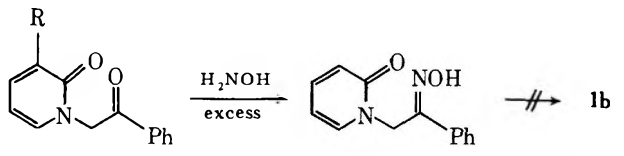
B, X = O, S, NR

of the π-excessive five-membered ring in the nitrogen-bridged polyazaindenes are known. We now wish to describe the synthesis and some chemical reactions of a member of this class of heterocyclic *N*-oxides, imidazo[1,2-*a*]pyridine 1-oxide (**1b**).



1a, R = H
b, R = Ph

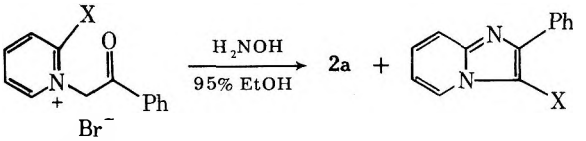
Since earlier work in our laboratory had shown that direct N-oxidation of imidazo[1,2-*a*]pyridines with peracids leads to cleavage of the five-membered ring,[3] we approached the *N*-oxide synthesis by indirect intramolecular cyclizations. When compound **2a**, obtained either by alkylation of 2-pyridone[4] or preferably by base hydrolysis of the pyridinium salts **4** (X = Cl, Br), is treated with hydroxylamine under acidic or neutral conditions, the reactions stop at the oxime stage, high yields of *syn*- and *anti*-oximes **3** being formed. The mixtures, largely the undesired anti isomer with respect to the phenyl substituent,[5] are stable at the melting point and thus not thermally convertible to the *N*-oxide **1b**.



2a, R = H

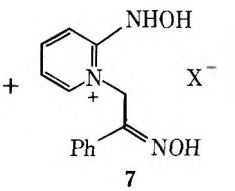
3 syn + anti

An attempt to prepare compound **1b** by reaction of the pyridinium salt **4** with hydroxylamine in 95% ethanol also gave



4a, X = Cl
b, X = Br

5, X = H
6a, X = Br
b, X = Cl



7

none of the desired product, but rather a mixture containing the pyridone **2a** (55%) and compounds **5** (8%) and **6a** and **6b** (3%). Another component had IR and mass spectral properties consistent with structure **7**. The formation of the imidazo[1,2-*a*]pyridines **5**, **6a**, and **6b** suggests that cyclization to the *N*-oxide **1b** may indeed have occurred, but that this compound is not stable under the reaction conditions. Further, formation of the pyridone **2a** implicates hydroxylamine in the hydrolysis of the pyridinium salt **4**, either as a general base catalyst or as a nucleophile.[6]

The reaction was therefore repeated under strictly anhydrous conditions in the presence of the hydroxylamine hydrochloride. Under these reaction conditions, the product

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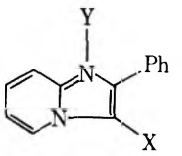
Table I. ^{1}H NMR Chemical Shifts (δ, ppm) of Imidazo[1,2-*a*]pyridines[a]

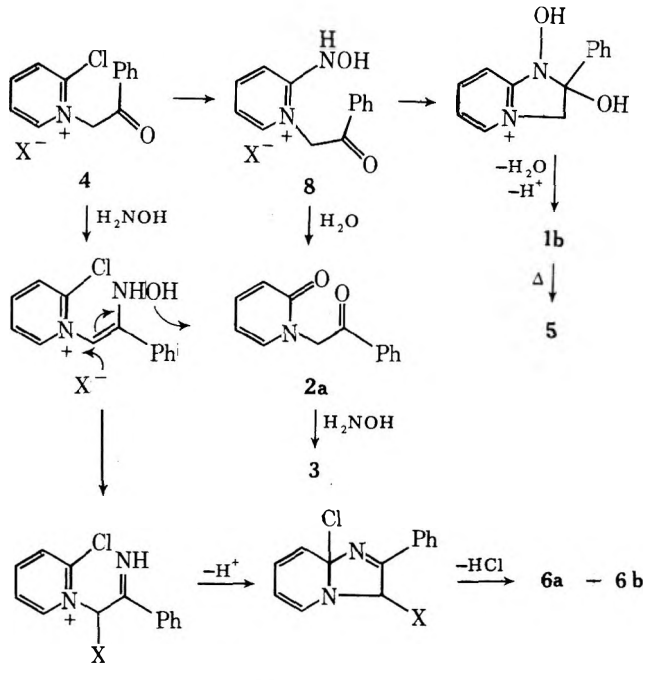


1b, X = H; Y = O
5, X = H; Y = nil
6a, X = Br; Y = nil
b, X = Cl; Y = nil
c, X = I; Y = nil
10,[b] X = H; Y = nil (Ph = H)
11a,[c] X = H; Y = OCH_3
13a, X = Br; Y = O

Compd	H-3	H-5	H-6	H-7	H-8	C_6H_5 o	C_6H_5 m,p
			Me_2SO-d_6				
5	8.44	8.56	6.92	7.27	7.62	8.02	7.48
1b	~8.40	~8.42	7.00	7.30	7.75	~8.42	7.49
10·HCl[b]	8.28, 8.53	9.07	7.56	~8.03	~8.03		
11a[d]	8.86	9.03	~7.69	8.18	8.36	7.96	~7.69
1b·TFAA[e]	8.72	8.89	~7.52	~8.02	~8.02	~8.02	~7.62
5·TFAA[e]	8.86	8.96	~7.60	~8.03	~8.03	~8.03	~7.60
13a·HBr		8.91	~7.75	~8.14	~8.14	~7.75	~7.75
			$CDCl_3$				
5[d]	7.88	8.13	6.78	7.16	7.66	8.00	~7.42
1b	7.69	8.02	6.78	7.15	7.86	8.26	7.40
11a[d]	9.36	9.66	~7.59	~8.18	~8.18	7.96	~7.59
13a		~8.10	7.00	7.28	7.98	~8.10	7.54
6a[f]		~8.16	6.90	7.24	7.63	~8.16	7.47
6b		~8.09	6.90	7.24	7.64	8.18	7.45
6c		8.23	6.94	7.26	7.65	8.01	7.48

[a] Solutions were 0.25 *m* unless otherwise stated. Chemical shift assignments are based on the splitting patterns, integrated areas, and analogy to those of other similar compounds. H-3 is a singlet; H-5, a doublet often showing further fine splitting ($J_{5,6}$ ~ 6, $J_{5,8}$ 0–1 Hz); H-6, a triplet ($J_{6,7}$ ~ 6 Hz); H-8, a doublet ($J_{7,8}$ ~ 9 Hz). In the protonated compounds the signals of H-7 and H-8 overlap; for these and other overlapping signals the center of the multiplet is given. [b] The unsubstituted imidazo[1,2-*a*]pyridine. [c] Iodide salt. [d] 0.14 *m* solutions. [e] An excess of trifluoroacetic acid was added to the solutions. [f] 0.30 *m* solution.

Scheme I

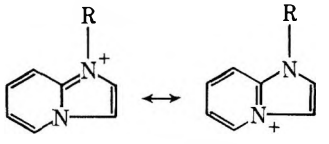


X = Cl, Br

distribution is drastically altered, and the desired *N*-oxide **1b** is formed in up to 65% yield. Variable amounts of the oximes **3** are also formed. Although other *N*-oxides have been prepared from both oximes and hydroxylamines,[1] the formation of compound **1b** is best rationalized as shown in Scheme I. Attack of hydroxylamine can in principle occur either at the carbonyl carbon to yield the oximes or afford the hydroxylamine derivative **8** by nucleophilic displacement of the chlorine in compound **4**. The hydroxylamine derivative **8** can cyclize or hydrolyze in the manner indicated above. The former affords the *N*-oxide **1b**, while the latter yields the pyridone **2a**, which can be converted to the oximes **3**. Initial attack by hydroxylamine at the carbonyl carbon of compound **4** affords the intermediate which can be transformed in the indicated manner to yield the 3-halo derivatives **6a** and **6b**.

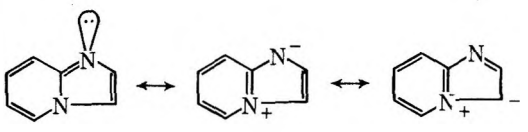
The mass spectrum of the yellow, hygroscopic *N*-oxide **1b** shows facile loss of an oxygen atom, while the remainder of the spectrum is essentially the same as the fragmentation pattern observed for 2-phenylimidazo[1,2-*a*]pyridine (**5**).

The ^{1}H NMR spectrum (in Me_2SO-d_6 or $CDCl_3$, cf. Table I) of the *N*-oxide is rather unique in that only the ortho hydrogens of the 2-phenyl substituent are strongly affected by the presence of the *N*-oxide (deshielded by about 0.40 ppm). This is contrary to the effect that either N-1 protonation or methylation has upon all of the proton chemical shifts (deshielding by 0.4–0.7 ppm) in nonoxygenated imidazo[1,2-*a*]-pyridines. The latter was shown by us to be due to resonance contributors to the ground state of the type shown in **9**.[7] The



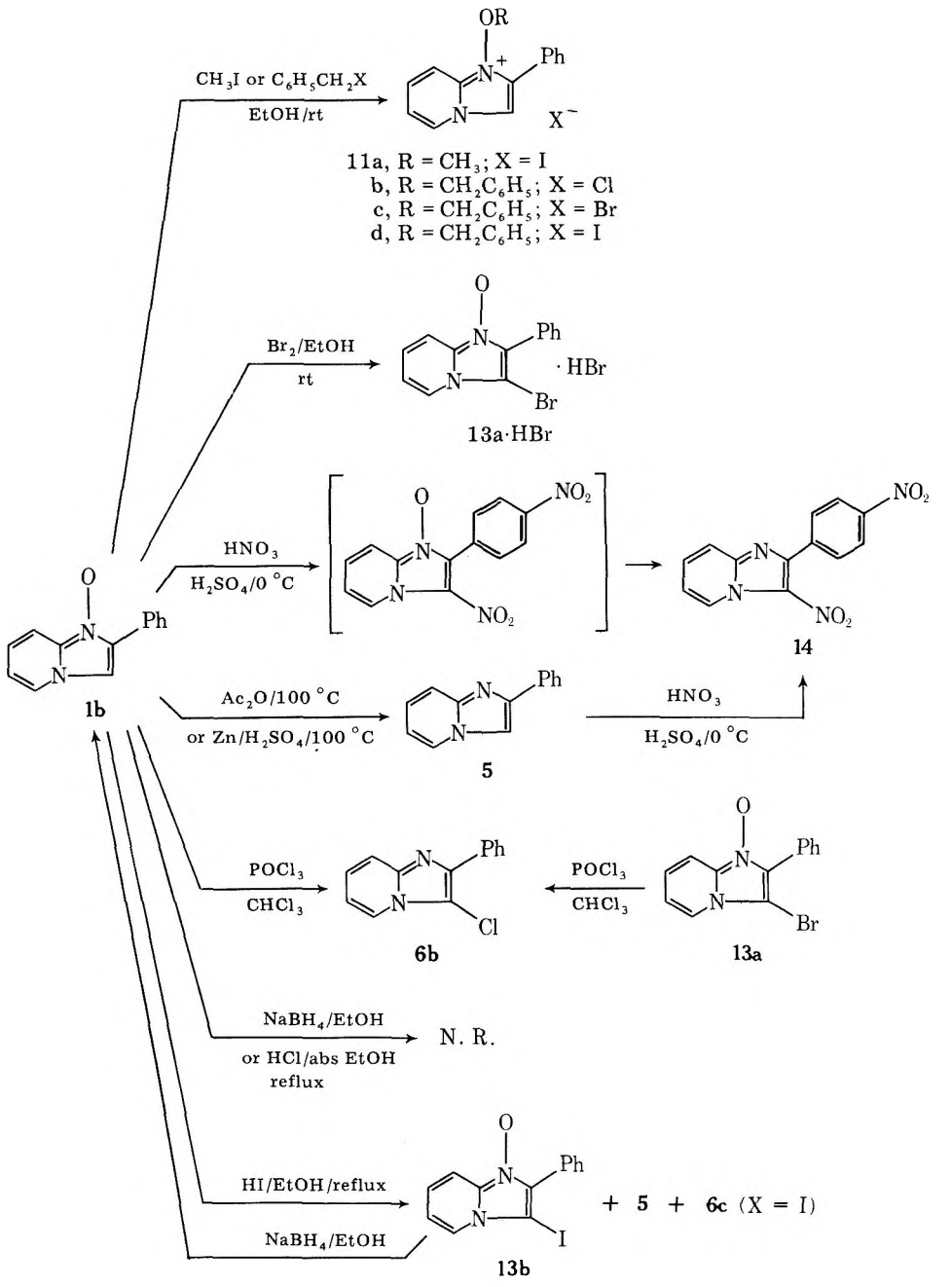
9, R = H, CH_3

absence of such chemical shift changes in the *N*-oxide implies that the ground-state contributors in the free base **10** are not



10

Scheme II



significantly effected by N-1 oxidation. This, in turn, suggests little back-donation by oxygen in the π-excessive *N*-oxide and points to the fact that the lone pair of electrons on N-1 of the free base is not involved in the resonance structures. However, in the methylated *N*-oxide **11a** (cf. Scheme II) the changes in the chemical shifts of all of the ring protons do parallel those observed when imidazo[1,2-*a*]pyridine is N-1 methylated (**9**, R = CH_3). This clearly implies the similarity in the ground-state contributing structures of the alkoxy (**11a**) and alkyl (**9**, R = CH_3) quaternary salts.

The above considerations lead to the prediction that the presence of the *N*-oxide function will not greatly alter the reactivity of the imidazo[1,2-*a*]pyridine system.

Some Reactions of the *N*-Oxide 1b. (1) Formation of a hemipicrate, $(C_{13}H_{10}N_2O)_2{\cdot}C_6H_3N_3O_7{\cdot}H_2O$ (**12**), parallels the basic salt formation $(Het^+\text{-}O^-)_2{\cdot}HX$ frequently encountered in π-deficient heteroaromatic *N*-oxides.[1]

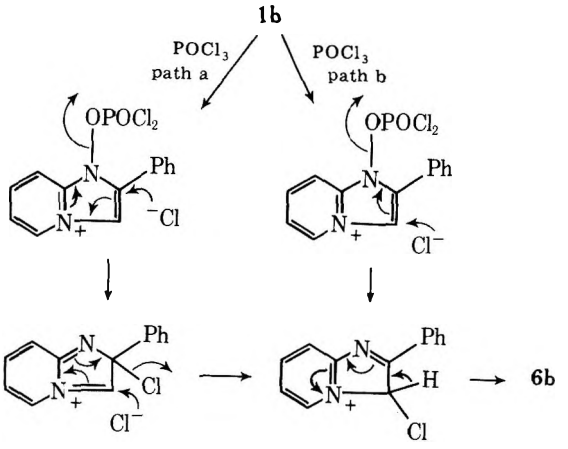
(2) The *N*-oxide **1b** is readily alkylated at room temperature by alkyl halides, in the order of reactivity $PhCH_2I > PhCH_2Br > CH_3I > PhCH_2Cl$, to give compounds **11a–d**. All of these compounds are sensitive to heat and the methiodide, especially, is sensitive to light.

(3) As with nonoxygenated imidazo[1,2-*a*]pyridines, facile electrophilic substitution occurs at the 3 position. Thus, bromination gives the 3-bromo *N*-oxide **13a**. Nitration takes place at both the 3 position and para in the phenyl substituent; the ultimate product, the deoxygenated compound **14**, may well be formed from the dinitro *N*-oxide during the workup procedure. Nitration of 2-phenylimidazo[1,2-*a*]pyridine (**5**) affords the same dinitro compound.

(4) The "classical" acetic anhydride reaction of π-deficient *N*-oxide chemistry, when applied to the *N*-oxide **1b**, yields at least seven components, of which only the deoxygenated material, compound **5** (25%), could be isolated. Since the *N*-oxide, on standing for several weeks or on brief heating at its melting point, becomes contaminated with the free base **5**, we envision the above reaction to be a thermal deoxygenation.

In contrast to this observation, 1-methylbenzimidazole 3-oxides[8] as well as 1-methylpyrazole 2-oxide[9] react with

Scheme III

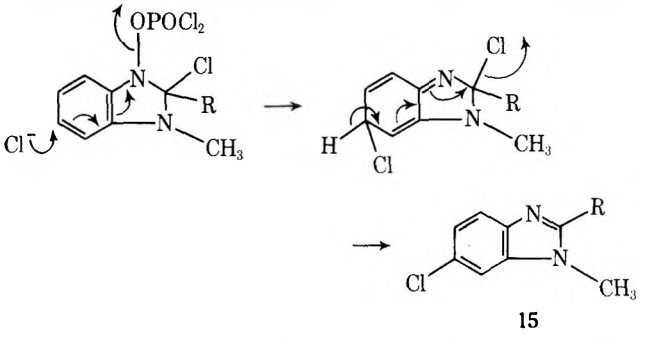


acetic anhydride to afford products analogous to those obtained in π-deficient *N*-oxides.

(5) Reaction of the *N*-oxide **1b** with $POCl_3$ affords a high yield (70%) of the deoxygenated 3-chloro derivative **6b**, along with traces of the deoxygenated compound **5** and polychloro compounds. In a control experiment, the parent compound **5** was shown to be unaffected by $POCl_3$.

The formation of this 3-chloro derivative can be rationalized by either of the following sequences (Scheme III). While path b is more direct, path a is more likely in view of our earlier work,[10] involving the reaction of 3-halo imidazo[1,2-*a*]pyridines with *tert*-butyl hypochlorite, where *nucleophilic* substitution at position 2 occurs when N-1 is substituted with a facile negative leaving group. When the 3-bromo-2-phenyl *N*-oxide **13a** is treated with $POCl_3$, deoxygenation *and* halogen exchange lead to 3-chloro-2-phenylimidazo[1,2-*a*]pyridine (**6b**) in 54% yield. Mechanisms similar to those delineated above account for this reaction.

The reaction of $POCl_3$ with 1-methylbenzimidazole 3-oxide[8] affords the deoxygenated 2-chloro derivative when C-2 is unsubstituted, while the 6-chloro derivative **15** is obtained



15

when the 2 position is blocked. It is of interest to comment that the formation of these 6-chloro compounds can be explained in a manner akin to path a above.

(6) Attempted reduction of the *N*-oxide **1b** with $NaBH_4$ in ethanol failed. In fact, 3-iodo-2-phenylimidazo[1,2-a]pyridine 1-oxide (**13b**) can be dehalogenated to the *N*-oxide **1b** with $NaBH_4$. Since the nonoxygenated iodo compound (**6c**, X = I) is also dehalogenated by this reagent,[11] the reactivity of the substituent is presumably unaffected by the presence of the *N*-oxide function. Under more vigorous conditions, zinc dust in the presence of acid, the deoxygenated compound **5** is rapidly formed (70% yield).

(7) Prolonged heating of the *N*-oxide **1b** with hydrogen iodide in ethanol leads to the gradual formation of the deoxygenated compound **5**, as well as the 3-iodo *N*-oxide **13b**, and its deoxygenated derivative (**6c**, X = I). Here, also, deoxygenation is most reasonably explained by thermal decomposition.

Introduction of iodine in the 3 position is envisioned to take place by electrophilic substitution, the necessary iodine being formed by air oxidation of iodide.

When the *N*-oxide **1b** is treated with refluxing ethanolic hydrogen chloride for 2 h, no decomposition product (**5**) can be detected by TLC. The protonated *N*-oxide thus appears to be more stable than the nonprotonated species.

Some aspects of the chemistry of the 1-alkoxy derivatives as well as the syntheses of related polyazaindene *N*-oxides will be the subjects of forthcoming publications.

Experimental Section

Woelm neutral alumina, Brockmann grade 3, was used for chromatography. Solutions were dried over anhydrous Na_2SO_4. Melting points are uncorrected. ^1H NMR spectra were recorded with a Varian HA-100 spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M instrument equipped with a solid sample injector; ionizing voltage was 73 eV. IR spectra were recorded of Nujol mulls with a Beckman AccuLab 1 instrument. Elemental analyses were determined by either the Analytical Services Laboratory of the University of Alabama Chemistry Department or Atlantic Microlab, Inc., Atlanta, Ga.

1-Phenacyl-2(1*H*)-pyridone (2a). (1) A mixture of 2-pyridone (2.0 g, 21 mmol) and phenacyl bromide (4.0 g, 20 mmol) was kept at its melting point for 3 h.[12] The cooled mixture was treated with hot H_2O and the brown solid was filtered. Fractional crystallizations from EtOAc or EtOH gave only impure product. Chromatography of the material in the mother liquors gave with 50% $C_6H_6/CHCl_3$ compounds **2b** (1.7%) and **2a**, mp 150.5–153 °C [after sublimation, 150 °C (0.02 Torr)] (lit.[13] mp 154.5 °C), total yield 30–40%. Compound **2b**, extracted into hexane, crystallized from very small amounts of MeOH: mp 123–125 °C; mass spectrum mol wt 291 and 293; ^1H NMR (δ, $CDCl_3$) 5.40 (s, CH_2), 6.10 (t, H-5), 7.2–8.04 (remaining protons).[14]

Anal. Calcd for $C_{13}H_{10}NO_2Br$: C, 53.42; H, 3.42; N, 4.79; Br, 27.40. Found: C, 53.44; H, 3.44; N, 4.88; Br, 27.29.

(2) Compound **2a** is best prepared by treating the salt **4a** with NaOH[13] (70% yield): ^1H NMR (δ, $CDCl_3$) 5.40 (s, CH_2), 6.23 (t, H-5), 6.62 (d, H-3), 7.2–8.1 (remaining protons).

2-Chloro-1-phenacylpyridinium Bromide (4a). This material had mp 170–170.5 °C (lit.[13] mp 179 °C for the monohydrate) and after drying for 2 h at 100–110 °C in vacuo did not retain H_2O of crystallization.

Anal. Calcd for $C_{13}H_{11}NOClBr$: C, 49.92; H, 3.52; N, 4.48; halide, 36.96. Found: C, 49.79; H, 3.52; N, 4.41; halide, 37.00.

2-Bromo-1-phenacylpyridinium Bromide (4b). Heating of 2-bromopyridine (9.5 g, 60 mmol) with phenacyl bromide (12 g, 60 mmol) at 120 °C for 20 min, cooling slightly, adding 25 mL of toluene, then heating at 100 °C for 2 days, filtering, and triturating with C_6H_6 and Et_2O gave compound **4b** (X = Br) in 83% yield. It crystallized from EtOH as sturdy rhombs, mp 178.5 °C.

Anal. Calcd for $C_{13}H_{11}NOBr_2$: C, 43.70; H, 3.08; N, 3.92; Br, 44.82. Found: C, 43.69; H, 3.10; N, 3.87; Br, 44.89.

Oximes of 1-Phenacyl-2(1*H*)-pyridone (3). (1) To an aqueous solution (3 mL) of H_2NOH·HCl (0.54 g, 7.7 mmol) neutralized with 10% NaOH (pH 7) were added compound **2a** (0.33 g, 1.55 mmol) and absolute EtOH (20 mL). When, after refluxing the resulting solution for 1.5 h, much starting material remained (TLC), another portion of neutralized H_2NOH·HCl (1.08 g) was added and heating was continued for 22 h. Some separated solid was filtered and rinsed with EtOH. The filtrate was treated with H_2O (20 mL) and concentrated (to 20 mL) when crystals (0.30 g, 85%, mp 161–175 °C) separated. This solid was a 1:5 syn/anti mixture of the oximes **3**: ^1H NMR (δ, Me_2SO-d_6) 5.22 and 4.97 (s, 5:1, CH_2), 11.87 and 11.17 (s, 5:1, OH), 6.15 (t, H-5), 6.22 (d, H-3), 7.2–7.6 (remaining protons). Crystallization from absolute EtOH did not appreciably change the isomer ratio, but raised the melting point to 175–185 °C.

Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.42; H, 5.26; N, 12.78. Found: C, 68.41; H, 5.45; N, 12.16.

Although this mixture turned brown on heating just above its melting point for 30 min, no change was detectable by ^1H NMR spectroscopy.

(2) When a solution of compound **2a** (0.33 g) and H_2NOH·HCl (0.54 g) in EtOH (25 mL) was refluxed for 1.5 h, no starting material remained (TLC). Evaporation to dryness and addition of H_2O (20 mL) to the residue gave the oximes **3**, mp 164–168 °C (0.30 g), as predominantly the anti isomer.

Reaction of the Salts 4 with Hydroxylamine. (1) An aqueous solution (10 mL) of H_2NOH·HCl (1.4 g, 20 mmol) was treated with

NaOH to pH 7 and added to a warm, aqueous solution (60 mL) of compound **4a** (3.1 g, 10 mmol). The solution became deep yellow, a gas was liberated, pH became ~5, and a gum that could not be induced to crystallize separated. After 30 min the mixture was extracted with 5 × 10 mL of $CHCl_3$. The $CHCl_3$ layers were dried and stripped of solvent to give a mixture from which compounds **6a** (and **6b**) (80 mg, 3%), **5**, and **2a** were isolated by chromatography, eluting with C_6H_6, 10% $CHCl_3/C_6H_6$, and 10% $CHCl_3/C_6H_6$, respectively. The aqueous layer (now pH 3) was neutralized with aqueous NaOH and extracted with 5 × 10 mL of $CHCl_3$. The extracts were dried and stripped of solvent to give a residue from which a solid (25 mg), tentatively assigned structure **7**, separated on addition of $CHCl_3$. The $CHCl_3$-soluble portion (0.66 g) on chromatography gave small amounts of compounds **5** (70 mg, 8% total) and **2a** (120 mg, 55% total).

Compound **6a** was identified by IR and ^1H NMR spectral comparisons with an authentic sample (see below). Its picrate showed the same strange melting behavior as, and no depression on admixture with, the authentic material (see below). Its mass spectrum, however, also contained peaks attributable to **6b** (~15%) (other chloro- and bromoimidazo[1,2-*a*]pyridines cannot be separated by chromatography). Compound **5**, after crystallization from hexane, had the same melting point, IR, and ^1H NMR as an authentic sample (see below). Compound **2a**, after crystallization from C_6H_5/hexane and EtOAc, had mp 153–153.7 °C and the same spectral properties as the authentic material (see above). Compound **7**, mp ~172 °C dec, had an IR spectrum quite different from those of the oximes **3** and the pyridone **2a**, but strongly reminiscent of those of the pyridinium salts **4**; the carbonyl absorption of **4** (at 1680 cm^{-1}) was absent, and broad bands were present at 2700–3400 cm^{-1}. Its mass spectrum showed *m/e* peaks at 227 (cation **7** -OH), 209, and 193.

(2) **Anhydrous Conditions: 2-Phenylimidazo[1,2-*a*]pyridine 1-Oxide (1b).** The starting materials were dried at 80 °C in vacuo for 6 h. A mixture of $H_2NOH{\cdot}HCl$ (1.4 g, 21 mmol) and compound **4b** (X = Br) (1.07 g, 3.0 mmol) in dry EtOH (50 mL) was heated with stirring at 80 °C for 5 h; reaction vessels were dried at 120 °C and protected with a Drierite-filled tube. The solvent was evaporated and the residue extracted with 3 × 10 mL of $CHCl_3$ from which a semisolid mixture was obtained that was fractionated by chromatography into the colorless compounds **6a** and **6b** (1.2%), **5** (1.7%), **2a** (6.8%) eluted as above, and the waxy, yellow, hygroscopic compound **1b** (0.41 g, 65%), mp 100–115 °C, eluted with 2% absolute EtOH/$CHCl_3$. The $CHCl_3$-insoluble residue, on treatment with H_2O, gave the insoluble oximes **3** (13%).

Changing the reaction conditions to 5 times the amount of salt **4b**, 5–10 times $H_2NOH{\cdot}HCl$, and 1.5–3 times EtOH lowered the yield of *N*-oxide **1b** to 30–40%. Lowering the temperature to 55 °C resulted in a 7% yield of *N*-oxide.

The *N*-oxide **1b**, when dry, is soluble in C_6H_6 and $CHCl_3$. After crystallization from C_6H_6, it has mp 117–118 °C, resolidifies partially, and is melted again by 162 °C; after cooling it then has mp ~158–168 °C (darkens). On exposure to (moist) air it becomes gummy. ^1H NMR spectra, concentration dependent, are the same of non- and recrystallized material. On standing several weeks some of the compound became deoxygenated (TLC).

The *picrate* **12**, formed by adding a hot absolute EtOH solution (3 mL) of picric acid (40 mg, 0.17 mmol) to a hot absolute EtOH solution (2 mL) of compound **1b** (40 mg, 0.18 mmol), crystallized from absolute EtOH as fine yellow needles, mp 201 °C dec.

Anal. Calcd for $(C_{13}H_{10}N_2O)_2{\cdot}H_2O{\cdot}C_6H_3N_3O_7$: C, 57.57; H, 3.75; N, 14.69. Found: C, 57.37; H, 3.55; N, 14.82.

The colorless *methiodide* **11a** rapidly turns yellow on exposure to light. Its preparation and purification were thus carried out in foil-wrapped vessels and as little light as possible. After standing 19 h a solution of compound **1b** (0.20 g, 0.95 mmol) and CH_3I (1 mL) in absolute EtOH (4 mL) was concentrated and EtOAc (ca. 5 mL) was added to the hot solution to the point of turbidity. Rapid cooling gave a colorless solid (75%) which was purified by dissolution in a little hot absolute EtOH and addition of EtOAc as above, and then had mp 146 °C dec.

Anal. Calcd for $C_{14}H_{13}N_2OI$: C, 47.73; H, 3.69; N, 7.95; I, 36.08. Found: C, 47.78; H, 3.73; N, 7.95; I, 35.97.

1-Benzyloxyimidazo[1,2-*a*]pyridinium Halides (11b–d). All manipulations were carried out in dimmed light. Exposure to heat was kept to a minimum, since the compounds are heat sensitive. Each colorless compound was prepared by treating the *N*-oxide **1b** (100 mg) in absolute EtOH (3 mL) with a ca. sixfold excess of benzyl halide.[15] Since with benzyl chloride much *N*-oxide remained after 5 h (TLC), the solution was left to stand for 6 days. With benzyl bromide, reaction was complete after ~10 min. All were worked up by concentrating the warmed solutions in a stream of N_2, adding EtOAc until the product separated as an oil, and scratching to induce crystallization. The *chloride* **11b**, mp 143–145 °C dec (67%), dissolved in a little hot absolute EtOH, reprecipitated with warm EtOAc, and rapidly cooled, had mp 135–145 °C dec.

Anal. Calcd for $C_{20}H_{17}N_2OCl{\cdot}H_2O$: C, 67.70; H, 5.36; N, 7.90. Found: C, 67.21; H, 5.45; N, 8.37.

The *bromide* **11c**, mp 170–172 °C dec (softens ~118 °C), was analyzed directly.

Anal. Calcd for $C_{20}H_{17}N_2OBr{\cdot}H_2O$: C, 60.15; H, 4.76; N, 7.02. Found: C, 60.74; H, 4.60; N, 7.21.

The *iodide* **11d** (93%), rapidly recrystallized from absolute EtOH, had mp 167 °C dec.

Anal. Calcd for $C_{20}H_{17}N_2OI$: C, 56.07; H, 3.97; N, 6.54. Found: C, 56.46; H, 4.04; N, 6.57.

Mass spectra showed only the peaks due to the *N*-oxide **1b** and the respective benzyl halides.

3-Bromo-2-phenylimidazo[1,2-*a*]pyridine 1-Oxide Hydrobromide (13a·HBr). To a solution of *N*-oxide **1b** (0.20 g, 0.95 mmol) in absolute EtOH (5 mL) was added dropwise an absolute ethanolic solution (3 mL) of Br_2 (0.30 g, 1.8 mmol). After 24 h the colorless solid was filtered. Concentration of the filtrate (to 4 mL) gave a second crop (0.31 g, 88% total), mp 210 °C dec (depends on rate of heating). The material crystallizes from absolute EtOH as either plates or needles.

Anal. Calcd for $C_{13}H_{10}N_2OBr_2$: C, 42.16; H, 2.70; N, 7.57; Br, 43.24. Found: C, 42.17; H, 2.76; N, 7.54; Br, 43.14.

The free base was obtained by mixing $NaHCO_3$ (28 mg, 0.33 mmol), H_2O (1 mL), compound **13a**·HBr (80 mg, 0.22 mmol), and EtOH (4 mL), evaporating to dryness in vacuo, and extracting the residue with $CHCl_3$. Evaporation of $CHCl_3$ gave yellow needles, mp 185–186 °C dec. The yellow solid **13a** (as well as the yellow mother liquor) obtained by recrystallization from dry C_6H_6 turned colorless on rinsing with (moist) ether and then had mp 135–138 °C. The color change is reversed when the compound is boiled with C_6H_6. An analytical sample of solid **13a**·H_2O was dried at 60 °C in vacuo for 4 h: mass spectrum, mol wt 288 and 290.

Anal. Calcd for $C_{13}H_9N_2OBr{\cdot}H_2O$: C, 50.81; H, 3.58; N, 9.12; Br, 26.06. Found: C, 50.69; H, 3.59; N, 9.02; Br, 25.93.

3-Nitro-2-(*p*-nitrophenyl)imidazo[1,2-*a*]pyridine (14). (1) To a stirred, cold (0 °C), orange solution of compound **1b** (0.10 g, 0.95 mmol) in concentrated H_2SO_4 (0.75 mL) was added dropwise concentrated HNO_3 (~0.5 mL), whereupon it turned deep red. After 15 min it was poured on ice and partially neutralized with aqueous 20% NaOH (pH 2) to give orange and colorless crystals, mp 220 °C dec (gradual darkening ≳140 °C) (70 mg, ~50%). On crystallization from absolute EtOH the colored material dissolved more readily than the colorless one, a light tan powder separating on cooling. The powder turned orange overnight and was then crystallized three times from acetone to give pale yellow needles: mp 262 °C dec (gradual darkening ≳200 °C); mass spectrum, mol wt 284; IR 850 cm^{-1} (para-substituted phenyl).

Anal. Calcd for $C_{13}H_8N_4O_4$: C, 54.93; H, 2.82; N, 19.72. Found: C, 54.75; H, 2.90; N, 19.64.

Its mass and IR spectra are the same as those of the dinitro compound prepared from compound **5** as described next.

(2) Compound **5** (0.12 g, 0.62 mmol) was treated as above to give a water-insoluble material (0.17 g, ~100%), mp 242–255 °C dec, that was recrystallized from acetone to give pale yellow needles: mp 263 °C dec (90 mg); ^1H NMR (δ, TFAA) 9.95 (d, H-5), 7.98 (t, H-6), 8.38 (overlap, H-7, 8), 8.15 (d, H_o), 8.62 (d, H_m). The material in the mother liquor was predominantly the mononitration product, 3-nitro-2-phenylimidazo[1,2-*a*]pyridine, according to its ^1H NMR spectrum (TFAA).

Treatment of the *N*-Oxide 1b with Acetic Anhydride. A solution of compound **1b** (0.10 g, 0.48 mmol) in acetic anhydride (0.5 mL) was heated at 100 °C for 22 h, when TLC indicated the presence of compounds **5**, **1b**, and at least six other components. The black solution was poured on ice, treated with aqueous 20% NaOH, and extracted with 4 × 5 mL of $CHCl_3$. The extracts were dried and subjected to chromatography to give compound **5** (20 mg, 25%), small amounts of the other components, and starting material **1b** (15 mg), eluted with 50% $C_6H_6/CHCl_3$ and 2% absolute EtOH/$CHCl_3$, respectively.

Treatment of the *N*-Oxide 1b with Phosphorus Oxychloride. To compound **1b** (0.20 g, 0.95 mmol) in $CHCl_3$ (2 mL) was added dropwise freshly distilled $POCl_3$ (1.5 mL). The solution was refluxed for 75 min. Evaporation in a stream of N_2 and in vacuo gave a thick brown oil that was treated with ice and aqueous 10% NaOH until the pH remained ca. 9. The mixture was extracted with 5 × 8 mL of $CHCl_3$; the extracts were dried, filtered, stripped of solvent, and

fractionated by chromatography with C_6H_6 into polychloro compounds (mass spectrum <5%) and compounds **6b**, mp 119–120.5 °C (70%), and **5** (~5%). After sublimation [115 °C (0.02 Torr)] compound **6b** had mp 120–122 °C, mass spectrum, mol wt 230 and 228.

Anal. Calcd for $C_{13}H_9N_2Cl$: C, 68.27; H, 3.94; N, 12.25. Found: C, 68.20; H, 3.97; N, 12.23.

Treatment of 2-Phenylimidazo[1,2-*a*]pyridine (5) with Phosphorus Oxychloride. When carried out as above, this reaction gave at the base treatment stage a solid which was filtered. Crystallization from hexane afforded pure starting material **5** (TLC and mixture melting point, 85% recovery).

Treatment of 3-Bromo-2-phenylimidazo[1,2-*a*]pyridine 1-Oxide (13a) with Phosphorus Oxychloride. On gently warming a mixture of the HBr salt of **13a** (0.30 g, 0.81 mmol), $NaHCO_3$ (0.13 g, 1.5 mmol), H_2O (3 mL), and EtOH (10 mL), solution was not achieved. The solvents were evaporated in vacuo and the dry residue was extracted with 3 × 10 mL of hot $CHCl_3$ to give the anhydrous free base **13a**. When $POCl_3$ was added as above, the solution turned red. It was heated and worked up as above by the $CHCl_3$ extraction method. The products were separated by chromatography with 50% hexane/C_6H_6. Mass spectra of early fractions indicated the presence of penta-, tetra-, tri-, and dihalo compounds. The last (30 mg, 14%) was primarily a dichloro compound, 3,8-dichloroimidazo[1,2-*a*]pyridine (mass spectrum) which decomposed on attempted crystallization from hexane: ^1H NMR (δ, $CDCl_3$) 8.05 (d, H-5), 6.85 (t H-6), 7.32 (d, H-7), 8.20 (m, H_o), 7.55 (m, H_m, H_p). Later fractions gave the 3-chloro-2-phenyl compound **6b** (100 mg, 54%).

Treatment of the *N*-Oxide 1b with Sodium Borohydride. When a solution of compound **1b** (0.21 g, 1 mmol) in EtOH (3 mL), treated with $NaBH_4$ (12.5 mg, 0.33 mmol) in EtOH (5 mL), was left to stand 30 min, only starting material was detectable by TLC. The solution was then heated on the steam bath for 1 h, left to stand overnight, filtered, and evaporated to dryness in vacuo to give starting material (0.20 g, 95% recovery; ^1H NMR).

Reaction of *N*-Oxide 1b with Zinc. After refluxing a stirred mixture of compound **1b** (0.17 g, 0.81 mmol), Zn dust (0.50 g, 7.6 mmol), and aqueous 5% H_2SO_4 (10 mL) for 30 min, no further starting material remained (TLC). A solid was filtered and rinsed with H_2O. When the filtrates were treated with aqueous 20% NaOH, a copious white precipitate was obtained that did not dissolve at pH 11–12. It was filtered, washed with H_2O, dried in vacuo and extracted with hot hexane to give compound **5** (90 mg). The aqueous filtrates, treated with dilute H_2SO_4 to pH 9, were extracted with 3 × 10 mL of $CHCl_3$. Extracted material was recrystallized from hexane to give a second crop of compound **5** (20 mg, 70% total).

Treatment of the *N*-Oxide 1b with Hydrogen Iodide. A solution of compound **1b** (50 mg) and aqueous 48% HI (0.2 mL) in absolute EtOH (3 mL) was refluxed. After 2 h, trace amounts of compound **5** had formed (TLC). I_2 was detectable with moistened starch paper. After 3 days, TLC indicated the presence of large amounts of compounds **5** and **6c** and small amounts of starting material and its iodination product **13b**, confirmed by mass spectra. After evaporating the solvent, dilution with ice/H_2O, and addition of 2.5 N NaOH to pH 10, the mixture was extracted with 3 × 5 mL of $CHCl_3$. The extracts were dried and stripped of solvent to give 71 mg of the four-component mixture.

Treatment of Compounds 6c and 13b with Sodium Borohydride. The above mixture was dissolved in absolute EtOH and treated with $NaBH_4$ (6 mg). TLC showed the presence of only the nonhalogenated compounds **5** and **1b** after 20 min. The solution was evaporated to dryness and the residue separated by chromatography into compounds **5** (30 mg, eluted with 50% C_6H_6/$CHCl_3$) and **1b** (15 mg, eluted with 2% absolute EtOH/$CHCl_3$).

Treatment of 3-Bromo- and 3-Chloro-2-phenylimidazo[1,2-*a*]pyridines (6a and 6b) with Sodium Borohydride. When a mixture of halo compounds **6a** and **6b** (from H_2NOH reaction with the salt **4**) was treated as above with $NaBH_4$ (tenfold molar excess), no dehalogenated material (**5**) could be detected by TLC. Workup as above gave a residue with mass spectrum identical with that of the starting material.

2-Phenylimidazo[1,2-*a*]pyridine (5). When a mixture of phenacyl bromide (2.0 g, 10 mmol) and 2-aminopyridine (1.0 g, 10 mmol) was heated, a vigorous reaction ensued.[17] After this subsided, the melt was kept at 80–100 °C for 2 h. It was dissolved in absolute EtOH (10 mL). Since addition of Et_2O gave an oil that could not be induced to crystallize, the supernatant was decanted, and the oil was treated with ice and aqueous 20% NaOH to pH 8. The separated oil was extracted with 3 × 15 mL of $CHCl_3$ and fractionated by chromatography into compound **5**, mp 130–131 °C (1.0 g, 60%, eluted with 50% C_6H_6/$CHCl_3$), and starting material (0.15 g, eluted with $CHCl_3$). Compound **5** crystallized from hexane as needles, mp 133–133.5 °C (lit.[16] mp 135 °C and lit.[17] mp 140 °C), mass spectrum, mol wt 194.

3-Bromo-2-phenylimidazo[1,2-*a*]pyridine (6a). To a stirred solution of compound **5** (0.19 g, 1 mmol) in absolute EtOH (5 mL) was added dropwise a solution of Br_2 (0.19 g, 1.2 mmol) in absolute EtOH (6 mL). When the Br_2 color no longer faded, addition was stopped, and the mixture was stirred an additional 5 min. The colorless, precipitated solid, **6a**·HBr, was filtered and rinsed with EtOH and Et_2O. Concentration of the filtrate gave a second crop (0.31 g total, 89%). Crystallization from EtOH gave needles, mp 249–250 °C dec.

Anal. Calcd for $C_{13}H_{10}N_2Br_2$: C, 44.07; H, 2.82; N, 7.91; Br, 45.20. Found: C, 44.05; H, 2.86; N, 7.90; Br, 45.09.

The free base, obtained by treating an aqueous solution of compound **6a**·HBr with aqueous 10% NaOH, followed by extraction with $CHCl_3$, was purified by sublimation [60 °C (0.02 Torr)] and had mp 63–64.5 °C (lit.[18] mp 83–85 °C and mp[19] 88–90 °C), mass spectrum, mol wt 272 and 274.

Anal. Calcd for $C_{13}H_9N_2Br$: C, 57.14; H, 3.30; N, 10.26; Br, 29.30. Found: C, 57.11; H, 3.37; N, 10.19; Br, 29.31.

The picrate, prepared by treating the free base **6a** (0.1 g, 0.36 mmol) in hot EtOH (5 mL) with picric acid (90 mg, 0.4 mmol) in hot EtOH (5 mL), crystallized as needles, partial melting ~140 °C, resolidifying, melting 151–152.5 °C, the same after crystallization from EtOH. Its ^1H NMR spectrum showed the presence of EtOH.

Anal. Calcd for $C_{13}H_9N_2Br{\cdot}C_6H_3N_3O_7{\cdot}0.75C_2H_5OH$: C, 45.85; H, 3.08; N, 13.05. Found: C, 46.39; H, 3.20; N, 13.45.

3-Iodo-2-phenylimidazo[1,2-*a*]pyridine (6c). An absolute EtOH solution (2 mL) of compound **5** (0.10 g, 0.5 mmol), treated with I_2 (0.20 g, 0.8 mmol) in absolute EtOH (3 mL), after standing 3 days deposited purplish-brown needles, mp 77 °C dec (0.24 g), of a mixture of compounds **6c**·HI and **6c**·HI_3. When this mixture was left to stand in aqueous dilute NaOH, it gradually changed to a colorless solid (**6c**, 67%) that was crystallized from hexane and then had mp 166 °C, mass spectrum, mol wt 320.

Anal. Calcd for $C_{13}H_9N_2I$: C, 48.75; H, 2.82; N, 8.75. Found: C, 48.84; H, 2.84; N, 8.63.

Registry No.—**1b**, 64413-99-6; **2a**, 952-75-0; **2b**, 64413-95-2; *syn*-**3**, 64413-94-1; *anti*-**3**, 64425-84-9; **4a**, 6273-90-1; **4b**, 7146-43-2; **5**, 4105-21-9; **6a**, 4044-95-5; **6a** HBr, 64413-93-0; **6a** picrate, 64413-92-9; **6b**, 64413-91-8; **6c**, 64413-90-7; **6c** HI, 64413-89-4; **6c** HI_3, 64440-83-1; **7**, 64413-88-3; **10** HCl, 34167-64-1; **11a**, 64413-87-2; **11b**, 64413-86-1; **11c**, 64425-85-0; **11d**, 64414-01-3; **12**, 64414-00-2; **13a**, 64413-98-5; **13a** HBr, 64413-97-4; **14**, 22244-94-6; phenacyl bromide, 70-11-1; 2-pyridone, 142-08-5; 2-bromopyridine, 109-04-6; hydroxylamine hydrochloride, 5470-11-1; picric acid, 88-89-1; methyl iodide, 74-88-4; acetic anhydride, 108-24-7; phosphorus oxychloride, 10025-87-3; 3,8-dichloroimidazo[1,2-*a*]pyridine, 64413-96-3.

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Reactions of 2-Methyl-2*H*-cyclopenta[*d*]pyridazine with Benzenediazonium Tetrafluoroborate and *N*-Nitrosoacetanilide[1,2]

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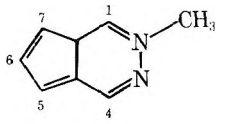
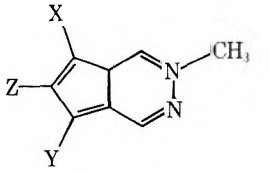
Reaction of **1** with 1 mol of $PhN_2^+BF_4^-$ in the presence of NaOAc gave the 5- (**2**) and 7-phenylazo derivatives (**3**) plus a little 5,7-diphenylazo product (**4**). Compound **4** was formed in high yield from **2** or **3**. Reaction of **1** with excess $PhN_2^+BF_4^-$ and NaOAc or with excess *N*-nitrosoacetanilide gave **4** and the 5,7-diphenylazo-6-phenyl derivative (**5**). Compound **5** was also obtained from **4** and *N*-nitrosoacetanilide or, in lower yield, from **4** and PhN_2^+ BF_4^- in the absence of NaOAc. Reaction of the 5,7-dibromo derivative (**6**) with excess $PhN_2^+BF_4^-$ gave the corresponding 6-phenylazo compound (**7**), electrophilic displacement of the 7-Br group (**9**), and introduction of the 6-phenylazo group plus displacement of the 7-Br (**8**) or 5-Br (**10**) groups. The 5,7-diiodo derivative reacted similarly. The substituent long-wavelength shifts were found to be approximately additive except for the 6-phenylazo group.

Preceding papers showed that 2-methyl-2*H*-cyclopenta[*d*]pyridazine (**1**) undergoes electrophilic mono- and diacylation[5] and mono-, di-, and trihalogenation.[6] The 5- and 7-trifluoroacetyl compounds, in contrast to the corresponding azulene derivatives, underwent disubstitution readily. The reactions of **1**, a π-excessive heteroanalogue of azulene, and several of its 5,7-disubstituted derivatives with benzenediazonium tetrafluoroborate and/or *N*-nitrosoacetanilide are now reported.



1

Reaction of **1** with 1.05 mol of benzenediazonium tetrafluoroborate in the presence of NaOAc readily formed the 5-phenylazo (**2**) and the 7-phenylazo (**3**) derivatives plus a small amount of the 5,7-diphenylazo compound (**4**). The ratio of **3** to **2** (2.5:1) corresponded approximately to those found previously for monoacylation[5] and monohalogenation[6] and provide additional evidence of the relative reactivity to electrophiles at the 5 and 7 positions. As for the acyl and halogen derivatives, the NMR chemical shift for H-4 was relatively larger than for H-1, *J* for the vicinal five-ring hydrogen coupling was smaller, and the NCH_3 was more deshielded for the 7-isomer (**3**). Treatment of **2** or **3** with 1 mol of the diazonium salt gave **4** in 100 or 82% yield, respectively. The formation of **4** under mild conditions (0 °C to room temperature) shows the high reactivity of the ring system despite the presence of the strong deactivating group (para σ = 0.64).



2, Y = PhN_2; X = Z = H
3, X = PhN_2; Y = Z = H
4, X = Y = PhN_2; Z = H
5, X = Y = PhN_2; Z = Ph
6, X = Y = Br; Z = H
7, X = Y = Br; Z = PhN_2
8, X = PhN_2; Y = Br; Z = H
9, X = Z = PhN_2; Y = Br
10, X = Br; Y = Z = PhN_2
11, X = Y = I; Z = H
12, X = PhN_2; Y = I; Z = H
13, X = Z = PhN_2; Y = I
14, X = I; Y = Z = PhN_2

The reaction of azulene with *N*-nitrosoacetanilide gives 1-phenylazoazulene and 1-phenylazulene.[7] It was of interest to see if **1** would exhibit this dichotomy of reactivity. Treatment of **1** with excess *N*-nitrosoacetanilide in benzene gave two products. The NMR spectrum of one (16%) showed a singlet at δ 8.2 which corresponded to those observed for H-6 in the previously characterized 5,7-bis(trifluoroacetyl), 5,7-dicarbomethoxy, and 5,7-diacetyl derivatives.[5] It possessed two phenylazo groups and was therefore assigned the structure of the expected 5,7-disubstitution product **4**. The major product (45%) was somewhat unexpected. It had a phenyl substituent in addition to two phenylazo groups. The absence of NMR absorption for H-6 and the finding that the compound was formed (34%) from *N*-nitrosoacetanilide and **4** led to assignment of position 6 for the phenyl group (**5**). The yield of the latter reaction was markedly decreased to 5% when a tenfold excess of acrylonitrile was present. This result points to a radical mechanism for the phenylation.

The reaction of **1** with excess benzenediazonium tetrafluoroborate and NaOAc in MeOH–DMF also gave **5** (50%) and **4** (19%). The correspondence of the yields to those from the reaction with *N*-nitrosoacetanilide is suggestive of common intermediates. In the absence of NaOAc, reaction of **4** with the diazonium salt gave a decreased yield (9%) of **5**. Thus, the major path for phenylation apparently involves acetate and is not an electron transfer from the aromatic ring to the diazonium ion.[8] In the presence of added acid (phenyl radical formation inhibited and **4** largely protonated), the yield of **5** was <1%, and 70% of **4** was recovered.

Heating **4** with an excess of phenylazotriphenylmethane in benzene gave only a trace of **5**, and this reaction with **1** gave no phenyl substitution. Azulene also gave a lower yield of phenylation product with phenylazotriphenylmethane than with *N*-nitrosoacetanilide.[7]

The behavior of several other 5,7-disubstituted derivatives of **1** was explored. Reaction of the 5,7-dichloro derivative[6] with either benzenediazonium tetrafluoroborate or *N*-nitrosoacetanilide gave a complex mixture of products in trace amounts which were not further studied. A complex mixture was also obtained from the reaction of the dibromo derivative **6**[6] with excess benzenediazonium ion but in amounts such that four products could be identified. The principal one (16.7%) was formed by the introduction of a phenylazo group, and the absence of the signal for H-6 indicated **7** to be the structure. This was the first example of phenylazo substitution at the 6 position. The second product (5.8%) contained a phenylazo group in place of one of the bromines (absorption in the H-6 region was still present), and the more reactive 7-position (to form **8**) was considered the more probable for this electrophilic displacement. The ultraviolet and visible spectra of this product (**8**) were very similar to those of **3** (and dissimilar to those of **2**), and, in keeping with other derivatives having a strongly electron-attracting group in the 7 position,[5,10] the NMR spectrum showed a relatively large (0.84 ppm) chemical-shift difference between H-1 and H-4. Analogous substi-

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tutions for groups other than hydrogen have been observed with azulene derivatives.[9] An attempt to isolate the isomeric 5-phenylazo-7-bromo compound, which would be expected to be formed in about one-third the amount of **8**, from the residual product mixture was not successful. Two isomeric products (4.6 and 1.7%) contained two phenylazo groups, one arising from the displacement of the 7- or 5-Br, respectively, and the other indicated to be at the 6 position by the absence of NMR absorption for this hydrogen. The ultraviolet and visible spectra of these compounds were similar to those of **3** and **2**, respectively. These data and the yield ratio (2.7:1) led to the assignments of structures **9** and **10**.

The reaction of the 5,7-diiodo derivative **11**[6] with 2 equiv of the diazonium salt also gave a complex product mixture, and it was possible to isolate only three compounds which were given structures **12** (7.4%), **13** (7.7%), and **14** (0.7%), corresponding to **8**, **9**, and **10**. As with the latter, comparisons of the ultraviolet, visible, and NMR spectra with those of **2** and **3**, as well as with those of **8–10**, were used in assigning the structures. The H-1, H-4 chemical-shift difference was 0.94 ppm for **12**. Spectral comparison was of particular importance for the unstable **14** for which an elementary analysis was not obtained. A possible alternative structure, the 5-phenylazo-7-iodo compound, was considered unlikely, since the wavelength of the strongest absorption band was at 413 nm, in the region (ca. 375–410 nm) found for **9**, **10**, and **13**, similar compounds which have two phenylazo groups, in contrast to the location of this band near 260 nm for **8** and **12** which have one phenylazo group.

The earlier studies[5,6] on electrophilic substitution products of **1** showed that halogen and trifluoroacetyl groups caused spectral shifts of the long-wavelength absorption which were qualitatively additive for substituents in the 5, 6, and 7 positions. The data for the phenylazo derivatives from the present study are given in Table I. While the results do not permit the direct calculation of many shift values, the shift additivity seems to hold approximately for the 5,7-di-N=NPh, 5-Br-7-N=NPh, and 5-I-7-N=NPh compounds, but not for those compounds containing a 6-N=NPh group. The presence of a 5- or 7-N=NPh group overshadows the presence of other groups [5-N=NPh (**2**), 7-Br-5,6-di-N=NPh (**10**), and 7-I-5,6-di-N=NPh (**14**), all absorb at 412 ± 1 nm, and 7-N=NPh (**3**), 5-Br-7-N=NPh (**8**), 5-Br-6,7-di-N=NPh (**9**), 5-I-7-N=NPh (**12**), and 5-I-6,7-di-N=N-Ph (**13**) all absorb at 471 ± 3 nm]. When both 5- and 7-N=NPh groups are present, the 7-N=NPh dominates [5,7-di-N=NPh (**4**) absorbs at 469 nm and 6-Ph-5,7-di-N=NPh (**5**) at 480 nm]. No reaction was observed between the 5,7-bis(trifluoroacetyl) compound[5] and *N*-nitrosoacetanilide or between the 5,7-dicarbomethoxy compound[5] and the benzenediazonium salt. Treatment of the diester with *N*-nitrosoacetanilide gave mostly recovered diester and a trace of red product which was not characterized.

Table I. Long-Wavelength Spectral Shifts for Phenylazo-Substituted 2-Methyl-2*H*-cyclopenta[*d*]pyridazines

Substituent	λ_{max}[a] (obsd)	$\Delta\lambda_{max}$[a]	λ_{max}[a,b] (calcd)
2-CH_3[c]	395		
5-N=NPh	412	17	
7-N=NPh	468	73	
5,7-di-N=NPh	469	74	485
6-Ph-5,7-di-N=NPh	480	85	
6-Ph[d]			406[d]
5,7-di-Br,6-N=NPh	476	81	
6-N=NPh[d]			451[e]
5-Br-7-N=NPh	473	78	(476)[f]
5-Br-6,7-di-N=NPh	470	75	(516)[f]
7-Br-5,6-di-N=NPh	411	16	(485)
5-I-7-N=NPh	474	79	(474)[g]
5-I-6,7-di-N=NPh	474	79	(530)[g]
7-I-5,6-N=NPh	413	18	(481)[h]
5,6-di-N=NPh[d]			394[i] (400)[j]
6,7-di-N=NPh[d]			(462)[f] (468)[h]

[a] Nanometers. [b] Calculated on basis of additivity of shifts. [c] Parent system. [d] Not known. Calculated from 6-Ph-5,7-di-N=NPh. [e] Calculated from 5,7-di-Br.[6] [f] From calculated shift for 5-Br.[6] [g] From calculated shift for 5-I.[6] [h] From calculated shift for 7-I.[6] [i] From 7-Br-5,6-di-N=NPh. [j] From 7-I-5,6-di-N=NPh.

Experimental Section

Melting points were taken on a Fisher or Kofler hot stage and are uncorrected. Ultraviolet and visible spectra were recorded on a Cary Model 14 spectrophotometer. NMR spectra were recorded in δ (ppm) on a Varian Model A-60, T-60, or DA-60-11 spectrometer with reference to tetramethylsilane. Mass spectra were recorded on an Associated Electrical Industries MS-9 spectrometer with reference to perfluorotributylamine. Elemental analyses were performed by Dr. A. Bernhardt, Elbach über Engelskirchern, Germany. Reaction solvents were dry unless obviously otherwise. Organic solutions of products were dried over $MgSO_4$ unless otherwise specified. Davison silica gel (200–325 mesh) was used for column chromatography. Silica gel G or Merck GF-254 was used for plate chromatography. The petroleum ether had bp 20–40 °C.

5-Phenylazo-, 7-Phenylazo-, and 5,7-Diphenylazo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (2, 3, and 4) from 1. To a stirred solution of 157 mg (0.818 mmol) of benzenediazonium tetrafluoroborate in 4 mL of DMF at −65 °C was added dropwise a solution of 102 mg (0.773 mmol) of **1** and 63.3 mg (0.773 mmol) of dry NaOAc. After 45 min at −65 °C and after 40 min with the bath removed, the mixture was poured into H_2O and extracted with CH_2Cl_2. The residue from the combined, washed (saturated NaCl), dried extracts was chromatographed (column, 1:1 ethyl acetate–hexane).

Preparative plate chromatography of the first fraction (159 mg) (CH_2Cl_2) separated 142 mg of crude **3** from 4.2 mg of by-product, and further elution (MeOH–CH_2Cl_2) gave 10 mg of crude **4**. Crystallization of the **3** from CH_2Cl_2, plate chromatography (CH_2Cl_2), and recrystallization from CH_2Cl_2–hexane gave 57.1 mg (33%) of **3** as red needles, mp 116–118 °C. The analytical sample had mp 117.5–118 °C; UV λ_{max} (Et_2O) ($\epsilon \times 10^{-3}$) 258 (19), 293 (11.7), 392 (15.2), and 468 nm (14.3); NMR (acetone) δ 4.31 (s, 3 H), 6.72 (d of d, 1 H, J = 4 and 1 Hz), 7.2–8.0 (m, 6 H), 8.61 (d, 1 H, J = 1 Hz), and 9.43 (br s, 1 H). The infrared spectrum was recorded. Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.01; H, 5.62; N, 23.60.

Trituration of the crude **4** with ether and recrystallization from acetonitrile gave 3.7 mg (1.4%) of **4** as red needles, mp 222.5–223.5 °C, and otherwise (UV, vis, NMR) identical with an authentic sample.

Plate chromatography (CH_2Cl_2) of the second fraction (37.8 mg) separated 24.7 mg from more polar material, and rechromatography gave 22.8 mg (13%) of **2** as orange needles: mp 126–127 °C; UV λ_{max} (Et_2O) ($\epsilon \times 10^{-3}$) 233 (12.9), 257 (16.8), 316 (10.8), and 412 nm (26); NMR (acetone) δ 4.15 (s, 3 H), 6.77 (d of d, 1 H, J = 4.5 and 1 Hz), 7.2–8.0 (m, 6 H), 8.77 (d, 1 H, J = 1 Hz), and 9.32 (br s, 1 H); MS m/e 236.106 (calcd 236.110). The infrared spectrum was recorded. Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12. Found: C, 70.85; H, 5.28.

5,7-Diphenylazo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (4) from 2 or 3. A. From 3. A solution of 15.1 mg (0.078 mmol) of benzenediazonium tetrafluoroborate in 2 mL of methanol was added slowly to a cold (ice bath), stirred solution of 18 mg (0.0763 mmol) of **2** and 7.1 mg (0.087 mmol) of dry NaOAc in 0.25 mL of CH_2Cl_2 and 1 mL of methanol. The mixture was allowed to come to room temperature (90 min), the solvent was removed, and the residue was extracted into CH_2Cl_2. Addition of hexane and concentration gave 21.3 mg (82%) of **4**, mp 221.3–222.3 °C. The analytical sample (from acetonitrile) had mp 222.5–223 °C; UV λ_{max} (EtOH) ($\epsilon \times 10^{-3}$) 251 (12), 275 (sh, 7.92), 348 (21.5), and 469 nm (23): NMR (acetone) δ 4.44 (s, 3 H), 7.1–8.0 (m, 10 H), 8.2 (s, 1 H), 9.54 (d, 1 H, J = 1.2 Hz), and 9.77 (d, 1 H, J = 1.2 Hz); the infrared spectrum was recorded. Anal. Calcd for $C_{20}H_{16}N_6$: C, 70.57; H, 4.74; N, 24.69. Found: C, 70.59; H, 4.83; N, 24.94.

B. From 2. As described in A, except that a several molar excess of benzenediazonium tetrafluoroborate and NaOAc was used and final purification was effected by plate chromatography, from 3.2 mg (0.014 mmol) of **2** was obtained 4.7 mg (ca. 100%) of **4**, mp 216–221.5 °C, and otherwise (UV, vis, R_f) identical with the material from A.

Reaction of 1 with *N*-Nitrosoacetanilide. A mixture of 36.5 mg

(0.309 mmol) of 1 and 295.9 mg (1.8 mmol) of *N*-nitrosoacetanilide was dissolved in 10 mL of dry benzene. After 4 h the mixture was chromatographed (column, CH_2Cl_2). The first red band (50:1 $HCCl_3$–acetone) was rechromatographed (plate, 1:1 petroleum ether–CH_2Cl_2) and recrystallization of the red solid (H_2O–acetone) gave 9.9 mg (45%) of 5,7-diphenylazo-6-phenyl-2-methyl-2*H*-cyclopenta[*d*]pyridazine (**5**) as red needles: mp 262–264 °C; UV λ_{max} (Et_2O) ($\epsilon \times 10^{-3}$) 248 (sh, 18), 295 (18), 384 (41), and 480 nm (22); NMR (HOAc) δ 4.18 (s, 3 H), 6.88 (m, 10 H), 7.17 (br s, 5 H), 9.28 (s, 1 H), and 9.37 (s, 1 H). Anal. Calcd for $C_{26}H_{20}N_6$: C, 75.00; H, 4.82; N, 20.19. Found: C, 74.80; H, 4.97; N, 20.02.

The material from the second red band (20:1 $HCCl_3$–acetone) was rechromatographed (plate, 1:1 petroleum ether–CH_2Cl_2) five times. Plate rechromatography of the less polar of the two major bands (four times with 1:1 petroleum ether–CH_2Cl_2 and three times with 2:1 petroleum ether–CH_2Cl_2) and then recrystallization (H_2O–acetone) gave 29.2 mg of **5**. The material from the more polar band was separated (plate chromatograph, CH_2Cl_2) into two fractions. Trituration of the more polar material with ether gave 14.6 mg (15.5%) of **4**. Both **4** and **5** were identical (mp, UV, vis) with authentic samples.

Reaction of 1 with Excess Benzenediazonium Tetrafluoroborate. After 4 days, the red solution from the reaction of 31 mg (0.235 mmol) of **1**, 127 mg (1.55 mmol) of NaOAc in 4 mL of 1:1 DMF–MeOH with 310 mg (1.6 mmol) of benzenediazonium tetrafluoroborate was poured into 100 mL of H_2O and 75 mL of CH_2Cl_2, and the whole was shaken. Column chromatography (CH_2Cl_2) of the red oil from the washed (H_2O), dried CH_2Cl_2 layer and plate chromatography (1:4 petroleum ether–CH_2Cl_2) of the red solid obtained gave 48.6 mg (50%) of **5**, mp 260–262 °C, identical (UV, vis, R_f) with an authentic sample, and another red solid which, after trituration with ether, gave 11 mg of **4**, mp 219–221 °C. An additional 4.5 mg, mp 220–221 °C (total 15.5 mg, 19%), of 4 was obtained from the triturate. The material was identical (UV, vis, R_f) with an authentic sample.

Reaction of 4 with *N*-Nitrosoacetanilide. A. Absence of Inhibitor. After 6 h the solution from the reaction of 22.3 mg (0.0656 mmol) of 4 and 85.9 mg (0.522 mmol) of *N*-nitrosoacetanilide in 10 mL of dry benzene was chromatographed on silica gel (300:1 CH_2Cl_2–acetone). Plate chromatography (three times) of the material from the less polar band (1:1 CH_2Cl_2–petroleum ether) separated major (less polar) and minor bands from minor impurities. The major band gave 9.4 mg (34%) of **5**, mp 255–260 °C, and otherwise (UV, vis, R_f) identical with an authentic sample. The minor band contained 5.8 mg of unchanged **4**. Plate chromatobraphy (three times) of the material from the original more polar band (1:1 CH_2Cl_2–petroleum ether) afforded an additional 1.9 mg of **4**.

B. Plus Acrylonitrile. The reaction described in A was repeated with the addition of 0.5 mL (0.8 mmol) of dry acrylonitrile. The first eluent was 50:1 CH_2Cl_2–acetone. The more polar band from the plate chromatograph gave 1.4 mg (5.1%) of **5**, mp 262–265 °C, having UV and vis spectra identical with those of authentic material. The less polar band yielded 14.8 mg (66.4%) of unchanged **4**.

Reaction of 4 with Benzenediazonium Tetrafluoroborate. A. In DMF–MeOH. After 70 h, the solution from the reaction of 22.7 mg (0.0668 mmol) of **4** and 195 mg (1.01 mmol) of benzenediazonium tetrafluoroborate in 4 mL of 1:1 DMF–MeOH was poured into 75 mL of H_2O and 50 mL of CH_2Cl_2, and the whole was shaken. Plate chromatography (CH_2Cl_2) of the concentrate from the separated, washed (H_2O), dried, and filtered CH_2Cl_2 solution resolved three major bands. The least polar band gave 2.6 mg (9.4%) of **5**, mp 262–265 °C, and spectrally identical (UV, vis) with authentic material. The second band gave 0.8 mg of dark-purple needles: mp 210–240 °C (dec); UV λ_{max} (Et_2O) (D_{max}) 246 (sh, 0.36), 303 (0.38), 402 (0.68), and 499 nm (0.52) and not otherwise characterized. From the third band was obtained 12.4 mg (54.6%) of unchanged **4**.

B. In Acidic Methanol. A mixture of 26.7 mg (0.0785 mmol) of **4**, 325.4 mg (1.68 mmol) of benzenediazonium tetrafluoroborate, and 5 drops of concentrated HCl in 10 mL of MeOH was stirred for 70 h and then poured into 100 mL of CH_2Cl_2 and 75 mL of H_2O. The mixture was neutralized (K_2CO_3) and shaken. The aqueous phase was extracted with CH_2Cl_2, and the solvent was removed from the combined, washed (H_2O), dried, and filtered CH_2Cl_2 layers. Plate chromatography (CH_2Cl_2) of the residual red oil gave two main bands. Recrystallization (H_2O–acetone) of the material from the lesser yielded 0.3 mg (0.9%) of **5**, mp 263–266°C, and, similarly, the larger gave 18.6 mg (70%) of unchanged **4**.

Reaction of 5,7-Dibromo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (6) with Benzenediazonium Tetrafluoroborate. After 3 h the solvent was removed from the reaction solution of 137.7 mg (0.474 mmol) of **6**[6] and 416.1 mg (2.17 mmol) of benzenediazonium tetrafluoroborate in 5 mL of CH_2Cl_2, 2 mL of DMF, and 2 mL of MeOH. Plate chromatography (twice, 1:1 petroleum ether–CH_2Cl_2) of the red residual oil gave four major bands with overlapping of the middle ones. Recrystallization (H_2O–acetone) of the solid from the least polar band gave 31.1 mg (17%) of 5,7-dibromo-6-phenylazo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (**7**) as red needles: mp 189–195 °C; UV λ_{max} (Et_2O) ($\epsilon \times 10^{-3}$) 263 (sh, 16), 273 (18), 297 (sh 12), 312 (sh 11), 384 (11), and 476 nm (11); NMR (acetone) δ 4.4 (s, 3 H), 7.3–8.1 (two br m, 5 H), 8.83 (s 1 H), and 9.72 (s, 1 H). Anal. Calcd for $C_{14}H_{10}Br_2$: C, 42.64; H, 2.54; N, 14.21. Found: C, 42.86; H, 2.72; N, 14.41.

Rechromatography of the combined middle bands (CH_2Cl_2) resolved three major fractions. Recrystallization (H_2O–acetone) of the solid from the least polar band gave 9.1 mg (4.6%) of 5-bromo-6,7-diphenylazo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (**9**) as red needles, mp 189–193 °C; UV λ_{max} (Et_2O) ($\epsilon \times 10^{-3}$) 249 (14), 283 (13), 371 (38), 454 (24), and 470 nm (24); NMR (acetone) δ 4.48 (s, 3 H), 7.3–8.2 (two br m, 10 H), 9.79 (s, 1 H), and 9.94 (s, 1 H). Anal. Calcd for $C_{20}H_{15}N_6Br$: C, 57.28; H, 3.58. Found: C, 57.50; H, 3.71. The second band was a mixture which was not characterized. Recrystallization (H_2O–acetone) of the solid from the most polar band gave 8.7 mg (5.8%) of 5-bromo-7-phenylazo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (**8**) as red needles: mp 147–148 °C; UV λ_{max} (Et_2O) ($\epsilon \times 10^{-3}$) 259 (18), 297 (12), 391 (9.4), and 473 nm (9.4); NMR (acetone) δ 4.4 (s, 3 H), 8.1–7.25 (two br m, 6 H), 8.79 (s, 1 H), and 9.63 (s, 1 H). Anal. Calcd for $C_{14}H_{11}N_4Br$: C, 53.33; H, 3.49. Found: C, 53.44; H, 3.69.

Recrystallization (H_2O–acetone) of the solid from the fourth original band gave 3.3 mg (1.7%) of 5,6-diphenylazo-7-bromo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (**10**) as red needles: mp 164–167 °C; UV λ_{max} (Et_2O) (D_{max}) 240 (1.4), 255 (1.4), 312 (1.25), and 411 nm (1.97) with ϵ ca. 2×10^4. Anal. Calcd for $C_{20}H_{15}N_6Br$: C, 57.28; H, 3.58. Found: C, 57.69; H, 3.76.

Reaction of 5,7-Diiodo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (11) with Benzenediazonium Tetrafluoroborate. To the solution of **11** as obtained from the reaction of 87.6 mg (0.664 mmol) of 1 and 397.3 mg (1.75 mmol) of NIS in 15 mL of CH_2Cl_2,[6] was added 4 mL of 1:1 DMF–MeOH and 230 mg (1.2 mmol) of benzenediazonium tetrafluoroborate. After 2 h the red concentrate was chromatographed (plate, 1:1 CH_2Cl_2–petroleum ether). Rechromatography of the red solid obtained resolved a major, two minor, and several trace bands. The major, least polar band gave 101.5 mg of red crystals, mp 135–145 °C. Recrystallization from acetone separated 23.9 mg (7.7%) of 5-iodo-6,7-diphenylazo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (**13**) as red needles: mp 218–219 °C; UV λ_{max} (Et_2O) ($\epsilon \times 10^{-3}$) 248 (14), 291 (14), 379 (36), 460 (21), and 474 nm (21); NMR (Me_2SO) δ 4.44 (s, 3 H), 8.2–7.3 (two br m, 10 H), 9.8 (s, 1 H), and 9.95 (s, 1 H). Anal. Calcd for $C_{20}H_{15}N_6I$: C, 51.50; H, 3.22. Found: C, 51.28; H, 3.38. Addition of H_2O to the filtrate and recrystallization of the precipitate from H_2O–acetone gave 33.4 mg of red needles which the NMR spectrum indicated to contain ca. 60% of **12**.

Recrystallization (H_2O–acetone) of the material from the second band gave 5.4 mg (2.3%) of 5-iodo-7-phenylazo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (**12**) as red needles, mp 171–173 °C. The second crop was 12.3 mg: mp 166–168 °C (total 17.7 mg, 7.4%); UV λ_{max} (Et_2O) ($\epsilon \times 10^{-3}$) 259 (14), 307 (12), 391 (8.8), and 474 nm (8.6); NMR (acetone) δ 4.46 (s, 3 H), 7.4–8.05 (two br m, 6 H), 8.7 (s, 1 H), and 9.64 (s, 1 H). Anal. Calcd for $C_{14}H_{11}N_4I$: C, 46.41; H, 3.04. Found: C, 46.25; H, 3.21.

Recrystallization (H_2O–acetone) of the solid from the third band gave 2.1 mg (0.7%) of red needles, mp 164–166 °C, tentatively characterized as **14** (spectral analogy to **10**): UV λ_{max} (Et_2O) (D_{max}) 233 (0.45), 250 (sh 0.41), 323 (0.4), and 413 nm (0.52).

Registry No.—**1**, 22291-85-6; **2**, 64414-29-5; **3**, 64414-28-4; **4**, 64414-27-3; **5**, 64414-26-2; **6**, 55268-20-7; **7**, 64414-25-1; **8**, 64414-24-0; **9**, 64414-23-9; **10**, 64414-22-8; **11**, 55268-23-0; **12**, 64414-21-7; **13**, 64414-20-6; **14**, 64414-19-3; benzenediazonium tetrafluoroborate, 369-57-3; *N*-nitrosoacetanilide, 938-81-8.

References and Notes

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(2) From the Ph.D. Thesis of L.D.G. (1970) and D.M.F. (1967), University of Washington.
(3) National Institutes of Health Fellow, 1968–1970.
(4) 3M Fellow, 1964–1965; National Science Foundation Summer Fellow, 1965.
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Relative Reactivity of Substituted 2-Alkoxy- and 2-Phenoxy-3,4-dihydro-2*H*-pyrans with *tert*-Butyl Hypochlorite. Effect of Substituents on Reactivity and Products[1]

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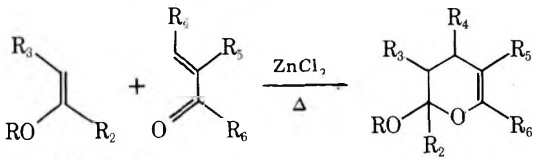
A series of substituted 3,4-dihydro-2*H*-pyrans were prepared: 2-methoxy- (**2a**), 2-methoxy-6-methyl- (**2b**), 2-methoxy-5-methyl- (**2c**), 2-methoxy-4-methyl- (**2d**), 2-methoxy-2-methyl- (**2e**), 2-methoxy-2,6-dimethyl- (**2f**), 2-ethoxy-3-methyl- (**2g**), 2-phenoxy- (**3a**), and 2-phenoxy-6-methyl-3,4-dihydro-2*H*-pyran (**3b**). The structure of each 3,4-dihydro-2*H*-pyran was discussed in terms of configuration, where applicable, and preferred conformation. Generally, addition of *tert*-butyl hypochlorite to 3,4-dihydro-2*H*-pyrans yields 1,2-addition products. However, in the 2-alkoxy-3,4-dihydro-2*H*-pyran series, an alkyl group at either position C-2 or C-6 results in some 1,4-addition product, and alkyl groups at both positions yield 1,4-addition products exclusively. The effect of substituents on the reactivity of the 3,4-dihydro-2*H*-pyran ring was determined using *tert*-butyl hypochlorite in competitive experiments with 3,4-dihydro-2*H*-pyran (**1**). The relative reactivities are **2f > 3b > 2b > 2d ≈ 2c > 1 > 2e > 2g > 2a ≈ 3a.**

Empirical observations in the course of our studies on the chemistry of 2-alkoxy-3,4-dihydro-2*H*-pyrans with various electrophilic reagents[2] has demonstrated an apparent dramatic effect of substituents on the reactivity of the 3,4-dihydro-2*H*-pyran ring, as well as on the course or outcome of the reaction.[1] The object of this study was to synthesize a series of substituted 2-alkoxy- (**2a–g**) and 2-phenoxy-3,4-dihydro-2*H*-pyrans (**3a,b**) and measure, in a relative sense with respect to 3,4-dihydro-2*H*-pyran (**1**), the effect of the substituent on both the reactivity of the 3,4-dihydro-2*H*-pyran ring system and product distribution using *tert*-butyl hypochlorite.

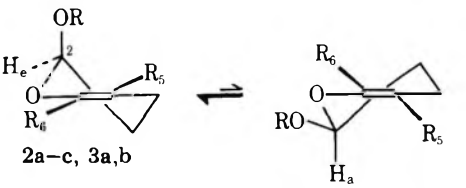
Synthesis and Structure. Substituted 2-alkoxy- and 2-phenoxy-3,4-dihydro-2*H*-pyrans generally are prepared by the thermally promoted cyclization[3] of appropriately substituted enol ethers and α,β-unsaturated aldehydes and ketones. We have found that the procedure[4] using various transition-metal salts as catalyst generally has an advantage over the thermally promoted cyclization, since both the temperature and reaction time for the cyclization can be drastically reduced. Because of this convenience, it is usually the method of choice even though the isolated yields for some of the substituted 3,4-dihydro-2*H*-pyrans are sometimes only moderate. Table I is a summary of the substituted 3,4-dihydro-2*H*-pyrans (**2a–g, 3a,b**) prepared by these procedures with the general reaction conditions and results.



R = CH_3, CH_3CH_2, C_6H_5
R_{2-6} = H, CH_3

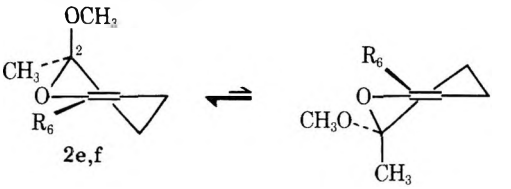
2a–g, 3a,b

The substituted 2-methoxy-3,4-dihydro-2*H*-pyrans **2a–c,** and the 2-phenoxy-3,4-dihydro-2*H*-pyrans **3a,b** all exist predominantly (ca. 80%, NMR analysis) in the conformation where the anomeric proton (H_e) is equatorial. The NMR signal for the anomeric C-2 proton at ca. δ 4.8 for the 2-methoxy-



2a–c, 3a,b

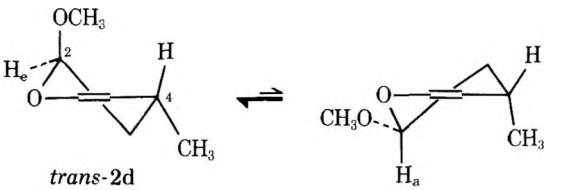
(**2a–c**) and at ca. δ 5.7 for the 2-phenoxy-3,4-dihydro-2*H*-pyrans (**3a,b**) is a superficial triplet ($J_{ea} \approx J_{ee}$ = ~3 Hz) as expected for an equatorial proton at this position. This preference in the conformational equilibrium of 2-alkoxy-3,4-dihydro-2*H*-pyrans has been previously observed[5] and is predicted by the anomeric effect (Edward–Lemieux effect).[6] Since there is also only one conformer detected (NMR and GLC analysis) for the 2-methoxy-2-methyl-3,4-dihydro-2*H*-pyran (**2e**) and its 6-methyl derivative **2f** (no anomeric



2e,f

proton in either), we assume the preferential conformation of these 3,4-dihydro-2*H*-pyrans to also have the C-2 methoxy group axial (anomeric effect), requiring the C-2 methyl to be in the favorable equatorial position.

In contrast, analysis (NMR and GLC) of 2-methoxy-4-methyl-3,4-dihydro-2*H*-pyran (**2d**) indicates a diastereomeric cis/trans mixture (60:40) at the anomeric C-2 carbon. The minor diastereomer *trans*-**2d,** derived from the exo approach



trans-2d

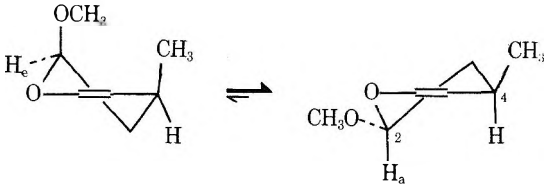
0022-3263/78/1943-0667$01.00/0

Table I. Synthesis of 2-Alkoxy- and 2-Phenoxy-3,4-dihydro-2*H*-pyrans[a]

Vinyl ether	α,β-Unsat carbonyl compd	Mole ratio, ether/carbonyl	Reaction Temp (°C)	Reaction Time (h)	Catalyst[b]	Product	Yield[c]
Methyl vinyl ether	Propenal	1.5:1	140	12		**2a**	44
Methyl vinyl ether	Methyl vinyl ketone	2:1	90	0.5	$ZnCl_2$	**2b**	35
Methyl vinyl ether	2-Methylpropenal	2.5:1	92	0.5	$ZnCl_2$	**2c**	10[d]
Methyl vinyl ether	*trans*-2-Butenal	1.2:1	200	12		**2d**	80[e]
Isopropenyl methyl ether	Propenal	2:1	60	1.5	$ZnCl_2$	**2e**	61
Isopropenyl methyl ether	Methyl vinyl ketone	1.2:1	25	5	$ZnCl_2$	**2f**	10[f]
1-Ethoxy-1-propene	Propenal	2.3:1	90	1.0	$ZnCl_2$	**2g**	68
Phenyl vinyl ether	Propenal	1.1:1	90	2.0	$ZnCl_2$	**3a**	36
Phenyl vinyl ether	Methyl vinyl ketone	1.1:1	90	0.75	$ZnCl_2$	**3b**	11[g]

[a] Reaction conditions are described in the Experimental Section for the synthesis of 2-methoxy-2-methyl-3,4-dihydro-2*H*-pyran (**2e**), which are the general procedures described in ref 3 (no catalyst) and 4 (catalyst). [b] For reactions using 0.4 mol of α,β-unsaturated carbonyl compound, 140 mg (1 mmol) of $ZnCl_2$ was used. [c] Distilled. [d] Low yield probably due to ease of polymerization of 2-methylpropenal. [e] Using conditions described in ref 4, 2 h at 70 °C in the presence of $ZnCl_2$, the yield was 68%. [f] Crude sample contaminated with 2,4-dimethoxy-4-methyl-1-pentene that required a spinning-band distillation to purify. The isopropenyl methyl ether dimer becomes a serious side product at higher temperatures. [g] Similar yield using 150 °C for 8 h with no $ZnCl_2$ conditions.

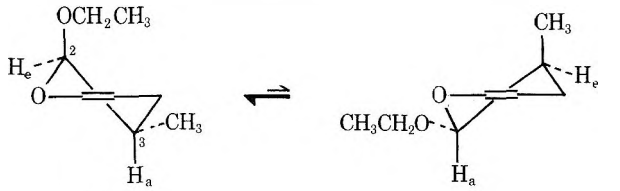
Diels–Alder type cyclization, exists predominantly in the conformation (equatorial anomeric proton) controlled by the anomeric effect. The NMR signal for the anomeric proton (H_e) is a triplet (J = ~3 Hz) at δ 4.76. The major diastereomer *cis*-**2d**, derived from the favored endo approach, exists pre-



cis-2d

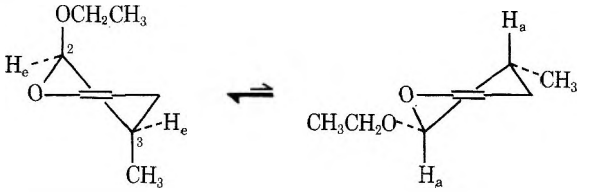
dominantly in the conformation where the anomeric proton is now axial. The NMR signal for H_a is a quartet (J = 7.5 and 2.5 Hz) centered at δ 4.72. In this diastereomer, the preferred equilibrium conformer is a result of the avoidance of the unfavorable 1,3-steric interaction of the axial methoxy group at C-2 and the pseudoaxial methyl group at C-4 rather than the influence of the anomeric effect.[5c,6d,7]

2-Ethoxy-3-methyl-3,4-dihydro-2*H*-pyran (**2g**) is also a diastereomeric cis/trans mixture (30:70) but at the C-3 carbon. The compounds were prepared from a cis/trans mixture of 1-ethoxy-1-propene. The product from the cis vinyl ether is *cis*-2-ethoxy-3-methyl-3,4-dihydro-2*H*-pyran (*cis*-**2g**), where



cis-2g

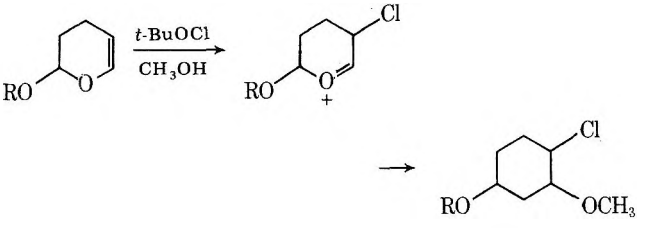
the cis configuration is retained in the adduct. The trans vinyl ether leads to the *trans*-**2g** adduct. Both diastereomers exist



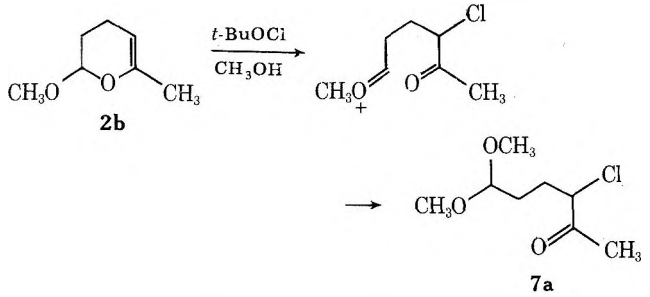
trans-2g

predominantly in the conformation where the anomeric proton at C-2 is equatorial, since the signal at δ 4.71 for this proton in the trans isomer is a doublet (J_{ee} = 1.3 Hz) and the signal at δ 4.51 for the cis isomer is a doublet (J_{ea} = 4.1 Hz).

Reaction and Products. The choice of *tert*-butyl hypochlorite as the electrophile for this study was made because of its reactivity, convenience in preparation and handling, and our familiarity with the reaction and the resultant products.[1] Table II is a listing of the products of the reaction of *tert*-butyl hypochlorite in methanol at 0 °C with each of the 2-alkoxy- (**2a–g**) and 2-phenoxy-3,4-dihydro-2*H*-pyrans (**3a,b**), as well as with 3,4-dihydro-2*H*-pyran (**1**). Generally, addition of *tert*-butyl hypochlorite to substituted 2-alkoxy-3,4-dihydro-2*H*-pyrans in alcohol solvents yields the corresponding 1,2-addition products. The 1,2-addition products are diastereomeric mixtures (usually two major and two minor isomers) that resulted from both cis and trans addition to the olefin.



In the 2-alkoxy series, alkyl substituents at either of two positions can result in a second type of product that has formed from 1,4-addition. When a methyl group is at either C-6 as in 2-methoxy-6-methyl-3,4-dihydro-2*H*-pyran (**2b**) or

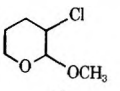
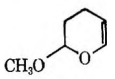
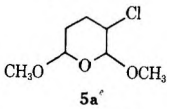
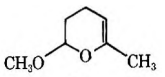
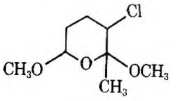
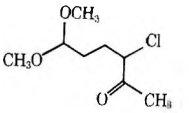
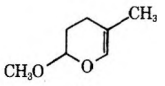
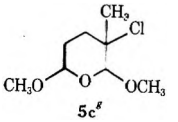
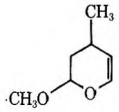
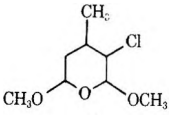
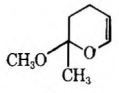
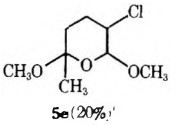
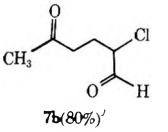
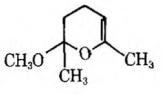
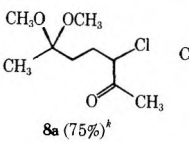
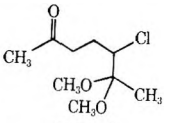
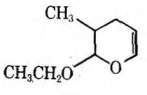
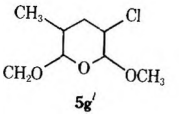
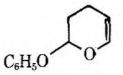
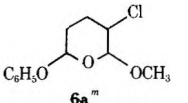
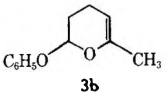
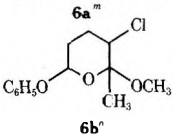


2b **7a**

C-2 as in 2-methoxy-2-methyl-3,4-dihydro-2*H*-pyran (**2e**), the second product is observed along with the 1,2-addition product. When an alkyl substituent is at both positions as is the case with 2-methoxy-2,6-dimethyl-3,4-dihydro-2*H*-pyran (**2f**), the 1,4-addition product forms *exclusively* (see Table II). It is not obvious why no 1,4-addition product was observed in the phenoxy series from 2-phenoxy-6-methyl-3,4-dihydro-2*H*-pyran (**3b**). However, at this time we can not rule out the possibility that some 1,4-addition product might be formed from a 2-alkyl or 2,6-dialkyl derivative.

Products of this nature, the 1,4-addition product as well as the 1,2-addition product, may prove to be useful synthons. In

Table II. *tert*-Butyl Hypochlorite Addition to 3,4-Dihydro-2*H*-pyrans[a]

Dihydropyrans[b]	Products[b] 1,2-Addition (yield)[c]	1,4-Addition (yield)[c]
 1	 4[d]	
 2a	 5a[e]	
 2b	 5b (48%)[f]	 7a (52%)
 2c	 5c[g]	
 2d	 5d[h]	
 2e	 5e (20%)[i]	 7b (80%)[j]
 2f		 8a (75%)[k]  8b (25%)[k]
 2g	 5g[j]	
 3a	 6a[m]	
 3b	 6b[n]	

[a] Reaction conditions are those described in the Experimental Section for 2-methoxy-2-methyl-3,4-dihydro-2*H*-pyran (2e) with *tert*-butyl hypochlorite. [b] Satisfactory composition analyses (±0.4% for C, H for the 3,4-dihydro-2*H*-pyrans and for C, H, Cl for the 1,2-addition products) were submitted to the editor. The 1,4-addition products were too unstable for satisfactory composition analyses. [c] Analyzed by GLC (% of volatiles). [d] A 85:15 cis/trans mixture. [e] A 38:62 diastereomeric mixture. [f] A 6:37:45:12 diastereomeric mixture. [g] A 25:20:55 diastereomeric mixture. [h] A 19:12:12:57 diastereomeric mixture. [i] Only one diastereomer formed. This ratio of products is reversed to 80:20 5e/7b when the reaction is performed at 45 °C. [j] Very unstable. Easily converted to the dimethoxy acetal in methanol. [k] Mixture decomposes readily to *m*-cresol. [l] A 40:35:7:11:7 diastereomeric mixture. [m] A 45:37:9:8 diastereomeric mixture. [n] A 46:5:14:35 diastereomeric mixture.

addition, the effect of substituents on the course of these reactions should now enable us to predict when to expect 1,4-addition products in our ongoing studies with other electrophilic reagents.

Relative Rate Studies. Relative rate studies between each of the substituted 3,4-dihydro-2*H*-pyrans (**2a–g, 3a,b**) and 3,4-dihydro-2*H*-pyran (1) were performed to measure the effect of substituents on the reactivity of the 3,4-dihydro-2*H*-pyran ring system. Equimolar mixtures of each substituted 3,4-dihydro-2*H*-pyran (**2a–g, 3a,b**) and 3,4-dihydro-2*H*-pyran (1) were allowed to compete for an equivalent of *tert*-butyl hypochlorite. The relative ratio (GLC analyses) of product material from the substituted 3,4-dihydro-2*H*-pyran and 3,4-dihydro-2*H*-pyran was then used to determine the reactivity of the substituted pyran relative to 3,4-dihydro-2*H*-pyran. These results are summarized in Table III. There is a substantial difference in the relative rates of the variously substituted 3,4-dihydro-2*H*-pyrans that must be directly attributable to the substituent or substituents. The most significant seems to be the deactivating effect of the axial alkoxy and phenoxy groups at the anomeric C-2 position and the activating effect of an alkyl group at C-6 toward electrophilic

Table III. Relative Reactivity of Substituted 3,4-Dihydro-2*H*-pyrans[a]

Pyran	Substituent(s)	Relative rate to Pyran 1[a]	Relative rate to Pyran 2a	Relative rate to Pyran 3a
1		1.00		
2a	2-Methoxy-	0.25 ± 0.08[b]	1.00	
2b	2-Methoxy-6-methyl-	3.60 ± 1.40	14.40	
2c	2-Methoxy-5-methyl-	1.42 ± 0.14	5.68	
2d	2-Methoxy-4-methyl-	1.43 ± 0.13	5.72	
2e	2-Methoxy-2-methyl-	0.80 ± 0.21	3.20	
2f	2-Methoxy-2,6-dimethyl-	5.40 ± 1.08	21.60	
2g	2-Ethoxy-3-methyl-	0.48 ± 0.13	1.92	
3a	2-Phenoxy-	0.24 ± 0.08		1.00
3b	2-Phenoxy-6-methyl-	5.10 ± 1.03		21.25

[a] Relative rate study conditions are those described in the Experimental Section for 2-methoxy-2-methyl-3,4-dihydro-2*H*-pyran (**2e**) vs. 3,4-dihydro-2*H*-pyran (**1**). [b] Standard deviation using experiments performed in triplicate.

reactions. Thus, the field effects for the axial alkoxy and phenoxy groups are electron withdrawing and for the methyl substituent directly attached to the unsaturation are electron donating as one might have predicted.[8]

When the reactivity of the alkyl-substituted 2-alkoxy- and 2-phenoxy-3,4-dihydro-2*H*-pyrans are calculated relative to 2-methoxy- (**2a**) and 2-phenoxy-3,4-dihydro-2*H*-pyran (**3a**), respectively, the effects of alkyl substituents on the 2-alkoxy- and 2-phenoxy-3,4-dihydro-2*H*-pyran ring systems are much more obvious (see Table III). For example, placing a methyl group on the 2-methoxy-3,4-dihydro-2*H*-pyran ring system at C-6 enhances the rate by a factor of ca. 14, and on the 2-phenoxy-3,4-dihydro-2*H*-pyran ring system by a factor of ca. 21.

Rate enhancements of this magnitude help explain our previous observations that peracid oxidations of 2-alkoxy-3,4-dihydro-2*H*-pyrans, which lead to 1,4-oxidation products, are sluggish compared to 2-alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans,[2a] that, although 2-alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans condense slowly with dimethyl acetylenedicarboxylate in refluxing toluene, 3,4-dihydro-2*H*-pyran (**1**) and its 2-alkoxy derivatives such as **2a** are seemingly inert,[2b] and, finally, that the 1,4-addition of tetracyanoethylene[9] to 2-alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans occurs at ambient temperatures and become exceedingly exothermic while the 2-alkoxy-3,4-dihydro-2*H*-pyrans react slowly with no detectable exotherm and require no external cooling.[2c] In addition, these relative reactivities will help in predicting which type of substituted 2-alkoxy-3,4-dihydro-2*H*-pyrans might be expected to react with various electrophilic reagents.

Experimental Section[10]

General Comments. The 2-alkoxy- (**2a–g**) and 2-phenoxy-3,4-dihydro-2*H*-pyrans (**3a,b**) were prepared by a general method previously described.[3,4] Dihydropyrans **1** and **2a** are available from Aldrich Chemical Co. The *tert*-butyl hypochlorite was prepared,[11] dried over $CaCl_2$, and stored in the dark below 0 °C. For best results it is recommended to use freshly prepared *t*-BuOCl. All solvents were reagent grade. All reactions were performed in oven-dried glassware under a static argon atmosphere. Gas chromatography analyses (GLC) were performed on 200 × 0.3 cm (i.d.) glass columns packed with 3.8% silicon gum rubber SE-30 (methyl) supported on 60–80 mesh Chromosorb W (AW, DMCS) or 10% silicon gum rubber XE-60 (25% cyanoethyl, methyl) or on a 150 × 0.3 cm (i.d.) glass column packed with 20% Carbowax 20M supported on 80–100 mesh Chromosorb W (AW, DMCS). Distillations were accomplished with a short-path or Kugelrohr apparatus; all boiling points are uncorrected. Column chromatography was performed on 60–100 mesh Floridin magnesium silicate (Florisil) or 70–230 mesh silica gel 60 (Merck) columns by eluting with pentane–Et_2O or hexane–benzene–Et_2O. The assigned structure of each product (or mixture) was consistent with the spectral data. Composition analyses (±0.4% for C, H, Cl) for all new dihydropyrans (**2c–g** and **3a,b**) and all new 1,2-addition products (**5c–e, 5g,** and **6a,b**) were submitted to the editor. The 1,4-addition products were too unstable for satisfactory composition analyses. Significant data on all new compounds are included in the Experimental Section. Representative experiments are described to illustrate these reactions.

2-Methoxy-2-methyl-3,4-dihydro-2*H*-pyran (2e). A 200-mL glass pressure bottle[12] that contained a mixture of 22.4 g (0.4 mol) of freshly distilled propenal, 200 mg of dihydroquinone, and 140 mg of anhydrous $ZnCl_2$ was charged with ca. 70 mL (0.8 mol) of 2-methoxypropene and heated with agitation at 60 °C for 1.5 h. After allowing the pressure vessel to cool, the vessel was carefully opened and the reaction mixture was removed, washed twice with water, and dried over anhydrous $MgSO_4$. Distillation yielded 30.8 g (61%) of **2e** as a colorless oil: bp 37 °C (16 Torr); n^{23}_D 1.4395; IR ($CHCl_3$) 1657 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 6.19 (1 H, d with further fine splitting, J = 7 Hz), 4.85–4.66 (1 H, m), 3.25 (3 H, s), 2.40–1.40 (4 H, complex m), 1.38 (3 H, s); mass spectrum *m/e* (rel intensity) 128 (M^+, 19), 113 (3), 97 (24), 72 (100), 42 (53).

Reaction of 2-Methoxy-2-methyl-3,4-dihydro-2*H*-pyran (2e) with *tert*-Butyl Hypochlorite. To a stirred solution (0–5 °C) of 640 mg (5.0 mmol) of 2-methoxy-2-methyl-3,4-dihydro-2*H*-pyran (**2e**) in 7.5 mL of methanol was slowly added 600 mg (5.5 mmol) of *tert*-butyl hypochlorite in 1.5 mL of methanol. After 10 min the reaction mixture was partitioned between brine and petroleum ether. The organic layer was separated, washed with water, and dried ($MgSO_4$). Removal of solvent in vacuo afforded 590 mg of a pale-yellow oil. Analysis (GLC) of the oil indicated a 20:80 mixture of 1,2-addition product **5e** and 1,4-addition product **7b**. Column chromatography (silica gel) afforded 90 mg (9%) of **5e** and 398 mg (54%) of **7b** as colorless oils.

3-Chloro-2,6-dimethoxy-6-methyltetrahydropyran (5e): bp 97–99 °C (14 Torr); NMR (100 MHz, $CDCl_3$) δ 4.42 (1 H, d, $J_{2,3}$ = 8.5 Hz, pseudoaxial anomeric proton at C-2), 3.62 (1 H, d of q, J = 8.5, 2.1, 1.6 Hz, C-3 proton), 3.51 (3 H, s), 3.27 (3 H, s), 2.30–1.90 (2 H, m), 1.90–1.50 (2 H, m), 1.34 (3 H, s); mass spectrum *m/e* (rel intensity) 165 (2), 163 (7), 136 (2), 134 (4), 105 (7), 94 (2), 92 (8), 72 (100), 42 (16).

2-Chloro-5-hexanon-1-al (7b):[13] bp 105 °C (13 Torr); IR ($CHCl_3$) 1733, 1717 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 9.43 (1 H, d, J = 1.8 Hz), 4.33 (1 H, t of d, J = 7, 1.8 Hz), 2.90–2.45 (2 H, m), singlet at 2.19 (3 H) superimposed on a multiplet at 2.45–1.50 (2 H); mass spectrum *m/e* (rel intensity) 148 (M^+, 0.5), 113 (5), 112 (5), 83 (9), 58 (26), 43 (100).

Relative Rate Study using Competitive Conditions. 2-Methoxy-2-methyl-3,4-dihydro-2*H*-pyran (2e) vs. 3,4-Dihydro-2*H*-pyran (1). To a stirred solution (0–5 °C) of 128 mg (1 mmol) of 2-methoxy-2-methyl-3,4-dihydro-2*H*-pyran (**2e**) and 84 mg (1 mmol) of 3,4-dihydro-2*H*-pyran (**1**) in 2 mL of methanol was added 108 mg (1 mmol) of *tert*-butyl hypochlorite in 0.2 mL of methanol. After 3 min the reaction mixture was worked up, as described above for the reaction with **2e**, and afforded an oil that was analyzed by GLC. The relative ratio of product material from **2e** vs. **1** was calculated by measuring the relative areas of all product peaks and then correcting these areas using predetermined response factors. These response factors[14] were determined under the analysis conditions by the use of standard solutions of known concentrations of each product or product mixture from each dihydropyran.

2-Methoxy-3,4-dihydro-2*H*-pyran (2a): bp 51 °C (80 Torr); n^{23}_D 1.4445; NMR (100 MHz, CCl_4) δ 6.11 (1 H, d with further fine splitting, J = 6 Hz), 4.77 (1 H, t, J = 3 Hz, equatorial anomeric proton), 4.73–4.54 (1 H, m), 3.37 (3 H, s), 2.22–1.62 (4 H, m).

2-Methoxy-6-methyl-3,4-dihydro-2*H*-pyran (2b): bp 52–54 °C (18 Torr); n^{23}_D 1.4447; NMR (100 MHz, CCl_4) δ 4.82 (1 H, t, J = 3 Hz, equatorial anomeric proton), 4.53–4.37 (1 H, m), 3.37 (3 H, s), 1.68 (3 H, broad singlet with fine splitting) superimposed on 2.20–1.50 (4 H, complex m).

2-Methoxy-5-methyl-3,4-dihydro-2*H*-pyran (2c):[5c] bp 56 °C (14 Torr); n^{23}_D 1.4483; IR (film) 1678 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 6.09–5.95 (1 H, m), 4.79 (1 H, t, J = 2.8 Hz, equatorial anomeric proton), 3.39 (3 H, s), 2.30–1.60 (4 H, m), 1.52 (3 H, br s); mass spectrum *m/e* (rel intensity) 128 (M^+, 50), 97 (37), 58 (42), 43 (80), 41 (100), 39 (75).

2-Methoxy-4-methyl-3,4-dihydro-2*H*-pyran (2d): bp 79–80 °C

(100 Torr); $n^{23}D$ 1.4420; NMR (100 MHz, CCl_4) δ 6.12 (0.6 H, q, J = 6.8, 2.3 Hz) overlapping 6.04 (0.4 H, q, J = 7.0, 2.3 Hz), 4.76 (0.4 H, t, J = 3 Hz, equatorial anomeric proton, trans isomer) overlapping 4.72 (0.6 H, q, J = 7.5, 2.5 Hz, axial anomeric proton, cis isomer), 4.59–4.40 (1 H, m), 3.39 (1.8 H, s, cis isomer), 3.36 (1.2 H, s, trans isomer), 2.50–2.10 (1 H, m), 2.10–1.70 (1 H, m), 1.60–1.20 (1 H, m), 1.02 (1.8 H, d, J = 6.8 Hz, cis isomer) overlapping 0.98 (1.2 H, d, J = 7.0 Hz, trans isomer); mass spectrum m/e (rel intensity) 128 (M^+, 100), 113 (51), 97 (34), 96 (28), 58 (98).

2-Methoxy-2,6-dimethyl-3,4-dihydro-2*H*-pyran (2f): bp 42 °C (1.5 Torr); $n^{23}D$ 1.4453; IR (film) 1685 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 4.56–4.42 (1 H, m), 3.21 (3 H, s), 1.70 (3 H, s with fine spitting), and 1.35 (3 H, s) superimposed on 2.30–1.30 (4 H, complex m); mass spectrum m/e (rel intensity) 142 (M^+, 34), 111 (40), 72 (100), 43 (60), 42 (40).

2-Ethoxy-3-methyl-3,4-dihydro-2*H*-pyran (2g): bp 52 °C (11 Torr); $n^{22}D$ 1.4380; IR (film) 1627 cm^{-1}; NMR (100 MHz, CCl_4) δ 6.04 (1 H, d of q, J = 6.3, 1.9 Hz), 4.71 (0.7 H, d, J_{ee} = 1.3 Hz, equatorial anomeric proton, trans isomer), and 4.51 (0.3 H, d, J_{ea} = 4.1 Hz, equatorial anomeric proton, cis isomer) superimposed on 4.75–4.45 (1 H, m), a complex system for the anisochronous ethoxy methylenes in the cis and trans isomers that includes four overlapping quartets centered at 3.86 (0.3 H, two overlapping q, J = 9.9, 7.2 Hz) and 3.76 (0.7 H, two overlapping q, J = 9.9, 7.2 Hz) and four overlapping quartets centered at 3.52 (0.7 H, two overlapping q, J = 9.0, 7.1 Hz) and 3.42 (0.3 H, two overlapping q, J = 9.0, 7.1 Hz), 2.40–1.35 (3 H, complex m), 1.18 (3 H, t, J = 7.2 Hz), 0.95 (3 H, d, J = 6.2 Hz); mass spectrum m/e (rel intensity) 142 (M^+, 15), 97 (14), 86 (70), 58 (100).

2-Phenoxy-3,4-dihydro-2*H*-pyran (3a): bp 98 °C (1 Torr); $n^{20}D$ 1.5931; IR (film) 1653 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 7.44–6.90 (5 H, complex m), 6.25 (1 H, d of q, J = 6.3, 2.7, 1.7 Hz), 5.69 (1 H, t, J = 3.1 Hz, equatorial anomeric proton), 4.95–4.75 (1 H, m), 2.60–1.80 (4 H, complex m); mass spectrum m/e (rel intensity) 176 (M^+, 18), 148 (3), 120 (9), 94 (56), 82 (100), 77 (20), 55 (45).

2-Phenoxy-6-methyl-3,4-dihydro-2*H*-pyran (3b): bp 104 °C (0.8 Torr); $n^{20}D$ 1.5316; IR (film) 1690 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 7.40–6.86 (5 H, complex m), 5.64 (1 H, t, J = 3.1 Hz, equatorial anomeric proton), 4.72–4.56 (1 H, m), 1.69 (3 H, singlet with fine splitting) superimposed on 2.56–1.46 (4 H, complex m); mass spectrum m/e (rel intensity) 190 (M^+, 10), 120 (7), 97 (100), 96 (95), 43 (75).

3-Chloro-2,6-dimethoxy-3-methyltetrahydropyran (5c): bp 115 °C (13 Torr); NMR (100 MHz, $CDCl_3$) δ 4.86 (0.3 H, superficial t, equatorial anomeric proton at C-6), 4.72 (0.7 H, t, J = ~4 Hz, equatorial anomeric proton at C-6), 4.65 (0.7 H, s, anomeric proton at C-2), 4.44 (0.3 H, s, anomeric proton at C-2), 3.52 (0.9 H, s), 3.46 (2.1 H, s), 3.44 (2.1 H, s), 3.42 (0.9 H, s), 2.20–1.95 (2 H, m), 1.95–1.60 (2 H, m), 1.55 (0.9 H, s), 1.52 (2.1 H, s); mass spectrum m/e (rel intensity) 195 (0.6), 193 (1.9), 165 (2), 163 (6), 136 (5), 134 (15), 108 (7), 106 (21), 85 (6), 71 (13), 58 (100).

3-Chloro-2,6-dimethoxy-4-methyltetrahydropyran (5d): bp 100–110 °C (11 Torr); NMR (100 MHz, CCl_4) δ 4.75 (0.7 H, superficial d, J = ~1.5 Hz, anomeric proton at C-2), 4.57 (0.7 H, d of d, J = 9.4, 3.7 Hz, anomeric proton at C-6) superimposed on 4.62 (0.3 H, t, J = ~2 Hz, anomeric proton at C-6) and 4.58 (0.3 H, d, J = ~1.5 Hz, anomeric proton at C-2), 3.89–3.81 (0.3 H, m), 3.78–3.69 (0.7 H, m), four singlets at 3.43, 3.41, 3.38, and 3.36 (6 H), 2.00–1.07 (3 H, complex m), 1.02 (2.1 H, d, J = 6.5 Hz) overlapping 0.99 (0.9 H, d, J = 6.5 Hz); mass spectrum m/e (rel intensity) 195 (1.2), 193 (3.7), 165 (5), 163 (16), 136 (1.8), 134 (5), 121 (5), 119 (14), 94 (21), 92 (67), 85 (32), 58 (100).

3-Chloro-6-ethoxy-2-methoxy-5-methyltetrahydropyran (5g): bp 90–95 °C (11 Torr); NMR (100 MHz, CCl_4) δ 4.63 (0.5 H, d, J = 3.1 Hz, anomeric proton at C-6), 4.53 (0.5 H, d, J = 2.8 Hz, anomeric proton at C-6), 4.40 (0.5 H, d, J = 3.8 Hz, anomeric proton at C-2), 4.35 (0.5 H, d, J = 5.5 Hz, anomeric proton at C-2), 4.05–3.64 (2 H, complex m), 3.40 (1.5 H, s) and 3.38 (1.5 H, s) superimposed on 3.61–3.21 (1 H, complex m), 2.30–2.05 (1 H, m), 2.05–1.35 (2 H, m), 1.19 (1.5 H, t, J = 7.4 Hz) overlapping 1.16 (1.5 H, t, J = 7.4 Hz), 0.93 (3 H, broadened d, J = ~6 Hz); mass spectrum m/e (rel intensity) 210 (M^+, 0.4), 208 (M^+, 1.1), 179 (1.5), 177 (4.5), 165 (3), 163 (8), 99 (12), 94 (32), 92 (100), 86 (88), 72 (18), 58 (46).

3-Chloro-2-methoxy-6-phenoxytetrahydropyran (6a): Fraction no. 4 (col chrom), crystals (1st major isomer): mp 62–65 °C; NMR (60 MHz, $CDCl_3$) δ 7.50–6.80 (5 H, complex m), 5.58–5.36 (1 H, superficial t, anomeric proton at C-6), 4.60 (1 H, d, J = 4 Hz, anomeric proton at C-2), 3.82–4.14 (1 H, m), 3.27 (3 H, s), 2.84–1.45 (4 H, m). Fraction no. 8 (col chrom), oil (ca. 17% 1st major isomer and 83% 2nd major isomer): NMR (100 MHz, $CDCl_3$) δ 7.40–6.90 (5 H, complex m), 5.64 (0.8 H, t, J = 3.0 Hz, anomeric proton at C-6) overlapping 5.58 (0.2, t, J = 3.0 Hz, anomeric proton at C-6), 4.71 (0.8 H, d, J = 7.2 Hz, anomeric proton at C-2) overlapping 4.67 (0.2 H, d, J = 7.0 Hz, anomeric proton at C-2), 3.82 (1 H, q, J = ~7 Hz), 3.35 (~2.5 H, s), 3.34 (~0.5 H, s), 2.44–2.13 (2 H, m), 2.13–1.80 (2 H, m); mass spectrum m/e (rel intensity) 244 (M^+, 4), 242 (12), 213 (1.6), 211 (5), 184 (2), 182 (6), 151 (30), 149 (92), 120 (100), 107 (36), 105 (67), 94 (34), 71 (66).

3-Chloro-2-methoxy-2-methyl-6-phenoxytetrahydropyran (6b): NMR (100 MHz, $CDCl_3$) δ 7.29–6.72 (5 H, complex m), 5.42 (0.60 H, t, J = 2.5 Hz, anomeric proton at C-6), 5.34 (0.15 H, t, J = 3.2 Hz, anomeric proton at C-6) overlapping 5.28 (0.25 H, q, J = 8.5, 3.2 Hz, anomeric proton at C-6), 4.08 (0.60 H, q, J = 5, 3.5 Hz), 3.93 (0.25 H, q, J = 5, 3.5 Hz), 3.82 (0.15 H, q, J = 5, 4 Hz), 3.38 (0.45 H, s), 3.36 (0.75 H, s), 3.03 (1.8 H, s), 2.95–2.0 (2 H, m), 2.0–1.65 (2 H, m), 1.49 (0.45 H, s), 1.48 (0.75 H, s), 1.42 (1.8 H, s); mass spectrum m/e (rel intensity) 258 (M^+, 2), 256 (M^+, 6), 243 (0.7), 241 (2), 227 (5), 225 (14), 199 (3), 197 (4), 184 (1), 182 (3), 165 (34), 163 (100), 133 (36), 120 (81), 119 (65), 94 (22), 85 (35), 77 (15), 43 (19).

3-Chloro-6,6-dimethoxy-2-heptanone (8a) and 5-Chloro-6,6-dimethoxy-2-heptanone (8b) Mixture.[15] Column chromatography (Florisil) yielded a 75:25 mixture of 3a/3b: IR (film) 1720 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 4.31 (0.75 H, q, J = 9, 6 Hz), 3.41 (0.25 H, q, J = 9, 2 Hz), 3.20 (6 H, s), 2.84–2.45 (0.5 H, m), 2.38 (2.25 H, s), 2.18 (0.75 H, s) superimposed on 2.4–1.4 (3.5 H, br m), 1.31 (3 H, br s); mass spectrum m/e (rel intensity) 127 (6), 121 (0.5), 119 (1.5), 100 (12), 89 (4), 78 (6), 58 (23), 43 (100).

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Registry No.—**1**, 110-87-2; **2a**, 4454-05-1; **2b**, 28194-35-6; **2c**, 38328-65-3; *cis*-**2d**, 38113-08-5; *trans*-**2d**, 38320-49-9; **2e**, 64331-96-0; **2f**, 64331-95-9; *cis*-**2g**, 60582-02-7; *trans*-**2g**, 60582-03-8; **3a**, 2720-53-8; **3b**, 64332-01-0; *cis*-**4**, 6559-29-1; *trans*-**4**, 6559-30-4; **5a**, 64331-94-8; **5b** isomer 1, 64331-93-7; **5b** isomer 2, 61092-60-2; **5b** isomer 3, 61092-61-3; **5b** isomer 4, 64331-92-6; **5c**, 64331-91-5; **5d**, 64331-90-4; **5e**, 64332-02-1; **5g**, 64332-00-9; **6a** isomer 1, 64331-99-3; **6a** isomer 2, 64331-98-2; **6a** isomer 3, 64331-97-1; **6a** isomer 4, 64331-83-5; **6b** isomer 1, 64331-82-4; **6b** isomer 2, 64331-81-3; **6b** isomer 3, 64331-80-2; **6b** isomer 4, 64331-79-9; **7a**, 61092-68-0; **7b**, 64331-78-8; **8a**, 64331-77-7; **8b**, 64331-76-6; *tert*-butyl hypochlorite, 507-40-4; methyl vinyl ether, 107-25-5; isopropenyl methyl ether, 116-11-0; *cis*-1-ethoxy-1-propene, 4696-25-7; *trans*-1 ethoxy-1-propene, 4696-26-8; phenyl vinyl ether, 766-94-9; propenal, 107-02-8; methyl vinyl ketone, 4170-30-3; 2-methylpropenal, 78-85-3; *trans*-2-butenal, 123-73-9; 5-chloro-6,6-dimethoxy-2-hexanone, 64331-75-5; 3-chloro-2,6-heptadione, 19995-88-1.

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(12) Washed in dilute NaOH solution, rinsed three times with distilled water, and oven dried immediately prior to use.
(13) Refluxing **7b** in methanol for 3 h yielded 5-chloro-6,6-dimethoxy-2-hexanone (89%): IR (film) 1717 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 4.36 (1 H, d, J = 6 Hz), 4.13–3.77 (1 H, complex m), 3.49 (6 H, s), 2.97–2.44 (2 H, complex m), 2.20 (3 H, s) superimposed on 2.44–1.46 (2 H, complex m); mass spectrum *m/e* (rel intensity) 165 (4), 164 (2), 163 (14), 162 (5), 127 (15), 107 (19), 105 (53), 75 (100), 47 (46), 43 (62).
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(15) This mixture is rather unstable. A refrigerated methanolic solution of **8a** and **8b** slowly decomposed to *m*-cresol in a few weeks. A stirred mixture of **8a** and **8b** in methanol at 25 °C for 4 days yielded 3-chloro-2,6-heptadione (83%): IR (film) 1725 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 4.33 (1 H, d of d, J = 8, 5.5 Hz), 2.9–2.4 (2 H, m), 2.35 (3 H, s) and 2.18 (3 H, s) superimposed on 2.4–1.7 (2 H, m), which after 24 h storage neat in a refrigerator had also decomposed to *m*-cresol.

Isoquinolines. 7.[1] Reaction of Ethylene Oxide with Isoquinolines. Novel Isoquinolone and Oxazolidine Formation

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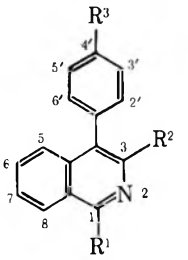
Aprotic deamination of 3-amino-1-bromo-4-nitrophenylisoquinoline (**6**) followed by partial reduction yielded 4-aminophenyl-1-bromoisoquinoline (**8**), and complete reduction yielded 4-aminophenylisoquinoline (**9**). Isoquinolines **8** and **9** when treated with excess ethylene oxide in acetic acid afforded 4-[*p*-bis(2-hydroxyethyl)amino]phenyl-2-(2-hydroxyethyl)-1-isoquinolone (**15a**) and 2-(2-acetoxyethyl)-4-[*p*-bis(2-hydroxyethyl)amino]phenyl-1-isoquinolone (**15b**). Evidence for a mechanism involving an oxazolidine intermediate is presented. When isoquinoline (**17**) was similarly treated with ethylene oxide, 2,3-dihydro-10b*H*-oxazolo[2,3-*a*]isoquinoline (**19**) was obtained.

In the course of preparing potential CNS antitumor agents, we recently reported that amine **1** afforded diol **2**, whereas amine **3** yielded a mixture of diol **4** and triol **5** when treated with excess ethylene oxide.[1] In continuation of this



Compd	R^1	R^2	R^3
1	Br	$NHCOCH_3$	NH_2
2	Br	$NHCOCH_3$	$N(CH_2CH_2OH)_2$
3	H	$NHCOCH_3$	NH_2
4	H	$NHCOCH_3$	$N(CH_2CH_2OH)_2$
5	H	$NH(CH_2)_2OH$	$N(CH_2CH_2OH)_2$
6	Br	NH_2	NO_2
7	Br	H	NO_2
8	Br	H	NH_2
9	H	H	NH_2
10a	Br	H	$N(CH_2CH_2OH)_2$
10b	Br	H	$NHCH_2CH_2OH$
10c	H	H	$N(CH_2CH_2OH)_2$

program we required isoquinolines lacking the 3-amino group. The deamination of **6**[2a] with isoamyl nitrite in dry THF yielded **7** (27–43%).[2b] Stannous chloride reduction of **7** yielded **8** (81%), and catalytic hydrogenation of **8** gave **9** (90%). Treatment of either **8** or **9** with excess ethylene oxide in acetic acid overnight at room temperature did not yield the expected isoquinoline diols **10a** or **10c** but gave isoquinolones **15a** and **15b** as shown in Scheme I. In particular, **8** afforded a mixture of **15a** and **15b** in 51 and 25% yield, respectively. The yield of **15a** from **9** was somewhat lower (34%). The reaction between isoquinolines and related compounds with epoxides has been previously observed,[3a–d] but only in one instance was isoquinolone formation noted.[4]

With the addition of excess sodium acetate to the reaction, monoacetate **15b** constituted as much as 50% of the product mixture. Compound **15b** could not be chromatographed on silica gel without extensive (50%) hydrolysis to **15a** and appeared thermally labile toward intermolecular acylation. Evidence for the intermolecular acylation was provided by the mass spectrum of **15b** which at 60 °C showed the expected molecular ion (*m/e* 410) and $M^+ - CH_2OH$ (*m/e* 379) as prominent peaks, but at 110 °C peaks assignable to a diacetate (*m/e* 452 M^+, *m/e* 421 $M^+ - CH_2OH$) and triacetate (*m/e* 494 M^+) of **15a** were also observed. In view of the instability of **15b**, mixtures of **15a** and **15b** were gently saponified to **15a** and treated with $SOCl_2$ in CH_3CN to give mustard **16** (49%) as shown in Scheme I.

A suggested mechanism for the transformation of **8** (X = Br) and **9** (X = H) to isoquinolones **15a** and **15b** is incorporated in Scheme I. Pertinent to the mechanism are the following observations: Diol **10a** can be isolated as the initial product in the reaction of **8** and ethylene oxide after short (2 h) reaction times. Prior to this study, solvent incorporation into isoquinolone products had not been reported, but the isolation and characterization of isoquinolone **15b** implicates intermediates **12–14** in the mechanism and precludes consideration of **11** as an intermediate in isoquinolone formation. Although a hydride transfer (X = H) has been suggested as the penultimate step in the reaction of **9** and ethylene oxide, the observation that no isoquinolone products are formed under conditions that rigorously exclude oxygen would argue for an oxidation step (X = OH or OOH) prior to oxazolinium

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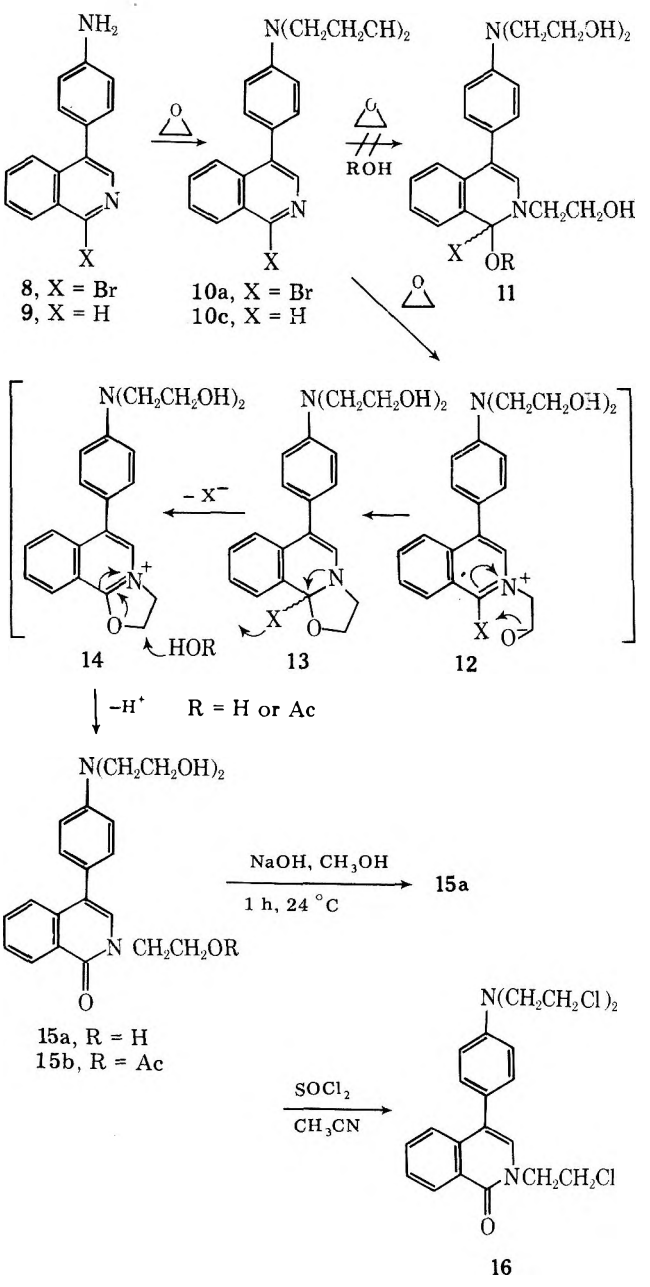
Scheme I



salt (**14**) formation.[5] The regiospecific attack of available nucleophile (H_2O or HOAc) on oxazolinium salt **14** at the methylene carbon adjacent to oxygen is precedented in analogous systems.[6a-c] Treatment of **8** in anhydrous CH_3OH with 30–60 equiv of ethylene oxide, with and without acid catalyst (TsOH), for 1–2 days led to a mixture of **10a** (26%) and **10b** (41%). No isoquinolone formation was noted.

Treatment of 3,4-dihydroisoquinoline with ethylene oxide has been shown by Schneider and Müller to yield an oxazolidine.[7] In our hands, the reaction of isoquinoline (**17**) and excess ethylene oxide at room temperature in acetic acid yielded transient intermediate **18** of undetermined structure which rapidly converted to oxazolidine **19** in 35% yield. No isoquinolone formation was observed. Compound **19** was stable for several days at room temperature in $CDCl_3$ solution, but while standing in air overnight it decomposed to a violet TLC (silical gel) immobile residue.[8] The structure of oxazolidine **19** as displayed in Scheme II is compatible with ^1H and ^{13}C NMR (Table I), IR, UV, and high- and low-resolution mass spectra.

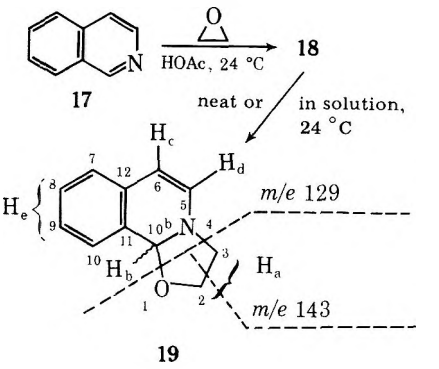
Analogues of **19** with substitution at positions 2 and 3 have been reported by the reaction of *N*-benzylisoquinolinium

Table I. NMR Spectra of 19[a]

^1H NMR	^{13}C NMR[b]
H_a 3.60 (m, 4)	C_2 62.307
H_b 5.25 (d, 1, $J_{b,d}$ = 0.5 Hz)	C_3 59.297
H_c 5.65 (d, 1, $J_{c,d}$ = 7.0 Hz)	C_5 130.486
H_d 6.30 (dd, 1, $J_{b,d}$ = 0.5 Hz, $J_{c,d}$ = 7.0 Hz)	C_6 102.529
H_e 7.50–7.00 (m, 4)	C_7 123.664[c]
	C_8 128.945
	C_9 124.842[c]
	C_{10} 133.899
	C_{10b} 76.122
	C_{11} 121.329
	C_{12} 134.441

[a] In $CDCl_3$. Chemical-shift values in parts per million downfield from internal $(CH_3)_4Si$. Proton and carbon assignments are shown in Scheme II. [b] Carbon assignments are based on both noise-decoupled and gated spectra with H irradiation applied during 0.33-s pulse delay after data acquisition. [c] The chemical-shift assignments for C_7 and C_9 are ambiguous and may be reversed.

Scheme II



halides with aldehydes.[9a,b] Furthermore, several methods of preparing more stable 5,6-dihydro analogues of **19** have been described.[7,10a-f] The present method represents an example of oxazolidine formation via epoxide insertion into an aromatic C=N bond. Unlike the reaction of isoquinoline and ethylene oxide, no oxazolidine was isolated from the reaction of **8** or **9** and ethylene oxide. The presence of the 4-phenyl group in putative oxazolidine intermediate **13** may promote oxazolinium salt (**14**) formation by facilitating leaving group (X) explusion. The lack of either isoquinolone or oxazolidine products when **1** or **3** is treated with ethylene oxide may reflect the decreased isoquinoline nitrogen nucleophilicity of **1** and **3**. In view of these observations, we are currently measuring pK_a values for this series of compounds.

Experimental Section

General Methods. Evaporations were carried out in a Büchi rotary evaporator in vacuo at temperatures below 50 °C. Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Samples for analysis were dried at 10^{-2} mm over silica gel at 55 °C. Thin-layer chromatography (TLC) was performed on 7 × 3 cm precoated silica gel 13179 poly(ethylene terephthalate) foils (Eastman Kodak, Rochester, N.Y.). Preparative TLC was carried out on silica gel plates (Analtech, 20 × 20 cm, 2000 μm). Detection was done by UV light (mineral light) or with iodine vapors. The IR spectra were measured in $CHCl_3$ or KBr on a Perkin-Elmer Model 700 spectrophotometer. The ^1H NMR spectra were obtained using a Varian T-60 spectrometer in $CDCl_3$ or CD_3SOCD_3 using $(CH_3)_4Si$ as an internal standard. The ^{13}C NMR spectra were obtained using a Varian XL-100 spectrometer with a Varian 620-I data system in $CDCl_3$ using $(CH_3)_4Si$ as an internal standard. The UV spectra were measured in EtOH using a Beckman DB-G grating spectrophotometer. Mass spectra were determined on a 12-90-G Nuclide (low resolution) mass spectrometer and a Dupont CEC-110 (high resolution) mass spec-

Table II. High-Resolution MS Data for 19

Peak (rel intensity) Calcd	Found	Empirical formula	Assignment
174.09188	174.09349 (2)	$C_{11}H_{12}NO$	$M^+ + 1$
173.08406	173.08787 (3)	$C_{11}H_{11}NO$	M^+
172.07623	172.08023 (4)	$C_{11}H_{10}NO$	$M^+ - 1$
143.07349	143.07539 (20)	$C_{10}H_9N$	$M^+ - CH_2O$
129.05784	129.05969 (100)	C_9H_7N	$M^+ - CH_2CH_2O$

trometer. Tetrahydrofuran (THF) and acetonitrile (CH_3CN) were distilled and dried over Linde molecular sieves prior to use.

1-Bromo-4-*p*-nitrophenylisoquinoline (7). A solution of 1.0 g (2.90 mmol) of amine **6**[29] in 60 mL of dry THF was added to a refluxing solution of 1.0 mL (872 mg, 7.5 mmol) of isoamyl nitrite (Aldrich 99%) in 20 mL of dry THF dropwise over the course of 1 h under N_2. The solution was stirred and refluxed under N_2 for 36 h and then cooled and stripped of excess solvent to yield 1.0 g of a yellow solid. The solid was recrystallized from 40 mL of CH_3CN, yielding 200 mg (21%) of **7** as a yellow solid, mp 216–219 °C. Concentration of the mother liquor to 20 mL and cooling to 4 °C yielded an additional 60 mg (6%) of **7**, mp 216–219 °C. Yields of recrystallized **7** varied from 27 to 43%. Preparative TLC (silica gel eluted with $CHCl_3$–Et_2O–hexane, 1:1:1) afforded an analytical sample of **7** (R_f 0.50): mp 222–224 °C; NMR ($CDCl_3$) δ 8.35 (m, 4), 7.70 (m, 5): IR ($CHCl_3$) 3000, 1600, 1550, 1525, 1355 cm^{-1}; UV_{max} (EtOH) 219 nm (log ε 4.47); MS *m/e* (rel intensity) 328 (100) M^+, 330 (96) $M^+ + 2$.

Anal. Calcd for $C_{15}H_9N_2O_2Br \cdot 0.5H_2O$: C, 53.27; H, 2.98; N, 8.29; Br, 23.63. Found: C, 53.50; H, 2.98; N, 8.19; Br. 23.48.

4-*p*-Aminophenyl-1-bromoisoquinoline (8). To a solution of 500 mg (1.5 mmol) of **7** in 10 mL of HOAc and 1.5 mL of concentrated HCl was added 2.0 g (9 mmol) of $SnCl_2 \cdot 2H_2O$ in 2 mL of concentrated HCl dropwise. The reaction was stirred at room temperature overnight and then cooled to 0 °C and filtered free of a yellow precipitate. The precipitate was dissolved in 25 mL of H_2O and the pH was adjusted to 11 with 20% aqueous NaOH. The aqueous solution was extracted with $CHCl_3$. Drying (Na_2SO_4), filtration, and evaporation of the $CHCl_3$ solution yielded 220 mg (49%) of **8** as a yellow solid. Basification and $CHCl_3$ extraction of the original acidic reaction filtrate yielded an additional 150 mg (33%) of amine **8**. Preparative TLC (silica gel eluted with $CHCl_3$–Et_2O–hexane, 1:1:1) afforded an analytical sample of **8** as an off-white amorphous solid (R_f 0.30): mp 152–154 °C; NMR ($CDCl_3$) δ 8.35 (m, 1, 8 H), 8.20 (s, 1, 3 H), 8.00–7.40 (m, 3), 7.30 (d, 2, J = 7 Hz), 6.80 (d, 2, J = 7 Hz), 3.90 (s, 2, NH_2, D_2O exchanges); IR ($CHCl_3$) 3450, 3350, 3000, 1620, 1550, 1520 cm^{-1}; UV λ_{max} (EtOH) 210 (log ε 4.46), 221 (4.56), 253 (4.33) nm; MS *m/e* (rel intensity) 298 (98) M^+, 300 (99) $M^+ + 2$.

Anal. Calcd for $C_{15}H_{11}N_2Br \cdot 0.5H_2O$: C, 58.45; H, 3.90; N, 9.09; Br, 25.93. Found: C, 58.71; H, 3.79; N, 8.99; Br, 25.80.

4-*p*-Aminophenylisoquinoline (9). A solution of 100 mg (0.33 mmol) of amine **8** and 100 mg (1 mmol) of Et_3N in 20 mL of absolute EtOH was Parr hydrogenated using 10 mg of 10% Pd/C at 40 psi of H_2 for 2 h (larger runs required longer periods of time and often catalyst change). The reaction was then gravity filtered and stripped of excess solvent. The residue was taken up in $CHCl_3$, washed with H_2O and brine, dried (Na_2SO_4), filtered, and evaporated to yield 66 mg (90%) of amine **9** as a glassy solid. Preparative TLC (silica gel eluted with EtOAc) provided an analytical sample of amine **9** (R_f 0.75): mp 45–55 °C; NMR ($CDCl_3$) δ 9.20 (s, 1, 1 H), 8.50 (s, 1, 3 H), 8.10–7.40 (m, 4), 7.30 (d, 2, J = 7 Hz), 6.80 (d, 2, J = 7 Hz), 4.00 (s, 2, NH_2, D_2O exchanges); IR ($CHCl_3$) 3450, 3350, 3000, 1620, 1570, 1520, 1495 cm^{-1}; UV λ_{max} (EtOH) 219 (log ε 4.73), 251 (4.18) nm; MS *m/e* (rel intensity) 220 (100) M^+.

Anal. Calcd for $C_{15}H_{12}N_2 \cdot 0.5H_2O$: C, 78.58; H, 5.71; N, 12.22. Found: C, 78.80; H, 5.30; N, 12.20.

***4-[p-Bis(2-hydroxyethyl)amino]phenyl-1-bromoisoquinoline* (10a) and 1-Bromo-4-*p*-(2-hydroxyethylamino)phenylisoquinoline (10b).** A solution of 300 mg (1 mmol) of amine **8** in 10 mL of dry [distilled from $Mg(OCH_3)_2$] CH_3OH and 1.5 mL (30 mmol) of ethylene oxide was allowed to sit at room temperature overnight. After this time solvent evaporation yielded 300 mg of a residue which was purified by preparative TLC (silica gel eluted with EtOAc) to yield 100 mg (25.8%) of diol **10a** (R_f 0.29): mp 73–78 °C; NMR ($CDCl_3$) δ 8.30 (m, 1, 8 H), 8.10 (s, 1, 3 H), 8.00–6.60 (m, 7), 4.50 (s, 2, OH, D_2O exchanges), 3.70 (m, 8); IR ($CHCl_3$) 3300, 3000, 1600, 1550, 1518, 1440, 1400 cm^{-1}; UV λ_{max} (EtOH) 213 (log ε 4.58), 221 (4.61), 266 (4.31) nm; MS *m/e* (rel intensity) 386 (52) M^+, 388 (41) $M^+ + 2$, 355 (100) $M^+ - CH_2OH$, 357 (69) $M^+ + 2 - CH_2OH$.

Anal. (molecular ion) calcd for $C_{19}H_{19}N_2O_2Br$: 386.06298, 388.06094. Found: 386.06288, 388.05888.

Alcohol **10b** (R_f 0.58) was isolated as a bright-yellow solid (140 mg, 40.8%): mp 149–152 °C; NMR ($CDCl_3$, CD_3SOCD_3) δ 8.30 (m, 1, 8 H), 8.15 (s, 1, 3 H), 8.00–6.70 (m, 7), 5.0 (s, 1, NH, D_2O exchanges), 4.50 (t, 1, J = 6 Hz, OH, D_2O exchanges), 3.80 (t, 2, J = 5 Hz, CH_2OH), 3.35 (t, 2, J = 5 Hz, CH_2NH); IR (KBr) 3250, 1600, 1520, 1440 cm^{-1}; UV λ_{max} (EtOH) 213 (log ε 4.55), 220 (4.61), 2.59 (4.25) nm; MS *m/e* (rel intensity) 342 (42) M^+, 344 (42) $M^+ + 2$, 311 (100) $M^+ - CH_2OH$, 313 (99) $M^+ + 2 - CH_2OH$.

Anal. Calcd for $C_{17}H_{15}N_2OBr$: C, 59.48; H, 4.41; N, 8.16; Br, 23.28. Found: C, 59.54; H, 4.60; N, 8.03; Br, 23.05.

4-[*p*-Bis(2-hydroxyethyl)amino]phenyl-2-(2-hydroxyethyl)-1-isoquinolone (15a) and Monoacetate (15b). From Amine 8. To 1.0 g (3.33 mmol) of amine **8** in 20 mL of glacial HOAc was added all at once 5 mL (100 mmol) of ethylene oxide at room temperature. After standing overnight at room temperature, the reaction was poured into 100 mL of ice water and basified with excess 20% aqueous NaOH. The solution was then extracted with $CHCl_3$. The $CHCl_3$ solution was washed with brine, dried (Na_2SO_4), filtered, and evaporated to yield 1.50 g of a froth. Purification by preparative TLC (silica gel eluted with 10% CH_3OH in EtOAc) yielded 620 mg (51%) of **15a** as a major product (R_f 0.30), negative Beilstein test: mp 75–80 °C; NMR (CD_3SOCD_3) δ 8.25 (m, 1, 8 H), 7.60–6.60 (m, 8), 4.40 (s, 3, D_2O exchanges), 4.10 (t, 2, J = 5 Hz, $CONCH_2$–), 3.60 (m, 10); IR ($CHCl_3$) 3350, 3000, 1639 (lactam C=O), 1610, 1590, 1520 cm^{-1}; UV λ_{max} (EtOH) 210 (log ε 4.54), 224 (4.31), 266 (4.31) nm; MS *m/e* (rel intensity) 368 (72) M^+, 366 (20) $M^+ - 2$ H, 337 (100) $M^+ - CH_2OH$. Anal. (molecular ion) Calcd for $C_{21}H_{24}N_2O_4$: 368.17360. Found: 368.17601.

Anal. Calcd for $C_{21}H_{24}N_2O_4 \cdot H_2O$: C, 65.27; H, 6.78; N, 7.25. Found: C, 65.55; H. 6.40; N, 7.18.

Monoacetate **15b** (R_f 0.60) was isolated as an oil (340 mg, 25%) contaminated with a small amount of **15a**. Spectra of monoacetate **15b**: NMR ($CDCl_3$) δ 8.50 (m, 1, 8 H), 7.60–6.60 (m, 8), 4.50–4.10 (m, 4), 4.00–3.50 (m, 8), 2.05 (s, 3, $COCH_3$); IR ($CHCl_3$) 3400, 3000, 1740 (acetate C=O), 1645 (lactam C=O), 1620, 1520 cm^{-1}; MS *m/e* (rel intensity) 410 (17) M^+, 379 (44) $M^+ - CH_2OH$. Anal. (molecular ion − 1) Calcd for $C_{23}H_{26}N_2O_5$: 409.17634. Found: 409.17856.

Mixtures of **15a** and **15b** were gently saponified with 1 equiv of NaOH in aqueous CH_3OH at room temperature for 2 h, yielding pure **15a**.

Diol **10a** could be isolated as the initial product of amine **8** and ethylene oxide after short (2 h) reaction times. In particular, 200 mg (0.66 mmol) of **8** yielded after workup and purification by preparative TLC (silica gel eluted with EtOAc) 70 mg (27%) of a froth (R_f 0.30), mp 73–78 °C, whose TLC mobility and IR and NMR spectra were identical to that of an authentic sample of **10a**.

From Amine 9. A solution of 700 mg (3.20 mmol) of amine **9** and 4.0 mL (80 mmol) of ethylene oxide in 20 mL of HOAc was allowed to sit at room temperature overnight. Workup in the usual fashion yielded 960 mg of a crude froth whose TLC (silica gel eluted with 10% CH_3OH in EtOAc) revealed the presence of isoquinolones **15a** and **15b**. In particular, preparative TLC (silica gel eluted with 10% CH_3OH in EtOAc) gave as a major product (R_f 0.30) 400 mg (34%) of a froth, mp 75–80 °C, whose TLC mobility and IR and NMR spectra were identical to isoquinolone **15a**. Conducting the reaction with the rigorous exclusion of O_2 resulted in a mixture of as yet unidentified products with no evidence of isoquinolone formation by IR.

4-[*p*-Bis(2-chloroethyl)amino]phenyl-2-(2-chloroethyl)-1-isoquinolone (16). To 300 mg (0.82 mmol) of **15a** in 70 mL of dry (stored over 4-Å molecular sieves) CH_3CN was added 0.125 mL (1.72 mmol) of $SOCl_2$ at room temperature. An immediate precipitate was observed but dissolved in the course of 1 h. After stirring overnight at room temperature, excess CH_3CN was stripped off and the residue was taken up in 40 mL of $CHCl_3$ and vigorously shaken with 1.0 g of $KHCO_3$ in 40 mL of H_2O. Drying (Na_2SO_4), filtration, and evaporation of the $CHCl_3$ solution yielded 424 mg of a brown froth. Purification by preparative TLC (silica gel eluted with $CHCl_3$–Et_2O–hexane, 2:1:1) afforded as a main product 170 mg (49%) of mustard **16** (R_f 0.50), positive Epstein and Beilstein tests: mp 171–173 °C; NMR ($CDCl_3$) δ 8.50 (m, 1, 8 H), 7.70–6.60 (m, 8), 4.35 (t, 2, J = 5 Hz, $CONCH_2$–), 4.10–3.50 (m, 10); IR ($CHCl_3$) 3000, 1650 (lactam C=O), 1620, 1520 cm^{-1}; UV λ_{max} (EtOH) 210 (log ε 4.65), 224 (4.43), 266 (4.43) nm; MS *m/e* (rel intensity) 422 (68) M^+, 424 (63) $M^+ + 2$, 426 (21) $M^+ + 4$, 373 (100) $M^+ - CH_2Cl$, 375 (79) $M^+ + 2 - CH_2Cl$, 377 (14) $M^+ + 4 - CH_2Cl$.

Anal. Calcd for $C_{21}H_{21}N_2Cl_3O$: C, 59.52; H, 5.00; N, 6.61; Cl, 25.10. Found: C, 59.38; H, 5.05; N, 6.50; Cl, 25.02.

2,3-Dihydro-10b*H*-oxazolo[2,3-*a*]isoquinoline (19). A solution

of 1.0 g (7.70 mmol) of isoquinoline and 12 mL (240 mmol) of ethylene oxide in 50 mL of glacial HOAc was allowed to sit at room temperature overnight. The solution (clear and colorless) was then cooled to 0 °C, basified with 20% aqueous NaOH, and extracted with $CHCl_3$. Drying (Na_2SO_4), filtration, and evaporation yielded 1.39 g of a yellow oil **18** that gradually turned deep red: NMR ($CDCl_3$) δ 7.20 (m, 4), 6.15 (d, 1, J = 7 Hz), 5.65 (d, 1, J = 7 Hz), 5.60 (s, 1), 3.50 (s, 4); IR ($CHCl_3$) 3000, 2940, 2875, 1625, 1560, 1490, 1460, 1430 cm^{-1}. After sitting overnight, the now red viscous oil was purified by preparative TLC (silica gel eluted with $CHCl_3$–Et_2O–hexane, 1:1:1) to yield 465 mg (35%) of oxazolidine **19** (R_f 0.50) as a viscous yellow oil. With exposure to air the oil turned violet: for ^1H and ^{13}C NMR ($CDCl_3$), see Table I; IR ($CHCl_3$) 3050, 3000, 2910, 1620, 1600, 1560, 1480, 1175 (OCN),[11a] 1120 (OCN),[11a] 1060 (OCN),[11a] 830 (OCN)[11b] cm^{-1}; UV λ_{max} (EtOH) 208 nm (log ε 3.97), 231 (3.67), 246 (3.45); For high-resolution MS data, see Table II.

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Registry No.—**6**, 31309-65-6; **7**, 64345-81-9; **8**, 64345-80-8; **9**, 64345-79-5; **10a**, 64345-78-4; **10b**, 64345-76-2; **15a**, 64345-77-3; **15b**, 64345-75-1; **16**, 64345-74-0; **19**, 64345-73-0; ethylene oxide, 75-21-8; $CHCl_3$, 67-66-3; isoquinoline, 119-65-3.

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Ozonation of Nucleophiles. 7.[1] Dibenzyl Sulfides

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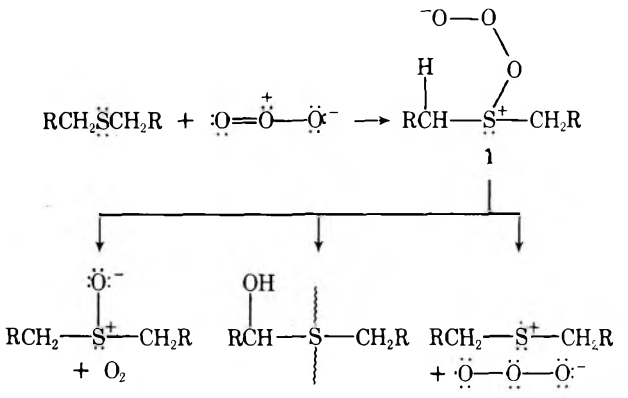
Ozonation of dibenzyl sulfide and two unsymmetrical benzyl sulfides afforded both sulfur and alkyl side-chain oxidation products. Sulfur oxidation was predominant in protic solvents and side-chain oxidation in hydrocarbon solvents. Ozonation of thianthrene produced the monoxide as the major product and the cation radical as a minor product. Mechanistic pathways are discussed.

Earlier papers in this series[1–5] elucidated the mechanistic pathways involved in the reactions of ozone with various types of aliphatic amines. After the initial reaction between the electrophilic ozone and the nucleophilic amine, four fates of the resulting adduct were proposed. Reactions analogous to the initial attack and three of the adduct fates should also be possible with suitable organic sulfides, as illustrated in Scheme I. These include sulfoxide formation (the only reaction previously shown to occur),[6–12] intramolecular side-chain oxidation, and cation–radical formation. It was the purpose of the present research to test this premise.

Scheme I



The ozonation of organic sulfides has been studied previously by several workers.[6–12] In all cases the only products isolated were the corresponding sulfoxides and/or sulfones, usually in high yields, although Barnard[11] reported the odor of butyraldehyde and butyric acid on the crude sulfone obtained from dibutyl sulfide. Maggiolo and Blair[9] and Horner et al.[10] found 1:1 and 1:2 sulfide–ozone stoichiometry in the conversions to sulfoxide and sulfone, respectively. For this and other reasons they[9,10] proposed electrophilic ozone attack, followed by loss of molecular oxygen from the adduct, as shown in Scheme I, followed by a similar attack on the sulfoxide. On the other hand, Barnard,[11] Boer and Kooyman,[8] and Thompson[12] stated that less than 1 mol of ozone per mole of sulfide was required. Thompson[12] found that close to three oxygen atoms (of ozone) per atom of sulfur participated in the oxidation.

In the earlier work just outlined,[6–12] protic solvents such as chloroform or water were used. Our studies were conducted with four different sulfides in both protic and nonprotic solvents and at two different temperatures. Table I displays the results obtained from ozonations of dibenzyl sulfide and of

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Table I. Ozonation of Dibenzyl Sulfides[a]

Expt	R and R′ in RCH_2SCH_2R'	Solvent	Temp, °C	Sulfide recovered, %	O_3/ sulfide reacting	C_6H_5CHO, %[b]	XC_6H_4CHO, %[b]	Sulfoxide, %[b]	Total product yield, %[b]
1	R = R′ = C_6H_5[h]	Pentane[c]	0	34	1.42	76	~	21	97
2	R = R′ = C_6H_5[h]	Isopentane[c]	0	41	1.46	75	~	27	102
3	R = R′ = C_6H_5[h]	CH_2Cl_2[d]	0	15	0.97	32	~	72	104
4	R = R′ = C_6H_5[h]	CH_2Cl_2[e]	−75	13	1.12	18	~	77	95
5	R = R′ = C_6H_5[h]	$CHCl_3$[d]	0	14	0.97	30	~	69	99
6	R = R′ = C_6H_5[h]	$CHCl_3$[f]	−40	11	0.85	16	~	84	100
7	R = R′ = C_6H_5[h]	CH_3OH[d]	0	6	0.85	2	~	97	99
8	R = R′ = C_6H_5[h]	CH_3OH[f]	−40	21	0.90	0	~	100	100
9	R = C_6H_5; R′ = p-ClC_6H_4[i]	Pentane[e]	−40	24	1.3	24	29	50	103
10	R = C_6H_5; R′ = p-ClC_6H_4[i]	$CHCl_3$[e]	−40	17	1.1	18	22	66	106
11	R = C_6H_5; R′ = p-ClC_6H_4[i]	CH_3OH[e]	−40	0	0.94	0	0	97	97
12	R = C_6H_5; R′ = p-$CH_3OC_6H_4$[j]	Pentane[f]	0[g]	0	1.0	16	12	48	76
13	R = C_6H_5; R′ = p-$CH_3OC_6H_4$[j]	CH_3OH[f]	0[g]	0	0.87	7	5	86	98

[a] Sulfide (3–5 mmol) and a 1:1 ratio of ozone to sulfide was employed. Neither the sulfide nor the ozone reacted quantitatively. The percentage of recovered sulfide is shown in column 5 and the ratio of reacted ozone to reacted sulfide is shown in column 6. Excess ozone was avoided in order to prevent oxidation of sulfoxide to sulfone and to minimize oxidation of any mercaptan produced. [b] Percent yield based on sulfide actually reacting (unrecovered) and an expected 1 mol of each product per mole of sulfide reacting by the route yielding this product. In cases where the total yield was greater than 100%, the discrepancy is probably due to mercaptan (produced along with aldehyde) also reacting with ozone to give aldehyde. [c] Solvent (25 mL) per millimole of sulfide. [d] Solvent (10 mL) per millimole of sulfide. [e] Solvent (55–65 mL) per millimole of sulfide. [f] Solvent (16 mL) per millimole of sulfide. [g] A higher temperature was used in these experiments in order to increase the proportion of side-chain oxidation products to sulfoxide. [h] Registry no.: 538-74-9. [i] Registry no.: 7693-40-5. [j] Registry no.: 16133-88-3.

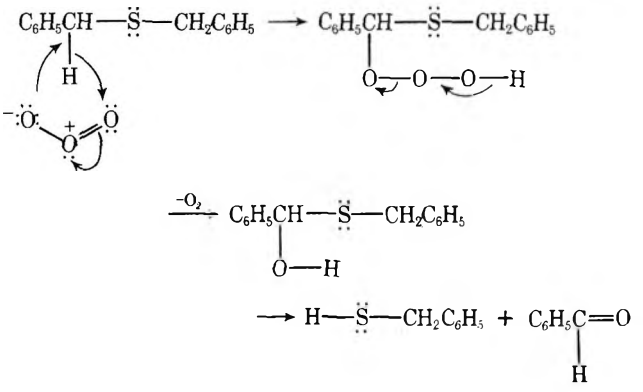
two unsymmetrically substituted dibenzyl sulfides, namely, the mono-*p*-chloro and -*p*-methoxy derivatives.

From a qualitative view of these data several facts are evident. First, both sulfur oxidation and alkyl group (side-chain) oxidation have occurred, in contrast to results of previous investigators. Second, side-chain oxidation is a major reaction only in hydrocarbon (nonprotic) solvents. Third, the more protic the solvent the lower the percentage of side-chain attack. Fourth, the lower the reaction temperature the lower the degree of side-chain attack.

These facts are reminiscent of the results obtained with *n*-butylamine[1] and tri-*n*-butylamine[2,3] and suggest that *side-chain attack occurs by a mechanistic pathway involving* the abstraction of a proton by the negative oxygen of adduct 1, as proposed earlier for amines with primary alkyl groups,[1-3] rather than by the 1,3-dipolar insertion mechanism[13] of Scheme II. Hydrogen bonding of the sulfide–ozone adduct 1 by the protic solvent would be expected[1-3] to slow down the proton abstraction, as required in the general equation of Scheme I. At low temperatures this abstraction would also be slow, and loss of oxygen to yield the sulfoxide should become increasingly favorable.

The results with the unsymmetrical dibenzyl sulfides also are qualitatively consistent with this mechanistic interpretation. With the *p*-chloro compound (experiments 9–11, Table I), the *ratio of p-chlorobenzaldehyde* to benzaldehyde was roughly 1.2, whereas the ratio of benzaldehyde to *p*-methoxybenzaldehyde from the *p*-methoxy sulfide (experiments 12 and 13) was 1.3–1.4. These results are more consistent with a carbanion-type transition state (Scheme I), which the *p*-chlorophenyl group should stabilize, than with a carbonium ion type transition state (Scheme II). However, the ratios are not as large as might be expected if the side-chain oxidation occurred entirely by the proton-abstraction mechanism. Therefore, it is quite possible that there is some competition from the mechanism of Scheme II. Both the *p*-chlorophenyl and the *p*-methoxyphenyl groups should stabilize the developing carbonium ion through resonance.

Scheme II



The proton-abstraction mechanism of Scheme I could proceed by at least three different pathways, as outlined in Scheme III. Pathways 1 and 2 are analogous to the pathways suggested for amines.[1-3] These would lead to benzaldehyde and benzyl mercaptan.

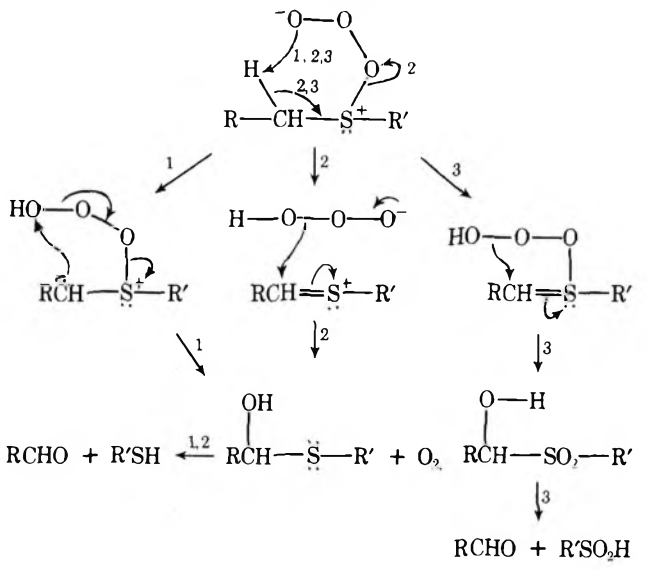
Pathway 3, which was not open to amines, would be available to sulfides because of the availability of the d orbitals of sulfur. It is analogous to the mechanism proposed by Corey and Ouannes[14] for oxidation of benzyl sulfides with singlet oxygen. It should lead to benzaldehyde and a sulfur acid (or oxygenated disulfides). We are unable to distinguish among these three pathways with the presently available data. The fact that benzyl mercaptan was not found among the products (even though it should have appeared on the column used to determine unreacted sulfide) would tend to favor pathway 3 of Scheme III. Further, the reaction mixture was acidic to litmus. On the other hand, the fact that the ratio of ozone reacting per mole of sulfide reacting was greater than 1 in the

Table II. Ozonation of Thianthrene[a]

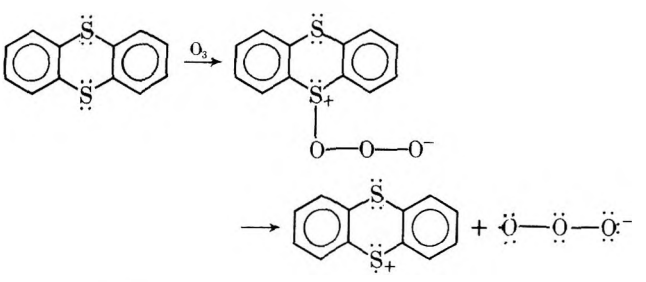
Expt	Solvent	Temp, °C	O_3/thianthrene[a] reacting	Thianthrene recovered, %	Sulfoxide,[b] %	Cation radical
1	CH_2Cl_2[a] (40 mL)	−45	1.09	27	98	~
2	12 mL of CH_2Cl_2,[a] 50 mL of 0.5 N H_2SO_4 in HOAc	25	0.95	32	93	+[c,d]
3	20 mL of CH_2Cl_2,[a] 30 mL of CH_3OH, 15 mL of H_2SO_4	25	1.28	19	96	+[c,e]

[a] All experiments involved 2.5 mmol of thianthrene in the solvent shown, into which was passed 2.5 mmol of O_3 in a nitrogen stream. [b] The percent yield was based on thianthrene reacting (unrecovered). The total accounting was 95–99%. [c] The pink color of the cation–radical was observed as soon as ozone was passed into the solution but not before. At the end of the reaction the solution had turned yellow. [d] No EPR signal for the cation–radical before ozone was passed or after the solution turned yellow. The pink solution gave an EPR signal of five lines with $g = 2.0074$. [e] A slight EPR signal was observed before ozone was passed and after the solution turned yellow; also a strong signal while pink.

Scheme III



Scheme IV



solvents which favored side-chain attack would appear to indicate that benzyl mercaptan was produced and then oxidized further by ozone. It was shown that ozonation of benzyl mercaptan does indeed give low yields of benzaldehyde. The slightly greater than 100% total for the sulfoxide and aldehyde yields found in some of these experiments also indicates this occurrence. At the present time we tend to believe that both pathway 3 and either 1 or 2 of Scheme III are occurring.

It also is of interest that with the experiments affording high sulfoxide yields, the ratio of ozone to sulfide reacting generally was less than one. A possible explanation is a competitive oxidation of the sulfide by either the ozone–sulfide adduct or the presumed singlet oxygen evolved from it (Schemes I and III). Thompson[12] showed that exposure of dimethyl sulfide to the triphenyl phosphate–ozone adduct caused oxidation of the sulfide to sulfoxide. It is not entirely certain whether the adduct itself or singlet oxygen was the oxidizing agent.[15] Singlet oxygen oxidation of dibenzyl sulfide produces benzaldehyde, along with other products.[14]

We also treated thianthrene (2) with excess ozone in a stream of nitrogen. The results are shown in Table II. The ozone to sulfide reacting ratios varied from 0.95 to 1.3. The only isolated product was the monosulfoxide in yields of 93–98%. However, when the ozonation was carried out in the presence of dilute sulfuric acid (Table II, experiment 2), the pink color of the thianthrene cation radical (EPR, five lines, $g = 2.0074$)[16] was observed. The color did not appear until ozone was passed into the solution; near the end of the ozonation the color changed to yellow. The EPR signal was observed only with the pink solution, showing that only ozone was responsible for the radical production.

However, when a greater concentration of sulfuric acid was employed (experiment 3, Table II), a weak EPR signal was observed both before ozone was passed and after the solution became yellow. Strong sulfuric acid is known to produce the cation radical.[16] The ozonate anion–radical was not observed. It probably was protonated by the sulfuric acid and subsequently destroyed.

In summary, three of the reaction types observed earlier in the reactions of ozone with amines[1-4] have now been shown to occur during organic sulfide ozonations. These are sulfur oxidation, side-chain oxidation, and cation–radical formation. The latter is illustrated in Scheme IV.

Experimental Section

Materials. Dibenzyl sulfide, dibenzyl sulfoxide, and benzyl mercaptan were obtained from K and K Chemicals. **4-Methoxybenzyl chloride** was prepared by the method of Rorig et al.[17] Benzyl *p*-methoxybenzyl sulfide[18] and benzyl *p*-chlorobenzyl sulfide were synthesized by the general method of Tuleen and Marcum.[19] The corresponding sulfoxides were obtained through *N*-chlorosuccinimide oxidation of the sulfides.[20] Thianthrene monoxide was synthesized by the method of Hilditch.[21] All other materials were obtained from standard commercial sources.

General ozonation*[22] *and EPR*[5] *procedures were as described previously.

Ozonations were performed at the temperatures shown in Tables I and II with 1 mol equiv of ozone. With the benzyl sulfides the volume was reduced to 15 mL, and GLC determinations were performed. Unsymmetrical sulfoxides were determined by evaporation of the reaction mixture, purification of the crude sulfoxide by recrystallization, and comparison with known samples. The thianthrene reaction mixtures were poured into ice water and the resulting mixtures were extracted with ether. The ether extracts were dried (ca. 50 mL) and analyzed by GLC.

GLC Determinations. The aldehyde, the symmetrical sulfoxide, and the unreacted sulfide yields were determined with an Aerograph Model A-90-P_3 chromatograph using a 0.25 in. × 5 ft, 20% cyanosilicone fluid, F 115C, on a Chromosorb P, 60–80, column for the aldehyde determination (column temperature 140 °C) and a 0.25 in. × 10 ft column of 5% silicone oil on Haloport F at 190 °C for the sulfoxide and unreacted sulfide determinations. Diphenylmethane was used as an internal standard. The thianthrene and its monoxide determinations were made with a 0.25 in. × 10 ft column of diethylene glycol on adipate at 200 °C.

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Registry No.—Thianthrene, 92-85-3.

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Synthesis of 4,5-Dicyano-2-methylthio-1,3-dithiolylium Salts: A Supposedly Impossible Alkylation

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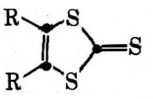
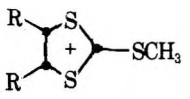
4,5-Dicyano-1,3-dithiol-2-thione and 4,5-dicarbomethoxy-1,3-dithiol-2-thione, two compounds that the literature states are impossible to alkylate, have been successfully alkylated with methyl fluorosulfonate in high yield. The alkylated salts undergo dye formation with both activated aromatic amines and methylene reagents.

Theoretical calculations and recent experimental data have shown quite conclusively that the C-2 carbon atom of a 1,3-dithiolylium cation is very electron deficient.[1,2] In our search for dye molecules that are easily reduced (reduction potential approaching zero), we prepared and measured the electrochemical reduction potentials of several 1,3-dithiolylium dyes. For this class of dyes (Table I) we found a range of reduction potentials of −0.9 to −0.5 V; however, a range of −0.5 to −0.2 V was desired. We therefore anticipated that placing electronegative groups such as cyano or carboxyl at the 4 and 5 positions of the dithiolylium ring would shift the reduction potentials of the corresponding dyes toward 0 V. A search of the literature quickly revealed that, although compounds such as 1 or 2 are easily synthesized, the alkylated derivatives 3 and 4, which would be derived from 1 and 2 and



1, R = $-CO_2CH_3$
2, R = CN–



3, R = $-CO_2CH_3$
4, R = CN–

would be necessary for dye formation, were by normal methods "*impossible to prepare by alkylation*".[2] Our problem thus became the synthesis of dithiolylium salts 3 and 4.

We found that thiones 1 and 2 are alkylated rapidly and exothermally by methyl fluorosulfonate.[3] Thione 1 reacts readily in refluxing methylene chloride. However, thione 2 requires elevated temperatures for alkylation to proceed; in fact, alkylation occurs readily only in refluxing methyl fluorosulfonate (92 °C). The reaction becomes exothermic at about 90 °C and gives 4 in 96% yield within a few minutes.

4,5-Dicyano-2-methylthio-1,3-dithiolylium fluorosulfonate (4) and to a lesser extent the diester 3 react readily with nucleophilic reagents. The salts appear hygroscopic but are in fact reacting with atmosphere moisture. The 2-methylthio group is rapidly hydrolyzed, yielding 4,5-cyano- (or carbomethoxy) 1,3-dithiol-2-ones.[4] The hydrolysis of 4 can be monitored by either IR or NMR spectroscopy. The increase in absorption due to a carbonyl group at 1660 cm^{-1} in a sample of 4 in KBr is virtually complete in 30 min. Displacement of the $-SCH_3$ group in 4 by D_2O is complete within 5 min in acetonitrile/D_2O (followed by the disappearance of $^+SCH_3$ absorption and the appearance of CH_3SD in NMR).

Reactions of methylthio salts 3 and 4 with active methylene reagents yield the dithiolylium dyes shown in Table I. Dye formation proceeds readily in acetic anhydride (minimizes hydrolysis) without the necessity of added base. In fact, addition of external nitrogen bases results in either the formation of a charge-transfer complex between the dye and base (R_3N) or an addition compound (with RNH_2).[5] Apparently, the dyes (Table I) are extremely electron deficient (as indicated by their reduction potentials) and are active as electron acceptors with the nitrogen bases acting as the donors.

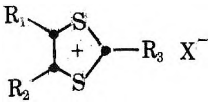
As expected, the dithiolylium dyes with electronegative groups in the 4 and 5 positions are more easily reduced electrochemically than the unsubstituted dyes. They exhibited reduction potentials in a range of −0.2 to −0.5 V. The increased (less negative) reduction potential was accompanied generally by a hyposochromic shift of the long-wavelength absorption maxima and a decrease in extinction coefficient.[6] It is unclear at this time whether this is a general phenomenon or a fortuitous correlation.

Experimental Section

All 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

0022-3263/78/1943-0678$01.00/0

Table I. Electrochemical Reduction Potential of 1,3-Dithiolylium Dyes



Registry no.	R_1	R_2	R_3	X^-	$-\epsilon^0$, V[a]	λ_{max}[b]	mp, °C[c]	%[d]
64457-14-3	H	H	9-Julolidinyl	BF_4	0.76	554	225 (dec)	96
64457-16-5	C_6H_5	H	9-Julolidinyl	BF_4	0.73	568	234	90
64457-18-7	C_6H_5	C_6H_5	9-Julolidinyl	BF_4	0.71	567	214	55
64457-20-1	CO_2CH_3	CO_2CH_3	9-Julolidinyl	FSO_3	0.51	552	165 (dec)	82
64457-22-3	CN	CN	9-Julolidinyl	BF_4	0.36	547	208 (dec)	78
64457-24-5	H	H	3-(1,2,5-Trimethylpyrrole)	BF_4	0.94	423	264 (dec)	97
64457-26-7	H	H	2-(2,4-Dimethyl-3-ethylpyrrcle)	BF_4	0.91	446	241	83
64457-43-8	C_6H_5	C_6H_5	α-(4-Methylene-2,6-diphenylpyran)	ClO_4	0.55	555	248	68
64457-41-6	CN	CN	*p*-(*N*,*N*-Dimethylaniline)	FSO_3		540	142 (dec)	76
64457-39-2	CN	CN	3-(1,2-Dimethylindole)	FSO_3		443	251 (dec)	76
64457-37-0	CN	CN	α-(4-Methylene-2,6-diphenylpyran)	ClO_4	0.23	493	245 (dec)	78
64457-35-8	CN	CN	α-(2-Methylene-4-phenyl-1,3-dithiole)	ClO_4	0.24	492	238 (dec)	86
64457-49-5	C_6H_5	H	α-(2-Methylene-4-phenyl-1,3-dithiole)	ClO_4		520	242	75
64457-33-6	H	H	3-(1,2-Dimethylindole)	BF_4		436	>300	96

[a] Measured in 2×10^{-4} M CH_3CN using cyclic voltammetry with 0.1 M tetra-*n*-butylammonium tetrafluoroborate as supporting electrolyte at a platinum electrode and SCE as reference electrode. Scan rate, 0.1 V/s. [b] Measured in acetonitrile unless otherwise noted. [c] Satisfactory combustion and spectral analyses were obtained for all new compounds. [d] Yields are not optimized.

spectra were taken with a Cary 17 spectrophotometer.

4,5-Dicyano-2-methylthio-1,3-dithiolylium Fluorosulfonate (4). 4,5-Dicyano-1,3-dithiol-2-thione[7] (1.8 g, 0.01 mol) and methyl fluorosulfonate[3] (10 mL) were slowly heated to reflux on a steam bath with stirring. At about 90 °C an exothermic reaction ensued and the solution refluxed gently. After 10 min, the mixture was cooled to ambient temperature, diluted with ethyl acetate (25 mL), and filtered. The pale-yellow solid was washed quickly with ethyl acetate and dried in a dry nitrogen atmosphere, giving 4,5-dicyano-2-methylthio-1,3-dithiolylium fluorosulfonate (2.8 g, 96%): NMR (CD_3CN) δ 3.0 (s), addition of D_2O caused the peak at 3.0 to disappear and a singlet to appear at δ 2.4 (CH_3SD); IR (KBr) 2220 (w, C≡N), 1307, 1282 (FSO_3), 1081, 1020, and 740 cm^{-1}. Exposure of the KBr pellet to air caused a peak at 1660 cm^{-1} to appear rapidly.[8]

4,5-Dicarbomethoxy-2-methylthio-1,3-dithiolylium Fluorosulfonate (3). 4,5-Dicarbomethoxy-1,3-dithiol-2-thione (1)[5] (2.5 g, 0.01 mol) and methyl fluorosulfonate (1.1 g, 0.1 mol) were refluxed in methylene chloride (20 mL) for 2 h. The addition of diethyl ether (20 mL) and cooling caused yellow crystals to precipitate. Filtration and drying under nitrogen gave 3.0 g (83%) of yellow crystals: NMR (CD_3CN) δ 3.9 (s, 6 H, OCH_3), 3.1 (s, 3 H, $-SCH_3$); IR (KBr) 1724 (C=O), 1563, 1280 (FSO_3) cm^{-1}.

Anal. Calcd for $C_8H_9FO_7S_4$: C, 26.4; H, 2.5; S, 35.2. Found: C, 26.0; H, 2.1; S, 34.8.

General Method for the Synthesis of Dithiolylium Dyes (Table I). A 2-methylthio-1,3-dithiolylium salt (0.01 mol) and the appropriate aromatic amine or methylene reagent (0.01 mol) were refluxed gently for 15–20 min in acetic anhydride (15 mL). Cooling and dilution with ethyl acetate (50 mL) gave the crystalline dye. The fluorosulfonate anion was exchanged for perchlorate or tetrafluoroborate anion by dissolving the dye in the minimum amount of ethanol at reflux, adding 70% perchloric or 47% tetrafluoroboric acid (3–5 mL), and cooling to give the crystalline dye as the perchlorate or tetrafluoroborate salt.

1:1 Addition Complex of 4,5-Dicyano-2-(9-julolidinyl)-1,3-dithiolylium Fluorosulfonate with *p*-Anisidine. 4,5-Dicyano-2-(9-julolidinyl)-1,3-dithiolylium fluorosulfonate (423 mg, 1.1 mmol) and *p*-anisidine (135 mg, 1.1 mmol) were dissolved in acetonitrile (20 mL) and refluxed for 5 min. Cooling followed by filtration gave green crystals which were washed with 50% ethyl acetate–acetonitrile and air dried: yield 280 mg (51%); mp 180 °C (dec); UV–vis (CH_3CN) (log ε) 610 (4.66), 520 (4.15) nm; IR (KBr) 2210 (C≡N), 1640, 1610, 1370, 1290 cm^{-1}; NMR (F_3AcOH) δ 7.4 (m, 6 H), 4.0–3.8 (2 s, 3 H), 3.8 (m, 4 H), 3.0 (m, 4 H), 2.4 (m, 4 H).

Anal. Calcd for $C_{24}H_{23}FN_4O_4S_3$ (1:1 adduct): C, 52.7; H, 4.2; N, 10.2; S, 17.6. Found: C, 52.5; H, 4.4; N, 9.9, S, 17.4.

Acknowledgments. I acknowledge the technical assistance of Ms. Lauren Smith of our Analytical Sciences Division for the determination of reduction potentials and Mr. John Loseser (summer follow) for help in synthesizing some of the dithiolylium dyes in Table I.

Registry No.—**1**, 7396-41-0; **2**, 1005-10-3; **3**, 64457-31-4; **4**, 64508-86-7; methyl fluorosulfonate, 421-20-5; perchloric acid, 7601-90-3; tetrafluoroboric acid, 16872-11-0; 4,5-dicyano-2-(9-julolidinyl)-1,3-dithiolylium fluorosulfonate 1:1 complex with *p*-anisidine, 64457-29-0; *p*-anisidine, 104-94-9; julolidine, 479-59-4; 1,2,5-trimethylpyrrole, 930-87-0; 2,4-dimethyl-3-ethylpyrrole, 517-22-6; 4-methylene-2,6-diphenylpyran, 15899-02-2; *N*,*N*-dimethylaniline, 121-69-7; 1,2-dimethylindole, 875-79-6; 2-methylene-4-phenyl-1,3-dithiole, 64457-27-8.

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(3) **Caution:** a death has occurred due to improper handling of this reagent. See *Chem. Eng. News*, **54 (36)**, 5 (1976).
(4) Some hydrolysis of the nitriles occurs also under these conditions.
(5) A bathochromic shift of the visible absorption spectrum is noted when a tertiary amine such as *N*,*N*-dimethylaniline is added to the dyes. No attempt was made to isolate the complexes.
(6) Extinction coefficients for the first, fourth, and fifth dyes in Table I are 6.7, 5.8, and 3.3×10^4 L/mol-cm.
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(8) Due to the hygroscopic nature of **4**, satisfactory elemental analysis could not be obtained.

Pteridines. 43. A Facile Synthesis of 6-Chloropterin and 2,4-Diamino-6-chloropteridine[1,2]

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6-Chloropterin (2) and 2,4-diamino-6-chloropteridine (5) have been prepared by reaction of pterin 8-oxide (1) and 2,4-diaminopteridine 8-oxide (4), respectively, with acetyl chloride. Nucleophilic displacement of the 6-chloro substituent in 2 and 5 occurs smoothly with arylthiols and with alkyl mercaptides to give a series of 6-substituted pterins (3) and 2,4-diaminopteridines (6), but all attempts to react 2 or 5 with amines failed, even in the presence of reducing agents.

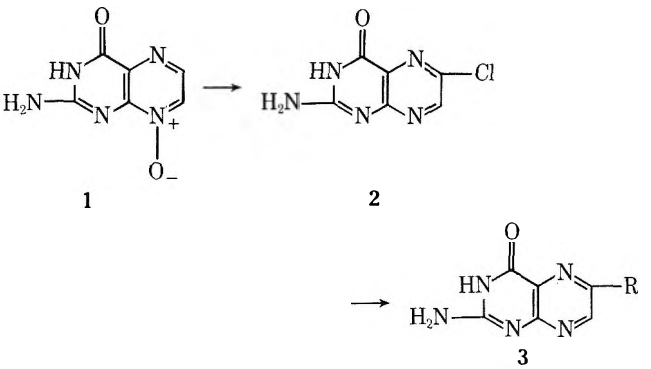
We have described in a recent series of papers[3-15] a new, general and unequivocal route to pteridine derivatives which has been utilized, inter alia, for the synthesis of 6-formylpterin,[15] 6-hydroxymethylpterin,[5] pteroic acid,[5] biopterin,[3,9] asperopterin B,[7] isoxanthopterin,[6] and xanthopterin.[6,12] In a number of these syntheses, pyrazine and pteridine *N*-oxides were utilized as key intermediates in the elaboration of the substituted pyrazine ring found in the final products. The synthesis of xanthopterin by rearrangement of pterin 8-oxide (1) is of particular interest, since it represents an unusual β-rearrangement reaction of a heterocyclic *N*-oxide which proceeds, in the above example, in quantitative yield under mild conditions. In the present paper, we describe extensions of this β-rearrangement reaction to the preparation of 6-chloropterin (2) and 2,4-diamino-6-chloropteridine (5) and some properties of these now readily accessible pteridine intermediates.

Treatment of a finely divided suspension of pterin 8-oxide (1) in trifluoroacetic acid with an excess of acetyl chloride at room temperature resulted in a vigorous exothermic reaction which was accompanied by the evolution of copious quantities of hydrogen chloride. 6-Chloropterin (2) hydrochloride was isolated in 98% yield upon dilution of the reaction mixture with anhydrous ether. The parent 6-chloropterin could be readily obtained in analytically pure form (91% yield) by dissolution of the hydrochloride in dilute sodium hydroxide followed by acidification with glacial acetic acid.

The above exothermic reaction could be avoided by utilizing previously chilled solvents and reagents. Phosphorus oxychloride could be used in place of acetyl chloride, but the rearrangement reaction was much slower, requiring some 60 h at room temperature. 6-Chloropterin could also be obtained from pterin 8-oxide by reaction in trifluoroacetic acid solution with diphenylimidoyl chloride. The structure of 6-chloropterin (2) was readily confirmed by alkaline hydrolysis to xanthopterin and by reaction with sodium methoxide to give 6-methoxypterin (3a) identical with an authentic sample prepared from xanthopterin by reaction with methanolic hydrogen chloride.[16]

In view of the ready accessibility of 6-chloropterin, we examined its possible utility as an intermediate for the synthesis of pterins bearing substituents at position 6 which might be introduced by the reaction of nucleophiles with what we anticipated to be a labile imidoyl chloride. An interesting example of such a 6-substituted pterin would be isofolic acid, which has been prepared by a rather laborious route commencing with a 6-chloro-5-nitropyrimidine.[17] To our intense disappointment, all attempts to displace the chloro substituent in 6-chloropterin by amines failed. Ammonia, benzylamine, para-substituted benzylamines (i.e., *p*-carboxybenzylamine), and 3,4-dichlorobenzylamine all failed to react under mild conditions, while the use of more strenuous conditions led only to extensive decomposition. However, 6-

Scheme I



1 2 3

a, R = OCH_3
b, R = SCH_3
c, R = SO_2CH_3
d, R = SC_6H_5
e, R = $SO_2C_6H_5$
f, R = $SCH_2C_6H_5$
g, R = SC_6H_4COOH-*p*
h, R = SC_6H_4Cl-*p*
i, R = $SO_2C_6H_4Cl$-*p*
j, R = $SC_6H_4CH_3$-*p*
k, R = $SO_2C_6H_4CH_3$-*p*
l, R = H

chloropterin reacted smoothly with sodium methyl mercaptide in methanol solution to give 6-methylthiopterin (**3b**), which could be smoothly oxidized to the corresponding sulfone (**3c**) with alkaline potassium permanganate. Despite the fact that methylthio and methylsulfonyl substituents are both considerably more reactive to nucleophilic displacement than halogens,[18] attempted reaction of either substrate with amines led to extensive decomposition, and no 6-substituted aminopterins could be isolated.

6-Chloropterin also reacted smoothly with thiophenol in dimethylformamide solution under reflux to give 6-phenylthiopterin (**3d**) in 85% yield. Under the same conditions, 6-methylsulfonylpterin could be converted in 71% yield to 6-phenylthiopterin. 6-Benzylthiopterin (**3f**) could similarly be prepared either from 2 or from **3c**. Additional 6-arylthiopterins prepared from 6-chloropterin and aryl mercaptans are described under the Experimental Section (see Scheme I).

The failure of 6-chloropterin to react with amines is surprising, since a wide variety of 2-, 4-, 6-, and 7-chloropteridines are known to undergo such displacements.[19-23] It seems evident that the halogen at position 6 in 2 is severely deactivated both by the 2-amino substituent and probably by anion formation in the pyrimidine ring by reaction with the amine. An attempt was made to overcome the deactivating influence of the 2-amino group by initial conversion of 6-chloropterin into its 2-acetyl derivative, but subsequent reaction with amines led only to deacetylation.

Both 6- and 7-chloropteridines, which do not possess deactivating substituents in the pyrimidine ring, react readily with nucleophiles;[21-23] 6-chloropteridine is thought to undergo displacement, at least in part, via a covalent solvate arising under the reaction conditions by addition of the attacking

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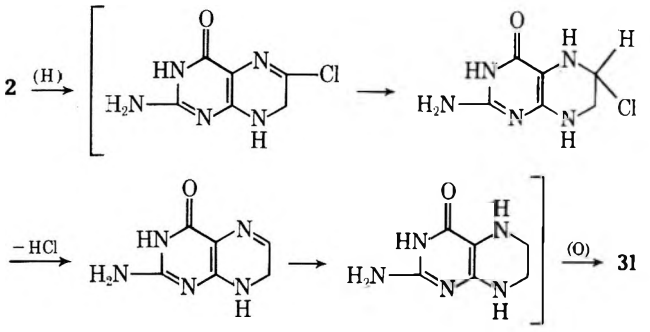
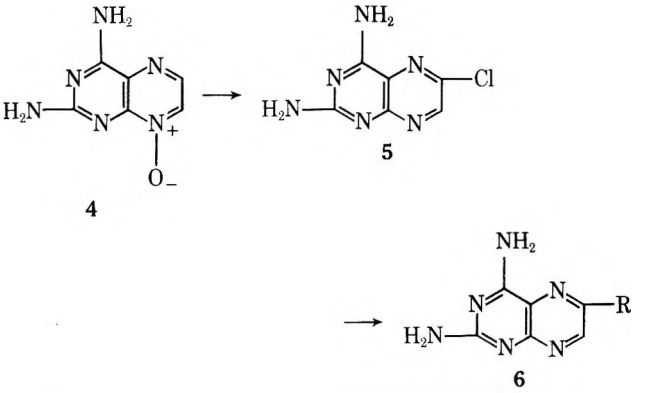
Scheme II



Scheme III



a, R = SC_6H_5
b, R = SC_6H_4Cl-*p*
c, R = $SC_6H_4CH_3$-*p*
d, R = $SC_6H_4C_2H_5$-*o*
e, R = $SC_6H_4C_2H_5$-*p*
f, R = $SC_6H_4C_3H_7$-*n*-*p*
g, R = $SC_6H_4C_4H_9$-*n*-*p*
h, R = SC_6H_4Cl-*o*
i, R = $SC_6H_4C_3H_7$-*i*-*o*
j, R = $SC_6H_4COOC_2H_5$-*p*
k, R = SCH_3
l, R = $SCH_2COOC_2H_5$
m, R = $SCH_2C_6H_5$
n, R = $SCH_2C_6H_4Cl$-*o*
o, R = $SCH_2C_6H_4COOCH_3$-*p*

amine across the 7,8 position.[21] The ease of hyrolysis of 6-amino- and 6-alkylaminopteridines has also been attributed to an initial acid-catalyzed covalent hydration of the 7,8-imine bond.[21,24] We therefore briefly investigated the possible intermediate conversion of 6-chloropterin into 6-chloro-7,8-dihydropterin in the presence of an added nucleophile in the hope that nucleophilic displacement would, by analogy, be facilitated. The reaction of 6-chloropterin with sodium dithionite in aqueous ammonium hydroxide led only to the formation of pterin (**31**) upon oxidative workup. It seems reasonable to suggest that the formation of pterin under these conditions is the result of an initial reduction (as anticipated) of the 7,8 double bond followed, however, by further reduction of the 5,6 imine bond, dehydrohalogenation, and (probably) further reduction to 5,6,7,8-tetrahydropterin; oxidation would then give pterin (see Scheme II). Similarly, 6-chloropterin was reduced with sodium borohydride; oxidative workup again gave pterin. An attempt to convert 6-chloropterin into 6-aminopterin by catalytic reduction in the presence of ammonia also failed;[25] pterin was the only product, in addition to unchanged starting material, isolated upon oxidative work. However, striking apparent substantiation of the enhanced reactivity of the 6-chloro substituent in a 7,8-dihydro derivative was found in the reaction of 6-chloropterin with thiophenol at room temperature in the presence of sodium bisulfite. 6-Phenylthiopterin (**3d**) was formed in 97% yield, and these very mild conditions contrast with the many hours of refluxing required for the same nucleophilic displacement in the absence of added sodium bisulfite.

A parallel can be drawn between our observations with 6-chloropterin and the report by Johnston, Broadbent, and Parish[26] that 2,4,7-triamino-6-methylsulfonylpteridine failed to undergo displacement of the methylsulfonyl group upon treatment with amines (only amine displacement was observed), although the methylsulfonyl substituent was smoothly displaced by reaction with thiophenol or *p*-chlorothiophenol. These results, combined with our own observations, point to a unique role of sulfur nucleophiles in displacement reactions with this type of 6-substituted pteridine derivative. It was attractive to postulate that the facile displacement of 6-chloro- and 6-methylsulfonyl substituents from these pteridine derivatives by sulfur nucleophiles might be occurring via a radical anion process, which has now been well established for some "nucleophilic displacement reactions" involving sulfur nucleophiles and certain halo-substituted π-deficient heterocycles.[27] However, no evidence to support this postulate could be obtained; the above displacement reactions proceed normally and in comparable yields in the presence of a variety of radical trapping agents (azobenzene, hydroquinone, *p*-dinitrobenzene, 1,1,4,4-tetraphenyl-1,3-butadiene).

We have extended the above series of reactions to the preparation of a series of 2,4-diamino-6-arylthio- and 2,4-diamino-6-alkylthiopteridines by utilization of 2,4-diamino-6-chloropteridine (**5**) which was prepared by acetyl chloride/F_3AcOH rearrangement of 2,4-diaminopteridine 8-oxide (**4**).[12] In contrast to the reaction of pterin 8-oxide with acetyl chloride (which was instantaneous at room temperature), this latter reaction required 24 h at room temperature. The crude product was obtained (as its hydrochloride) by precipitation with ether; 2,4-diamino-6-chloropteridine itself was readily prepared by neutralization of a suspension of the salt in water. This compound has been made previously by a six-step sequence of reactions starting from 2-amino-3-carbomethoxypyrazine;[28] the present route, which gives 2,4-diamino-6-chloropteridine (**5**) in only three steps from noncyclic starting materials, is much more convenient.

As was the case with 6-chloropterin, all attempts to convert 2,4-diamino-6-chloropteridine into 6-amino derivatives by reaction either with primary alkylamines or with aromatic amines led only to extensive decomposition. In an independent study, Elslager had recently reported[29] that only dialkylamines reacted satisfactorily with 2,4-diamino-6-chloropteridine. By contrast, however, 2,4-diamino-6-chloropteridine reacts smoothly with substituted thiophenols or sodium alkyl mercaptides (thus paralleling the behavior of 6-chloropterin as described above) (see Scheme III). These latter results appear to be confirmed by recent observations of Elslager.[29]

Experimental Section

6-Chloropterin (2) from Pterin 8-Oxide (1). By Reaction with Acetyl Chloride/F_3AcOH. A suspension of 8.0 g of pterin 8-oxide[6,12] in 40 mL of acetyl chloride was cooled to −60 °C, and 40 mL of trifluoroacetic acid (F_3AcOH), precooled to −60 °C, was added. The mixture was sealed in a glass pressure bottle and gradually warmed to room temperature. The pterin 8-oxide slowly dissolved, and after about 2 min at room temperature a pale yellow solid started to precipitate from the reaction mixture. It was stirred at room temperature for an additional 45 min, the pressure bottle opened (careful! HCl is released), the suspension diluted with dry ether, and the pale yellow solid collected by filtration and dried in vacuo. The yield of 6-chloropterin hydrochloride was 10.4 g (98%).

6-Chloropterin was prepared by dissolution of the above hydrochloride (1.0 g) in 10 mL of 5% cold sodium hydroxide solution. After 15 min of stirring at room temperature, the clear pale yellow solution was filtered and the filtrate acidified with glacial acetic acid. After stirring for 30 min, the resulting suspension was filtered, and the collected solid was washed thoroughly with water and then with acetone and dried at 100 °C (0.01 mm) for 1 h: yield 765 mg (91%); mp >330 °C.

6-Chloropterin could also be prepared from pterin 8-oxide by stirring at room temperature for 60 h in a solution of F_3AcOH with

an excess of phosphorus oxychloride (94% yield) or by stirring at room temperature for 6 h with diphenylimidoyl chloride in F_3AcOH solution (73% yield).

Hydrolysis of 6-Chloropterin to Xanthopterin. A solution of 100 mg of 6-chloropterin in 10 mL of 5% sodium hydroxide solution was heated under gentle reflux for 15 h. The cooled solution was filtered and the filtrate acidified with glacial acetic acid. The orange precipitate which separated was collected by filtration, washed with water and then with acetone, and dried at 100 °C (0.01 mm) for 5 h to give 860 mg (91%) of an orange solid which was shown to be identical (TLC) with an authentic sample of xanthopterin.

6-Methoxypterin (3a). A solution of 500 mg of crude 6-chloropterin hydrochloride in methanolic sodium methoxide (prepared from 500 mg of metallic sodium in 100 mL of methanol) was heated under reflux for 24 h, cooled, and filtered, and the filtrate was evaporated to dryness under reduced pressure. The solid residue was triturated with glacial acetic acid and filtered, and the collected solid was washed thoroughly with water and then with acetone and dried at 100 °C (0.01 mm) for 5 h to give 310 mg (63%) of a bright-orange solid identified as 6-methoxypterin by comparison with an authentic sample prepared by the method of Pfleiderer.[16]

6-Methylthiopterin (3b). A solution of 5.0 g of 6-chloropterin in methanolic sodium methyl mercaptide (prepared from 5 g of sodium in 500 mL of methanol and an excess of methyl mercaptan) was heated under reflux for 24 h. The reaction mixture was then heated an additional 30 min with decolorizing charcoal and filtered, and the filtrate was evaporated to a small volume under reduced pressure. The residue was dissolved in 500 mL of warm water and filtered, and the filtrate was acidified with glacial acetic acid. The pale-yellow solid which separated was collected by filtration, washed well with water and then with acetone, and dried at 100 °C (0.01 mm) for 5 h: yield 5.2 g (98%) of a microcrystalline orange solid; mp > 330 °C.

6-Methylsulfonylpterin (3c). A cold, stirred solution of 100 mg of 6-methylthiopterin in 10 mL of water containing 100 mg of sodium hydroxide was treated with 200 mg of potassium permanganate, and the reaction mixture was stirred at room temperature for 45 min. At the end of this time, TLC analysis showed no residual starting material and the presence of a new, bright-blue fluorescent material. Excess oxidant and precipitated MnO_2 were removed by bubbling in sulfur dioxide until the reaction mixture was colorless. It was then made alkaline by the addition of sodium hydroxide solution, precipitated MnO_2 was removed by filtration, and the filtrate was acidified with glacial acetic acid. The product which precipitated was collected by filtration, washed well with water, ethanol, and finally ether, and dried to give 85 mg (74%) of a colorless solid, mp >330 °C. The analytical sample was prepared by dissolution in DMF followed by precipitation by the addition of diethyl ether.

6-Phenylthiopterin (3d). Method A. From 6-Chloropterin. A hot solution of 500 mg of 6-chloropterin in 200 mL of DMF was treated with 3 mL of thiophenol, and the solution was heated under reflux for 3 h, by which time TLC analysis showed the displacement reaction to be complete. The hot reaction mixture was treated with 100 mg of Norite and 200 mg of Celite, heated for an additional 5 min, and filtered hot. Cooling of the filtrate resulted in the separation of a bright-yellow solid. The mixture was cooled at 0 °C overnight and then filtered to give 0.58 g (85%) of a microcrystalline yellow solid, mp >330 °C.

Method B. From 6-Methylsulfonylpterin. A hot solution of 100 mg of 6-methylsulfonylpterin in 25 mL of DMF was treated with 2.5 mL of thiophenol, and the mixture was heated under reflux for 2 h. It was worked up as described above under method A to give 80 mg (71%) of 6-phenylthiopterin, identical in every respect with the product obtained by method A.

Method C. From 6-Chloropterin in the Presence of Sodium Bisulfite. A suspension of 100 mg of 6-chloropterin in 30 mL of water and 5 mL of THF containing 1 mL of thiophenol and 1 g of sodium bisulfite was stirred at room temperature for 24 h and then filtered. The collected solid was washed thoroughly with water followed by ethanol: yield 133 mg (97%) of 6-phenylthiopterin, identical in every respect with the product obtained by methods A and B as described above.

6-Phenylsulfonylpterin (3e). A solution of 100 mg of 6-phenylthiopterin in 4 mL of glacial acetic acid containing 4 drops of concentrated hydrochloric acid was treated with 0.5 mL of 30% hydrogen peroxide, and the reaction mixture was stirred at room temperature for 30 min. By the end of this time, TLC analysis showed only one compound (not starting material) to be present. The reaction mixture was diluted with 20 mL of water, and the precipitated solid was collected by filtration, washed with ethanol and then with ether, and dried in vacuo at 100 °C to give 94 mg (75%) of a very light yellow solid, mp >330 °C.

6-Benzylthiopterin (3f). Method A. From 6-Chloropterin. A solution of 5.00 g of 6-chloropterin in a methanolic solution of sodium benzyl mercaptide (prepared from 1 g of sodium, 500 mL of methanol, and 6 g of benzyl mercaptan) was heated under reflux for 30 h. At the end of this time, the copious pale-yellow solid which had separated was collected by filtration and washed with methanol and then with ether. The filtrate was heated for an additional 42 h with an additional quantity of sodium benzyl mercaptide (prepared from 1 g of sodium, 50 mL of methanol, and 6 g of benzyl mercaptan). At the end of this time, the reaction was apparently (by TLC) complete. Solvent was removed by evaporation under reduced pressure, the residue was triturated with glacial acetic acid, and the product was collected by filtration. The combined solids were then recrystallized from 1 L of DMF to give 5.93 g (83%) of bright-yellow platelets, mp >330 °C.

Method B. From 6-Methylsulfonylpterin. A hot solution of 100 mg of 6-methylsulfonylpterin in 25 mL of DMF and 2.5 mL of benzyl mercaptan was heated under reflux for 22 h. At the end of this time, TLC analysis indicated that starting material was absent and that only one product had been formed. The bright-orange solution was cooled and filtered, and the collected solid was washed with ether and recrystallized from DMF to give 83 mg (70%) of a bright-orange microcrystalline solid identical in every respect with the material prepared above by method A.

6-(*p*-Carboxyphenylthio)pterin (3 g). Method A. From 6-Chloropterin. A hot solution of 500 mg of 6-chloropterin in 200 mL of DMF containing 3 g of *p*-carboxythiophenol was heated under reflux for 5 h, decolorized with 100 mg of Norite and 200 mg of Celite, and filtered hot. The product crystallized from the hot filtrate upon cooling and was collected by filtration, washed with ethanol and then with ether, and dried in vacuo at 100 °C: yield 0.63 g (80%) of a bright-yellow microcrystalline solid; mp >330 °C.

Method B. From 6-Methylsulfonylpterin. A solution of 100 mg of 6-methylsulfonylpterin and 166 mg of *p*-carboxythiophenol in 15 mL of DMF was heated under reflux for 42 h and evaporated to dryness under reduced pressure, and the filtrate was triturated with methanol and filtered. The collected product was dissolved in DMF (charcoal) and precipitated by the addition of methanol: yield 95 mg (77%) of a bright-yellow solid identical in every respect with the compound prepared as described above by method A.

6-(*p*-Chlorophenylthio)pterin (3h). This compound was prepared as a bright-yellow microcrystalline solid, mp >330 °C, in 88% yield from 500 mg of 6-chloropterin and 3 g of *p*-chlorothiophenol in 200 mL of DMF (reflux for 45 min) and was isolated as described above under the preparation of **3d.**

6-(p-Chlorophenylsulfonyl)pterin (3i). This compound was prepared in 94% yield by oxidation of 6-*p*-chlorophenylthiopterin with hydrogen peroxide in a mixture of aqueous acetic acid and concentrated hydrochloric acid as described above under the preparation of **3e.**

6-(*p*-Methylphenylthio)pterin (3j). This compound was prepared in 87% yield from 6-chloropterin and *p*-thiocresol in DMF, as described above under the preparation of **3d.**

6-(*p*-Methylphenylsulfonyl)pterin (3k). This compound was prepared in 90% yield by oxidation of 6-(*p*-methylphenylthio)pterin with hydrogen peroxide in a mixture of aqueous acetic acid and concentrated hydrochloric acid as described above for the preparation of **3e.**

Reduction of 6-Chloropterin in the Presence of Amines. Formation of Pterin (31). A solution of 50 mg of 6-chloropterin in 10 mL of ammonium hydroxide was heated to reflux, a solution of 100 mg of sodium dithionite in 2 mL of water was added dropwise over a period of 1 h, and the reaction mixture was heated under reflux for 8 h. By this time, all starting material had disappeared. The mixture was cooled, the pH was adjusted to 13 with sodium hydroxide, and 200 mg of potassium permanganate dissolved in 10 mL of water was added. After several minutes of stirring, sulfur dioxide was bubbled into the reaction mixture until excess oxidant and precipitated MnO_2 had dissolved. The suspended colorless solid was then collected by filtration, washed well with alcohol and then with ether, and recrystallized from DMF to give 20 mg (50%) of pterin, identical in every respect with an authentic sample.

Repetition of the above experiment utilizing sodium borohydride rather than dithionite as the reducing agent gave identical results.

Pterin was also the sole product formed by catalytic reduction of a solution of the sodium salt of 6-chloropterin in dry methanol in the presence of 10% Pd/C catalyst and an excess of benzylamine, followed by oxidative workup as described above.

2,4-Diamino-6-chloropteridine (5). A suspension of 1.0 g of 2,4-diaminopteridine 8-oxide[6,12] in 5 mL of trifluoroacetic acid and

5 mL of acetyl chloride was stirred at room temperature for 24 h. During this time the starting material slowly dissolved, and the product then started to precipitate from the reaction solution. The resulting mixture was diluted with 200 mL of ether, and the pale-yellow hydrochloride of 2,4-diamino-6-chloropteridine was collected by filtration, washed with ether, dried, and then converted into the free base by dissolution in water followed by neutralization with cold dilute sodium hydroxide. The precipitated solid was collected by filtration, washed thoroughly with water and then with ethanol and ether, and dried: yield 1.0 g (91%); mp >330 °C. The analytical sample was prepared by vacuum sublimation at 250 °C, followed by recrystallization of the sublimate from DMF.

2,4-Diamino-6-phenylthiopteridine (6a). A solution of 2.0 g of 2,4-diamino-6-chloropteridine in a mixture of 50 mL of DMF and 4 g of thiophenol was heated under reflux for 20 min, by which time TLC showed the absence of starting material. The hot reaction solution was diluted with ether, and the precipitated solid was collected by filtration, washed with ether, and dried. Excess acid was removed by trituration with a solution of triethylamine in ether; the solid was again collected by filtration, washed thoroughly with water and then with ethanol, and dried: yield 1.3 g (47%); mp > 330 °C. The analytical sample was prepared by dissolution in DMF followed by precipitation with ether.

The following compounds were prepared in the same manner as described above.

2,4-Diamino-6-(*p*-chlorophenylthio)pteridine (6b): 39% yield; mp >330 °C (after sublimation at 250 °C) (0.05 mm).

2,4-Diamino-6-(*p*-methylphenylthio)pteridine (6c): 34.5% yield; mp >330 °C (from DMF).

2,4-Diamino-6-(*o*-ethylphenylthio)pteridine (6d): 66% yield; mp >330 °C (from aqueous methanol).

2,4-Diamino-6-(*p*-ethylphenylthio)pteridine (6e): 69.5% yield; mp >330 °C (from DMF).

2,4-Diamino-6-[*p*-(*n*-propylphenylthio)]pteridine (6f): 52% yield; mp >330 °C (from DMF).

2,4-Diamino-6-[*p*-(*n*-butylphenylthio)]pteridine (6g): 56.5% yield; mp >330 °C (from DMF).

2,4-Diamino-6-(*o*-chlorophenylthio)pteridine (6h): 65% yield; mp >330 °C (from DMF).

2,4-Diamino-6-(*o*-isopropylphenylthio)pteridine (6i): 74% yield; mp >330 °C (from DMF).

2,4-Diamino-6-(*p*-carbethoxyphenylthio)pteridine (6j): 76% yield; mp >330 °C (from DMF).

2,4-Diamino-6-methylthiopteridine (6k). A solution of 2 g of sodium in 1 L of dry methanol was saturated with methyl mercaptan, and to this solution was added 1 g of 2,4-diamino-6-chloropteridine. The reaction mixture was heated under reflux for 3 h and evaporated to dryness, the residual solid was triturated with water and filtered, and the collected solid was dried and recrystallized from DMF to give 760 mg (72%), mp >300 °C.

2,4-Diamino-6-(carbethoxymethylthio)pteridine (6l). A solution of 0.5 g of 2,4-diamino-6-chloropteridine in sodium methoxide (prepared from 0.5 g of sodium in 660 mL of dry methanol) containing 3 g of ethyl thioglycolate was heated under reflux for 16 h and then worked up as described above: yield 375 mg (51%); mp >300 °C.

2,4-Diamino-6-benzylthiopteridine (6m). This compound was prepared as described above for the 6-(carbethoxymethylthio) derivative except for the substitution of benzyl mercaptan for ethyl thioglycolate: yield 79%; mp >300 °C.

2,4-Diamino-6-(*o*-chlorobenzylthio)pteridine (6n): 54% yield; mp >300 °C.

2,4-Diamino-6-(*p*-carbomethoxybenzylthio)pteridine (6o): 70% yield; mp >300 °C.

Registry No.—**1**, 42346-89-4; **1** HCl, 64507-67-1; **2**, 64507-68-2; **3a**, 64507-69-3; **3b**, 64507-70-6; **3c**, 64507-71-7; **3d**, 58858-76-7; **3e**, 64507-72-8; **3f**, 58858-80-3; **3g**, 64507-73-9; **3h**, 64507-74-0; **3i**, 64507-75-1; **3j**, 58858-78-9; **3k**, 64507-76-2; **3l**, 2236-60-4; **4**, 42346-93-0; **5**, 17714-06-6; **6a**, 58858-77-8; **6b**, 64507-77-3; **6c**, 58858-79-0; **6d**, 64507-78-4; **6e**, 64507-79-5; **6f**, 58858-83-6; **6g**, 64507-80-8; **6h**, 64507-81-9; **6i**, 58858-82-5; **6j**, 64507-64-8; **6k**, 64507-63-7; **6l**, 64507-62-6; **6m**, 58858-81-4, **6n**, 64507-61-5; **6o**, 64535-86-0; acetyl chloride, 75-36-5; xanthopterin, 119-44-8; sodium methoxide, 124-41-4; sodium methyl mercaptide, 5188-07-8; thiophenol, 108-98-5; sodium benzyl mercaptide, 3492-64-6; benzyl mercaptan, 100-53-8; *p*-carboxythiophenol, 1074-36-8; *p*-chlorothiophenol, 106-54-7; *p*-thiocresol, 106-45-6; o-ethylthiophenol, 4500-58-7; *p*-ethylthiophenol, 4946-13-8; *p*-propylthiophenol, 4527-44-0; *p*-butylthiophenol, 4946-15-0; o-chlorothiophenol, 6320-03-2; o-isopropylthiophenol, 6262-87-9; *p*-carbethoxythiophenol, 28276-32-6; methyl mercaptan, 74-93-1; ethyl thioglycolate, 623-51-8; *o*-chlorobenzylthiol, 39718-00-8; *p*-carbomethoxybenzylthiol, 6302-65-4.

References and Notes

(1) For the previous paper in this series, see: E. C. Taylor and J. V. Berrier, *Heterocycles*, **6**, 449 (1977).
(2) This work was supported by a grant (CA-12876) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service. We are also grateful to Eli Lilly & Co., Indianapolis, and Lonza, Ltd., Basle, for additional support and for generous gifts of chemicals.
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Protecting Groups. 7. A Novel Type of Neighboring Group Participation Involving Pyridine *N*-Oxides in Acylation and Phosphorylation. 1[1]

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Competitive acylation of 2-(ω-hydroxyalkyl)pyridine 1-oxides **3a** and **3b** and benzyl alcohol (**13**) with *p*-nitrobenzoyl chloride in pyridine afforded 2-[ω-(*p*-nitrobenzoxy)alkyl]pyridine 1-oxides **4a** and **4b** almost exclusively. Even in the presence of a large excess (viz. 30 molar excess) of **13** the same result was obtained. Analogous competitive phosphorylation of 4-methoxy-2-pyridinemethanol 1-oxide (**5**) and 1-butanol (**17**) with 2,2,2-trichloroethyl phosphorodichloridate (**16**) gave rise to a 55.6% yield (based on **16**) of *n*-butyl 4-methoxy-2-picolyl 2,2,2-trichloroethyl phosphate 1-oxide (**7**) via 4-methoxy-2-picolyl 2,2,2-trichloroethyl phosphorochloridate 1-oxide (**6**). A mechanism of the selective acylation, together with a possibility of the application of the 4-methoxy-2-picolyl 1-oxide group as the 2′-O-protecting group which might assist phosphorylation at 3′-OH of the ribonucleoside, is discussed.

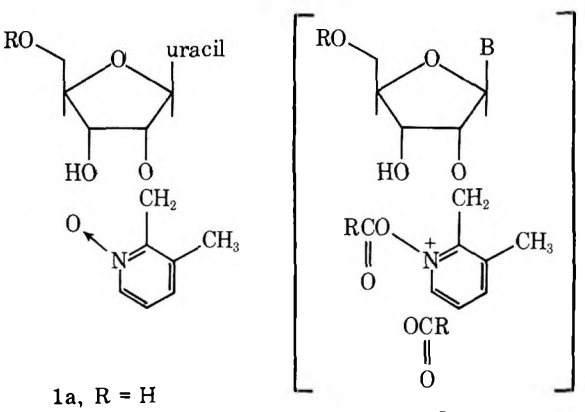
Introduction of a blocking group often causes reduction in the reactivity of the adjacent functional group due, mainly, to steric hindrance by the group introduced.[2] For example, condensation of 2′-*O*-(1-ethoxyethyl)uridine with 2-cyanoethyl 2′,5′-di-*O*-(1-ethoxyethyl)uridine 3′-phosphate afforded only 2′,5′-di-*O*-(1-ethoxyethyl)uridylyl-(3′–5′)-2′-*O*-(1-ethoxyethyl)uridine 2-cyanoethyl ester. The fact that no 3′–3′ isomer was detected in the reaction mixture indicates the inhibition of phosphorylation on the 3′-OH by the 2′ substituent of the nucleoside.[3]

Although this feature permits the use of nucleosides unprotected at 3′-OH in the synthesis of diribonucleoside monophosphates by the "two-step procedure",[4,5] this often offers serious problems in oligoribonucleotide synthesis. Thus, DCC or TPS-activated phosphorylation of 2′,5′-di-*O*-methoxytetrahydropyranyladenylyl-(3′–5′)-2′-*O*-methoxytetrahydropyranyladenosine with 2-cyanoethyl phosphate did not occur. An attempt to condense 2′,3′-*O*-methoxymethyleneuridine 5′-phosphate and 2′,5′-di-*O*-methoxytetrahydropyranyladenylyl-(3′–5′)-2′-*O*-methoxytetrahydropyranyladenosine has failed.[6] These results can be attributed to the steric hindrance of the bulky ketal function adjacent to the free 3′-OH group. Thus, further progress may not easily be possible without introduction of a better 2′-O protecting group. In order to solve this problem we have concentrated our efforts in search of a novel type of 2′-*O* protection that is capable of assisting 3′-*O* phosphorylation.

It is known that the oxygen atom of pyridine 1-oxide is sufficiently nucleophilic to react rapidly with acyl chloride (at room temperature in $CDCl_3$) to form *N*-acyloxypyridinium chloride which is recognized as a good acylating agent.[1b,7] Therefore, pyridine 1-oxide may be a possible candidate as a 2′–O protecting group which would be acylated to form the *N*-acyloxypyridinium salt.[8] The latter would acylate (or phosphorylate) the adjacent 3′-OH group.

In a previous report from our laboratory,[9] acylation or phosphorylation of 2′-*O*-(3-methyl-2-picolyl 1-oxide)uridine (**1a**, R = H) was described. Although we did not discuss the mechanism, the acylation on the 3′-OH group might have proceeded via the *N*-acyloxypyridinium intermediate **2**. It is, however, difficult to assess exactly the possible neighboring participation of the *N*-oxide on acylation because of the complexity of the system.[10]

In order to show definitely the participation in acylation and the high nucleophilicity of the *N*-oxide group toward sp^2 carbon or sp^3 phosphorus, competitive acylation was designed using a model system. Finally, competitive acylation between 3-methyl-2-picolyl 1-oxide protected pyrimidine nucleosides and benzyl alcohol (**13**) with benzoyl halide was attempted.



1a, R = H
b, R = trityl

2

Results

A mixture of benzyl alcohol (**13**) and 2-(ω-hydroxyalkyl)pyridine 1-oxides **3a** and **3b** was treated with *p*-nitrobenzoyl chloride (**14**) in pyridine. We chose **3a**, **3b**, and **13** as substrates for the competitive acylation because of their apparent steric similarity. *p*-Nitrobenzoyl chloride (**14**) was selected as the acylating agent because of its strong ultraviolet-absorbing nature and different mobilities on thin-layer chromatography of the expected products, benzyl *p*-nitrobenzoate (**8**) and 2-[ω-(*p*-nitrobenzoxy)alkyl]pyridine 1-oxides **4a** and **4b** (Scheme I).

A solution of 1 mmol (1 equiv) of 2-(ω-hydroxyalkyl)pyridine 1-oxides **3a** or **3b** and a 30 molar excess of **13** in chloroform was treated with ~0.55 equiv of **14** in the presence of a limited amount of pyridine overnight at room temperature. The reaction mixture was analyzed by thin-layer chromatography using *p*-nitrotoluene (**10**) as the internal standard. The TLC plate was developed first by benzene and then by $CHCl_3$–EtOH to obtain a clear separation of each component (including the internal standard) of the mixture. The relative ratio of a pair of products (one partner being the internal standard **10**) was calculated on the basis of $A_{262\ nm}$ values exhibited by the extract of each spot. The results are listed in Tables I and II which show that, under the above conditions, **4a** or **4b** was obtained almost exclusively. Even in the presence of a 30 molar excess of **13** acylation nearly exclusively occurred on the ω-hydroxyl group. The preferential acylation of the ω-hydroxyl group of the side chain was thus observed.

Analogous treatment of 2-pyridinemethanol 1-oxide (**3a**) with 2,2,2-trichloroethyl phosphorodichloridate (**16**) in the presence of 1-butanol (**17**) afforded *n*-butyl 2-picolyl 2,2,2-trichloroethyl phosphate 1-oxide (**18**). In this case, however,

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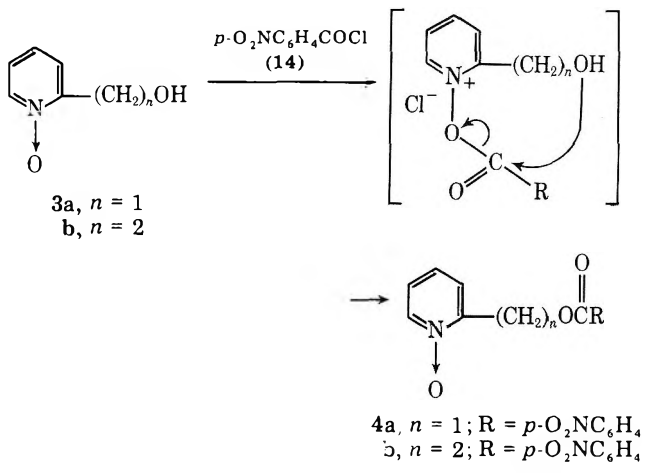
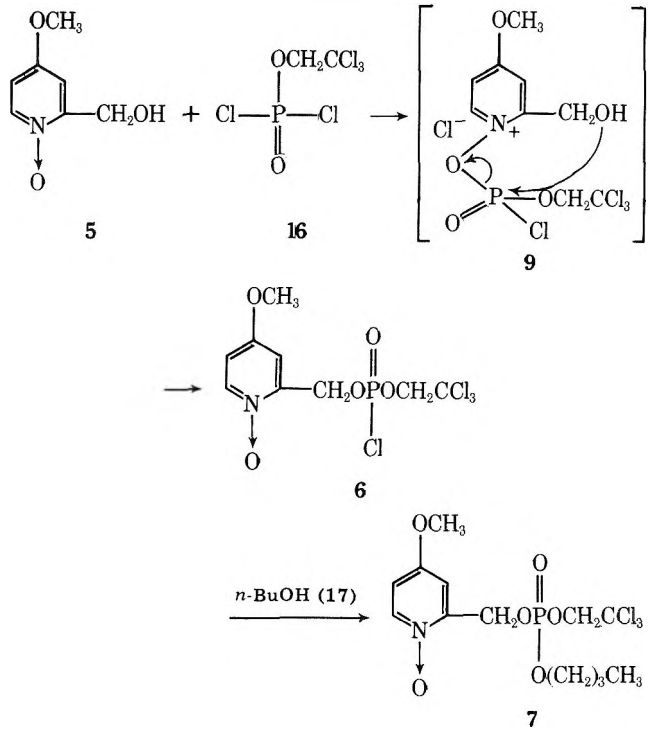
Scheme I



Scheme II



the yield never exceeded 11.9%. On the other hand, when 4-methoxy-2-pyridinemethanol 1-oxide (**5**) and **17** were used as substrate, competitive reaction under comparable conditions afforded *n*-butyl 4-methoxy-2-picolyl 2,2,2-trichloroethyl phosphate 1-oxide (**7**) in 56% (isolated) yield. In the absence of **17** this reaction afforded 4-methoxy-2-picolyl 2,2,2-trichloroethyl phosphorochloridate 1-oxide which was capable of phosphorylating **17** rapidly to give **7**, whereas, under comparable conditions, 1-butanol did not react with **16** to any considerable extent. Thus, again the preferential phosphorylation of the ω-hydroxyl group of **5** (but not **3a**) with **16** was observed (Scheme II).

Finally, a similar competive acylation of 2′-*O*-(3-methyl-2-picolyl 1-oxide)-5′-*O*-trityluridine (**1b**) and **13** with *p*-nitrobenzoyl chloride (**14**) in pyridine and chloroform at room temperature was found to give, contrary to our expectation, benzyl *p*-nitrobenzoate (**8**) as the exclusive product, **1b** being recovered intact in quantitative yield. In sharp contrast, acylation of 3′-*O*-(3-methyl-2-picolyl 1-oxide)-5′-*O*-trityl-N^4-benzoylcytidine (**11**, 1 equiv) and **13** (2 equiv) with benzoyl bromide (**15**, 1 equiv) in the presence of 2,4,6-trimethylpyridine afforded a 19% yield (based on **15**) of 3′-*O*-(3-methyl-2-picolyl 1-oxide)-5′-*O*-trityl-$O^{2'}$,N^4-dibenzoylcytidine (**12**), whose anomeric proton signal appeared relatively downfield, as compared to that of **11**. The structure of **12** was also confirmed by elemental analysis (Scheme III).

Table I. Amounts of Benzyl *p*-Nitrobenzoate (8) and 2-Picolyl 1-Oxide *p*-Nitrobenzoate (4a) Formed in Competitive Acylation with *p*-Nitrobenzoyl Chloride (14) between 2-Pyridinemethanol 1-Oxide (3a) and Benzyl Alcohol (13)[a]

Run	1	2	3	4	5
3a, mmol	1.00	1.02	1.02	1.02	1.03
13, mmol	5.13	10.18	15.1	20.1	30.1
14, mmol	0.55	0.54	0.56	0.57	0.54
A_{4a}/A_{10}[b]	3.31	3.05	3.71	3.16	3.39
A_8/A_{10}[b]	0.18	0.14	0.13	0.10	0.09
Yield of **4a**, mg	112	98	125	106	115
Yield of **4a**, %[c]	75.1	67	81	69	77
Yield of **8**, mg	9.0	7.0	6.5	5.0	4.5
Yield of **8**, %[c]	6.4	5.0	4.5	3.5	3.1

[a] In the presence of a limited amount of pyridine (0.56–0.77 mmol) in chloroform (4 mL) at 23 °C. [b] For the definition of A_{4a}/A_{10} and A_8/A_{10}, see the Experimental Section. [c] Based on the acylating agent **14**. Besides **4a** (67–81%) and **8** (4.5–9.0%), **14** was recovered as *p*-nitrobenzoic acid in 15–20% yields.

Table II. Amounts of Benzyl *p*-Nitrobenzoate (8) and 1-(2-Pyridyl 1-oxide)-2-(*p*-nitrobenzoxy)ethane (4b) Formed in Competitive Acylation with *p*-Nitrobenzoyl Chloride (14) between β-(2-Pyridyl 1-oxide)ethanol (3b) and Benzyl Alcohol (13)[a]

Run	1	2	3	4	5
3b, mmol	0.968	1.03	1.32	1.06	1.05
13, mmol	0.986	3.22	5.42	15.1	30.4
14, mmol	0.542	0.538	0.560	0.548	0.553
A_{4b}/A_{10}[b]	3.66[c]	3.39[c]	3.09[d]	3.07[d]	3.10[d]
A_8/A_{10}[b]	0.00	*d*	0.00	*d*	0.10
Yield of **4b**, mg	135	117	114	111	112
Yield of **4b**, %[e]	85.2	74.3	71.0	69.3	69.2

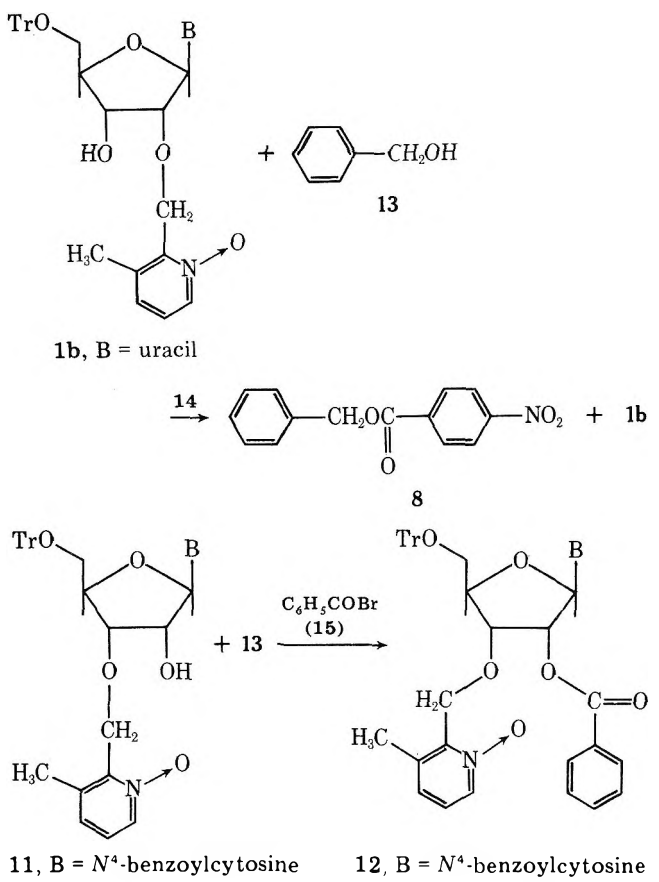
[a] In the presence of a limited amount of pyridine (0.46–0.82 mmol) at 23 °C. [b] For the definition of A_{4b}/A_{10} and A_8/A_{10}, see the Experimental Section. [c] Averaged values of three determinations. [d] Averaged values of two determinations. [e] Based on the acylating agent **14**. Besides **4b** (66–80%), **14** was recovered in 15–25% yields as benzoic acid.

Discussion

It is well established that, under comparable conditions, nucleophilic substitution at an unsaturated center such as ester formation from acyl halide and alcohol is controlled by steric factors associated with both reagents and the nucleophilicity of attacking groups (alcohols). The structure of 2-pyridinemethanol 1-oxide (**3a**) resembles that of benzyl alcohol (**13**) except that the former has an *N*-oxide group. It is reasonable, therefore, to assume that the steric factors associated with both alcohols are nearly equal, and, consequently, the relative rate of the ester formation between two competing alcohols is apparently a reflection of the difference in nucleophilicity of the two.

Ample examples are known that hydrogen-bonded hydroxyl groups behave as stronger nucleophiles than non-hydrogen-bonded hydroxyl groups toward a hard[11] carbonyl center.[12] The existence of weak hydrogen bonding in the alcohol [**13**, **3a**, **3b**, or 4-methoxy-2-pyridinemethanol 1-oxide (**5**)] was indicated by NMR spectra [signals due to respective hydroxyl groups of **13**, **3a** **3b**, and **5** appear at δ ($CDCl_3$) 3.88, 7.43, 5.52, and 5.42]. However, the difference of the degrees in hydrogen bonding is too slight to expect the dramatic difference in the

Scheme III



relative rate of acylation among these alcohols.[13] The only remaining possibility to invoke the explanation of the observed selective acylation of the ω-hydroxyl group of 2-pyridyl 1-oxide alcohols, **3a** and **3b**, to **13** is the neighboring group participation of the *N*-oxide group, assuming that the nucleophilicity of this group toward the sp^2 carbon is higher than that of the hydroxyl group of **13**. This assumption may not be farfetched, because the *N*-oxide group is hard.[14]

As far as we are aware,[15] the present paper is the first to demonstrate that the *N*-oxide group of pyridine 1-oxide may be more nucleophilic (harder) than the hydroxyl group of an alcohol.[16] It is also of interest to note that the nucleophilicity of the *N*-oxide group of **3a** toward the sp^3 center of the phosphorodichloridate may not be high enough to form the corresponding pyridinium intermediate (at room temperature), whereas the *N*-oxide group of **5** was reactive enough to give a pyridinium intermediate (see Scheme II). This trend is in reasonably good agreement with that previously observed.[1b]

In the absence of **13**, 2′-*O*-(3-methyl-2-picolyl 1-oxide)-5′-*O*-trityluridine (**1b**) was acylated to afford the corresponding 3′-*O*-(*p*-nitrobenzoyl) derivative. In its presence, however, benzyl *p*-nitrobenzoate (**8**) was formed under the "standard conditions" (see the Experimental Section), **1b** remaining completely intact.

In order to find the factors causing the remarkable difference in reactivity between **1b** and **3a**, an inspection of the space-filling molecular model was made. The molecular model for the former showed that the 2′-*O*-(3-methyl-2-picolyl 1-oxide) group and the uracil moiety of the former are capable of readily stacking together, the *N*-oxide oxygen sticking out away from the 3′-OH group, and a considerably high barrier has to be overcome to twist the 2′-O protecting group to form a cyclic intermediate (structure **2** in Scheme I) that could transfer the acyl group to the 3′-OH group. Evidence for the strong stacking interaction of the two aromatic rings in **1b** (not in its 3′-O isomer) has already been obtained[9] by the larger hypsochromicity in its UV spectrum and its lower solubility in aqueous methanol.

In regard to the hypsochromicity and the solubility, a similar trend could be observed between 2′-*O*-(3-methyl-2-picolyl)-5′-*O*-trityl-N^4-benzoylcytidine and its 3′-O isomer **11**. The competitive acylation with benzoyl bromide (**15**, 0.9 equiv) between the scarcely stacked[17] nucleoside **11** (1 equiv) and **13** (2.15 equiv) afforded an 18% yield of the corresponding nucleoside **12**, as expected. This fact presumably corroborates the above explanation.

It appears to be an attractive challenge to elaborate a 2′-O protecting group for the ribonucleosides that might be capable of assisting phosphorylation of the 3′-OH group. The present investigation suggests that, to achieve this, at least two requirements must be fulfilled by the protecting group. This should be a heterocyclic *N*-oxide that would be stacked with the aromatic ring of the nucleoside to the least extent when attached to the 2′-oxygen, and the sp^3 phosphorus nucleophilic activity of the oxygen atom of the *N*-oxide must be comparable to or superior to that of 4-methoxy-2-picoline 1-oxide.

Experimental Section

Melting points were determined in capillaries, heated in an oil bath on a Yamato instrument, and are not corrected. Nuclear magnetic resonance (NMR) spectra were determined in chloroform-*d* at 60 MHz on a Hitachi spectrometer, Model R24. Chemical shifts were reported in parts per million downfield from Me_4Si. Mass spectra were obtained on a Hitachi RMU-6E spectrometer. The progress of the reactions was routinely followed either by thin-layer chromatography (TLC) or NMR. TLC was run on glass plates coated with silicic acid in the following systems: solvent A, benzene; solvent B, $CHCl_3$–EtOH (7:1) and the mixture of other proportions was also used. In order to obtain quantitative data, the plate was carefully heated at ca. 150 °C for 3 h prior to use.

2-Pyridinemethanol 1-oxide (**3a**, mp 138–141 °C),[18] β-(2-pyridyl 1-oxide)ethanol (**3b**, mp 93–95 °C, from dry ethyl acetate),[19] γ-(2-pyridyl 1-oxide)propanol [**3c**, mp 52–54 °C, bp 120 °C (0.1 mm)],[20] 2,2,2-trichloroethyl phosphorodichloridate [**16**, 116–118 °C (14 mm)],[21] and benzyl *p*-nitrobenzoate (**8**, mp 84.5–85 °C)[22] were prepared as reported.

4-Methoxy-2-pyridinemethanol 1-Oxide (5). To a solution of 4-methoxy-2-picoline 1-oxide (11 g, 0.071 mol) in chloroform (20 mL) was added acetic anhydride (30 mL). The solution was heated for 4 h at refluxing temperature. The cooled solution was poured into ice and water. The solution was adjusted with saturated Na_2CO_3 to pH 9. The product was extracted with chloroform (40 mL × 3). The dried ($MgSO_4$) solution was concentrated to dryness. The residue was applied to a silica gel (200 g) column. The column was washed with $CHCl_3$–EtOH (1000:15) and the fractions containing 4-methoxy-2-pyridylacetoxymethane were collected. Evaporation of the eluate afforded the desired product. The structure was confirmed by NMR [δ 2.13 (s, 3 H, CH_3CO), 3.83 (s, 3 H, CH_3O), 4.77 (s, 2 H, $-CH_2OAc$), 6.71 (q, 1 H, H_5), 6.88 (q, 1 H, H_3), 8.37 (d, J = 7 Hz, 1 H, H_6)]. The yield was 8.5 g (65%). The above product (8.2 g, 45.3 mmol) was treated with hydrogen peroxide (30%, 7.67 g) in acetic acid (20 mL) at 40 °C for 12 h. After ascertaining by TLC ($CHCl_3$–EtOH, 40:5) that the reaction was complete, the mixture was concentrated to dryness. The residue was treated with saturated methanolic ammonia (40 mL) for 3 h at room temperature. The product was purified on a silica gel column [silica, 50 g; EtOH–$CHCl_3$ (100:1)]. The crude yield was 4.6 g. Crystallization from EtOH–*n*-pentane afforded an analytical sample: mp 135–137 °C; yield 3.0 g (42%); NMR δ 3.83 (s, 3 H, CH_3O), 4.77 (s, 2 H, CH_2OH), 6.63 (m, 1 H), 7.06 (m, 1 H), 8.07 (d, J = 7 Hz, 1 H, H_6). Anal. Calcd for $C_7H_9NO_3$: C, 54.10; H, 5.81; N, 9.03. Found: C, 54.00; H, 5.82; N, 9.05.

1-(2-Pyridyl 1-oxide)-2-(*p*-nitrobenzoxy)ethane (4b). An authentic sample of **4b** was prepared by a standard procedure from *p*-nitrobenzoyl chloride and **3b**: mp 124–126 °C (crystallized from ethanol). Anal. Calcd for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.16; N, 9.72. Found: C, 58.31; H, 4.17; N, 9.72.

4-Methoxy-2-picolyl 2,2,2-Trichloroethyl Phosphorochloridate 1-Oxide (6), HCl Salt. To a solution of 4-methoxy-2-pyri-

Table III. Calibration of Analysis of 8

Run	1	2	3
8, mg	17.0	52.0	147.3
10, mg	53.0	56.3	63.9
Wt_8/wt_{10}[a]	0.309	0.923	2.305
A_8/A_{10}	0.316	0.905	2.156

[a] Wt_8/wt_{10} refers to the ratio of the weight of 8 to that of 10. [b] For the definition of A_8/A_{10}, see the Experimental Section.

dinemethanol 1-oxide (5, 155.4 mg, 1 mmol) in chloroform-*d* (1 mL) containing pyridine (90.9 mg, 1.15 mmol) was added a solution of 2,2,2-trichloroethyl phosphordichloridate (16, 267.1 mg, 1 mmol) in chloroform-*d* (0.5 mL) with stirring at room temperature. After a 20-min period of stirring, a white precipitate formed which in turn was added with chloroform-*d* (1 mL). The product was collected by filtration. The yield of 6 (HCl salt) was 250 mg (50%). The structure was confirmed after neutralization by NMR (see Table IV).

Competitive Reaction I. Reaction of 2-(ω-Hydroxyalkyl)-pyridine 1-Oxides 3a–c and Benzyl Alcohol (13) with *p*-Nitrobenzoyl Chloride (14). a. 2-Pyridinemethanol 1-Oxide (3a). The following operations were all performed at room temperature (~23 °C). To a solution of 2-pyridinementhanol 1-oxide (**3a**, 125 mg, 1.0 mmol), 13 (554.8 mg, 5.09 mmol), and pyridine (58.8 mg, 0.74) in chloroform (4 mL) was added with stirring a solid sample of 14 (102.8 mg, 0.554 mmol). After a 5-min period of stirring, complete solution resulted. Stirring was continued overnight. The reaction mixture was added to 53.3 mg (0.784 mmol) of *p*-nitrotoluene (10) as an internal standard for the subsequent spectrometric analysis. An aliquot (~100 $A_{262\ nm}$ units) was applied to a TLC plate. The same plate was spotted alongside, at separate points (from each other as well as the spot of the reaction mixture), with three respective solutions of the following authentic samples: 10, 8,[23] and 2-picolyl 1-oxide *p*-nitrobenzoate (**4a**).[24] These samples were developed first with benzene to a distance of ~15 cm and subsequently (after being redried) developed with solvent B. Spots were visualized under a UV lamp. Each compound including pyridine hydrochloride could be cleanly separated, the order of larger mobility being **10, 8, 4a**, and pyridine hydrochloride. Each spot along with a blank spot of the same area was scratched out and transferred to a centrifuge tube. There was then added 4 mL of EtOH. After being well shaken for 25 min, silica was centrifuged off (2600 rpm, 30 min). A 0.3-mL volume of the supernatant layer was pipetted and added to 4 mL of EtOH, and the solution was well shaken. The absorbance of each solution was determined in a quartz cell of 1-cm width at 262 nm, using a solution similarly prepared from the blank spot as a control. The entire procedure (including the competitive acylation) was repeated five times. In one run, the following $A_{262\ nm}$ values were obtained (A_{10} is short for the $A_{262\ nm}$ value of 10 and so forth): A_8, 0.045; A_{4a}, 0.584, and A_{10}, 0.181. Therefore, A_8/A_{10} (a ratio of A_8 to A_{10}) = 0.257; A_{4a}/A_{10} = 3.32.[25] The averaged value of five runs is listed in Table I.

Similar experiments were performed by the use of 1.099 g (9.97-fold, experiment 2), 1.6387 g (14.82-fold, experiment 3), 2.179 g (19.83-fold, experiment 4), or 3.259 g (29.30-fold, experiment 5) of 13, other conditions being virtually the same as the above. Each experiment was duplicated. A_{4a}/A_{10} and A_8/A_{10} were similarly obtained and also listed in Table I.

b. (2-Pyridyl 1-oxide)ethanol (3b). Parallel competitive acylation was performed with **3b**. Each experiment was carried out three times. The averaged values are listed in Table II.

c. γ-(2-Pyridyl 1-oxide)propanol (3c). Parallel (but preliminary) competitive acylation was performed with **3c**. A similar trend as in the case of a and b above was observed.

d. Calibration of the Above Analysis. In order to calibrate the above analysis, an artificial solution prepared by dissolving various amounts of 8 together with a definite amount of *p*-nitrotoluene (10) in 3 mL of chloroform was analyzed. Each A_8/A_{10} value obtained is given in Table III. When these are plotted against wt_8/wt_{10} (ratio of the weight of 8 to that of 10) as abscissa, they are located in a straight line which coincides with the origin (namely, a calibration curve for 8 was obtained but is not shown). A good calibration curve for **4a** or **4b** was analogously obtained.

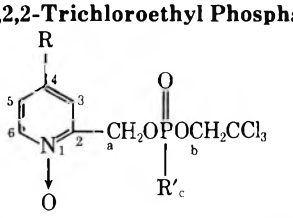
II. Reaction of 4-Methoxy-2-pyridinemethanol 1-Oxide (5) and 1-Butanol (17) with 2,2,2-Trichloroethyl Phosphorodichloridate (16). 16 (140 mg, 0.525 mmol) dissolved in chloroform (1 mL) was added with stirring to a cooled (~15 °C) chloroform solution (5 mL) of 5 (153.1 mg, 0.99 mmol) and 1-butanol (17, 85 mg, 1.15 mmol) containing 2,4,6-trimethylpyridine (collidine, 92.8 mg, 0.776 mmol). The mixture was allowed to stand at room temperature for 24 h and then added with vigorous stirring to $NaHCO_3$ solution (pH 10, 20 mL). The chloroform layer was separated and concentrated to dryness. The residue was purified by preparative TLC (silica gel; solvent system $CHCl_3$–EtOH, 7:1). The yield of *n*-butyl 4-methoxy-2-picolyl 2,2,2-trichloroethyl phosphate 1-oxide (7) was 124 mg (55.6% yield, based on the phosphorylating agent 16). The structure of 7 was confirmed by NMR (see Table IV) and mass spectrometry: *m/e* 405, 407 (M − O); 370, 372 (M − OCl).

III. Reaction of 2-Pyridinemethanol 1-Oxide (3a) and 1-Butanol (17) with 2,2,2-Trichloroethyl Phosphorodichloridate (16). To a magnetically stirred solution of **3a** (127.1 mg, 1.02 mmol), 1-butanol (17, 92.8 mg, 1.25 mmol), and collidine (128.4 mg, 1.06 mmol) in $CHCl_3$ (5 mL) was added, with slight cooling (overcooling may result in no reaction), a $CHCl_3$ solution (1 mL) of 16 (127.1 mg, 0.48 mmol). The basified (to pH 10 with aqueous solution of $NaHCO_3$) solution was applied to two TLC plates (silica gel; solvent system $CHCl_3$–EtOH, 10:1). The band corresponding to *n*-butyl 2-picolyl 2,2,2-trichloroethyl phosphate 1-oxide (18) (whose structure was confirmed by NMR, see Table IV) was scratched out and extracted with $CHCl_3$ (4 mL). Silica was filtered off. Concentration of the filtrate left an almost pure sample of 18 (the purity was checked by NMR): mass spectrum *m/e* 392.391 (M), 375.377 (M − O), 306.308 (M − Cl), 340.342 (M − OCl); yield 22.4 mg (11.9% on the basis of 16).

IV. Reaction of 2′-*O*-(3-Methyl-2-picolyl 1-oxide)-5′-*O*-trityluridine (1b) and 13 with *p*-Nitrobenzoyl Chloride (14). Reaction of 1b[9] (318.9 mg, 0.525 mmol) and 13 (121.4 mg, 1.124 mmol) with 14 (82.2 mg, 0.759 mmol) in pyridine (42.3 mg, 0.523 mmol) and chloroform (4 mL) at room temperature (overnight) gave, after separation on TLC (solvent B), 8 (mp 83.5–84.5 °C)[23] as the exclusive product, 1b being recovered intact in quatitative yield. The reaction mixture was also analyzed according to the above assay method using 56 mg of 10 as the internal standard. The value (the averaged value of three runs) of A_8/A_{10} was obtained, this value corresponding to 48 mg (by the use of the calibration curve) of 8 (42.1%, on the basis of 14).

3′-*O*-(3-Methyl-2-picolyl 1-oxide)-5′-*O*-trityl-*N*⁴-benzoylcytidine (11). To a solution of N^4-benzoylcytidine[26] (24.5 g, 70.6

Table IV. Proton Chemical Shifts for 2-Picolyl 2,2,2-Trichloroethyl Phosphate 1-Oxides[a]



Compd	Chemical shifts (ppm) and coupling constants (Hz)						
	H-6	H-3	H-5	H_a	H_b	H_c[b]	OMe
6, R = OMe; R′ = Cl	8.12 d (7.2)[c]	7.06 d (3.2)	6.85 q (7.2, 3.2)	5.42 d (7.6)	4.74 d (7.2)		
7, R = OMe; R′ = *n*-BuO	8.24 d (7.4)	7.14 d (3.4)	6.90 q (7.2, 3.4)	5.43 d (7.7)	4.67 d (7.0)	4.25 q	3.91 s
18, R + H; R′ = *n*-BuO	8.3			5.41 d	4.65 d	4.24 q	

[a] In $CDCl_3$ at room temperature. [b] H_c, $-OCH_2$ in R′ = OC_4H_9. [c] Number in parentheses refers to the coupling constant.

mmol) in DMF (400 mL) was added, with stirring, successively stannous chloride dihydrate (400 mg) and 1-oxido-2-pyridyldiazomethane, prepared from 40 g (131.1 mmol) of the *p*-tosylhydrazone of 3-methyl-2-formylpyridine 1-oxide.[24] The stannous chloride was added twice (400 mg, each) at the interval of a 2-h period. The stirring was continued at room temperature overnight. The reaction mixture was concentrated to leave a residue which was dissolved in chloroform (200 mL) and applied to a column of silica gel (200 g). The column was washed with 1.5 L of chloroform (the eluate being discarded) and then washed with 1.5 L of $CHCl_3$–EtOH (10:1). Concentration of the latter fraction gave a mixture of 2′-*O*- and 3′-*O*-(3-methyl-2-picolyl 1-oxide) nucleosides. Attempted fractional crystallization failed from Me_2SO, but a crystalline isomeric mixture having correct combustion values was obtained. The yield was 29 g (88%). Anal. Calcd for $C_{23}H_{24}N_4O_9 \cdot H_2O$: C, 56.79; H, 4.94; N, 11.52. Found: C, 56.88; H, 5.26; N, 11.33.

A suspension of the isomeric mixture (2 g, 57.6 mmol) in pyridine (400 mL) was treated with triphenylchloromethane (27 g, 96 mmol) at 40 °C for 3 days. The mixture was then concentrated to leave a residue which was dissolved in 200 mL of satruated Na_2CO_3 solution. The solution was treated with chloroform (3 × 300 mL). The dried (Na_2SO_4) chloroform solution was concentrated to dryness. The residue was applied to a column of silica gel (700 g) which was washed with $CHCl_3$–EtOH (100:3). From the fast traveling fraction, the 2′-O isomer was obtained as a homogeneous (in solvent B) foam (8.9 g, 21%): NMR (Me_2SO-d_6) δ 2.42 (s, 3 H, 3″-CH_3[27]), 6.02 (s, 1 H, $H_{1'}$). Anal. Calcd for $C_{42}H_{38}N_4O_7 \cdot 0.5H_2O$: C, 70.09; H, 5.28; N, 7.78. Found: C, 70.15; H, 7.73; N, 7.69.

From the slower traveling fraction, **11** was obtained as a homogeneous (in solvent B) foam (25 g, 61%): NMR (Me_2SO-d_6) δ 2.34 (s, 3 H, 3″-CH_3[27]), 5.87 (s, 1 H, $H_{1'}$). According to Reese's rule,[28] an isomer whose anomeric proton signal appears comparatively upfield (5.87 vs. 6.02 ppm) has been assigned as 3′-O isomer. Anal. Calcd for $C_{42}H_{38}N_4O_7 \cdot 0.5H_2O$: C, 70.09; H, 5.28; N, 7.78. Found: C, 70.11; H, 5.52; N, 7.53.

V. Competitive Reaction of 11 and 13 with Benzoyl Bromide (15). **15** (172.8 mg, 0.944 mmol) dissolved in chloroform (4 mL) was added with stirring to a cooled (10 °C) chloroform solution (8 mL) of **11**[26] (724 mg, 1.02 mmol) and **13** (232 mg, 2.14 mmol) containing 137.7 mg (1.13 mmol) of collidine. The mixture was kept at room temperature overnight. The mixture was added with $NaHCO_3$ (500 mg). TLC examination showed that the reaction mixture contained 3′-*O*-(3-methyl-2-picolyl 1-oxide)-5′-*O*-trityl-$O^{2'}$,N^4-dibenzoylcytidine (**12**) and benzyl benzoate in addition to the starting material. The mixture was applied to a silica gel column (silica, 20 g; solvent system $CHCl_3$–EtOH, 100:3). The fraction containing the nucleoside **12** was collected and the solvent was stripped off to leave **12** (145.4 mg, 19%, based on **15**). Crystallization from *n*-C_6H_{14}–$CHCl_3$ gave an analytical sample of **12**: NMR ($CDCl_3$) δ 2.09 (s, CH_3), 5.44 (d, J = 2.4 Hz). Anal. Calcd for $C_{49}H_{42}N_4O_8 \cdot 2H_2O$: C, 69.33; H, 5.42; N, 6.60. Found: C, 69.10; H, 5.13; N, 6.40.

Registry No.—**1b**, 54618-09-6; **3a**, 10242-36-1; **3b**, 64364-85-8; **3c**, 64364-84-7; **4a**, 50808-24-2; **4b**, 64364-96-1; **5**, 64364-95-0; **6**, 64364-94-9; **6**·HCl, 64364-93-8; **7**, 64364-92-7; **8**, 14786-27-7; **11**, 64364-91-6; **12**, 64364-90-5; **13**, 100-51-6; **14**, 122-04-3; **15**, 618-32-6; **16**, 18868-46-7; **17**, 71-36-3; **18**, 64364-89-2; 4-methoxy-2-picoline 1-oxide, 6890-60-4; acetic anhydride, 108-24-7; 4-methoxy-2-pyridylacetoxymethane, 16665-37-5; N^4-benzoylcytidine, 13089-48-0; 1-oxido-2-pyridyldiazomethane, 50908-23-1; 2′-*O*-(3-methyl-2-picolyl 1-oxide)nucleoside, 64364-87-0; 3′-*O*-(3-methyl-2-picolyl 1-oxide)nucleoside, 64364-86-9; 2′-*O*-(3-methyl-2-picolyl 1-oxide)-5′-*O*-trityl-N^4-benzoylcytidine, 64364-88-1.

References and Notes

(1) (a) Presented in part at the 3rd National Meeting of Nucleic Acid Chemistry in Sapporo, Japan, Sept 1975; (b) for part 6, see Y. Mizuno and T. Endo, *J. Org. Chem.*, accompanying paper in this issue.

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(4) The "two-step procedure" refers to a synthetic procedure which consists of two steps for the synthesis by the triester approach of dinucleoside monophosphate: the initial phosphorylation of suitably protected nucleosides to the corresponding 3′-phosphates (without isolating this intermediate), followed by condensation of the latter with another nucleoside bearing free 5′-OH in the same reaction vessel. This is in contrast to a direct condensation of a nucleoside phosphate and nucleoside leading to a dinucleoside monophosphate.

(5) T. Neilson and E. S. Werstiuk, *J. Am. Chem. Soc.*, **96**, 2295 (1974). They have successfully used this two-step procedure for the preparation of the nonanucleotide corresponding to the anticodon loop In *E. coli* $tRNA^{fMet}$.

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(7) (a) Y. Mizuno, M. Itoh, and H. Tagawa, *Ind. Chem.*, 1498 (1965); (b) L. A. Paquette, *J. Am. Chem. Soc.*, **87**, 1407 (1965).

(8) V. J. Traynelis in "Mechanisms of Molecular Migrations", Vol. II, B. S. Thyagarajan, Ed., Interscience, New York, N.Y., 1969, pp 1–42.

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(10) Apparently 2′-*O*-(3-methyl-2-picolyl 1-oxide)uridine (1, B = uracil) might be a more suitable substrate for competitive acylation between 3′-OH and 5′-OH. However, because of a low solubility of **1** (B = uracil) in conventional solvents (in addition to the reason described in the text), we chose a mixture of 2-(ω-hydroxyalkyl)pyridine 1-oxides and benzyl alcohol initially as a model system.

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(12) (a) K. W. Bucke, J. M. Duxburg, A. B. Foster, A. R. Perry, and J. M. Weber, *Carbohydr. Res.*, **2**, 122 (1966); (b) K. W. Buck, A. B. Foster, A. R. Perry, and J. H. Webber, *J. Chem. Soc.*, 4171 (1963).

(13) In view of the fact that signals (in NMR) due to intramolecularly hydrogen-bonded OH appear in the range 5.5 ~ −17.2, these observed δ values cannot be considered to suggest the occurrence of strong intramolecular hydrogen bonding with compounds **3a–c**, [N. F. Chamberlain, "The Practice of NMR Spectroscopy", Plenum Press, New York, N.Y., 1974, p 119; see also G. D. Allen and R. A. Dwek, *J. Chem. Soc. B*, 161 (1966); J. D. Bartels-Keith and R. F. W. Cieiuch, *Can. J. Chem.*, **46**, 2593 (1968); J. L. Burdett and M. T. Rogers, *J. Am. Chem. Soc.*, **86**, 2105 (1964); E. Marcus, J. K. Chan, and C. B. Strow, *J. Org. Chem.*, **31**, 1369 (1966); M. Saquet, *Bull. Soc. Chim. Fr.*, 2841 (1967)].

(14) M. N. Marmur and S. Swern, *J. Am. Soc.*, **93**, 2719 (1971).

(15) Pertinent to the present discussion is the work by Omura et al. who have observed that the competitive reaction of trifluoroacetic anhydride with methyl sulfoxide and benzhydryl alcohol (at −60 °C) gave rise almost exclusively to di(trifluoromethyl)sulfonium trifluoroacetate. It is safely assumed that N → O and S → O, whose common feature is to bear a dative bond, are better nucleophiles than the OH group of alcohol toward the "hard" carbonyl center [K. Omura, A. K. Sharma, and D. Swern, *J. Org. Chem.*, **41**, 957 (1976)].

(16) Preliminary competitive acylation using methanol or ethanol was performed to give exclusively the esters of **3a–c**. For example, competitive acylation between ethanol (100 mg) and **3b** (300 mg) with benzoylimidazolide hydrochloride also exclusively gave the ester **10** corresponding to **3b**. Gas chromatographic examination (for conditions, see footnote 19 of ref 9) showed the absence of ethyl *p*-nitrobenzoate in the reaction mixture.

(17) By analogy to the case of a pair of **1b** and its 3′-O isomer, as well as by analogy to the observation of Christensen et al. [L. F. Christensen and A. D. Broom, *J. Org. Chem.*, **37**, 3398 (1972)], it is highly probable that **11** may be less stacked relative to the 2′-O isomer.

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(25) The respective ratio (A_8/A_{10} or A_{4a}/A_{10}), calculated on the basis of the amount of *p*-nitrotoluene (**10**) which had been actually added to the reaction mixture (in the case of the above example, 53.3 mg), was standardized to the value per 50 mg of **10**. The latter was further standardized to the value per 100 mg of *p*-nitrobenzoyl chloride. For example, since, in the example, 102.5 mg of the latter was actually used, a value of 0.257 for A_8/A_{10} was obtained by 0.045/0.181 × 53.3/50 × 100/102.5. Other ratios were similarly obtained.

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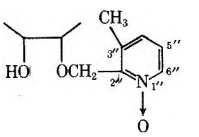
(27) Double prime for the numbering, e.g., 3″-CH_3, refers to the protecting group, and the numbering of the pyridine ring is as follows.



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Syntheses and Chiroptical Properties of (−)-Ditwist-brendane and (+)-D_3-Trishomocubane

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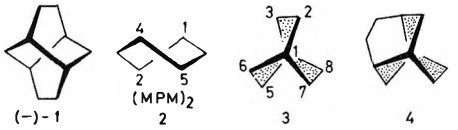
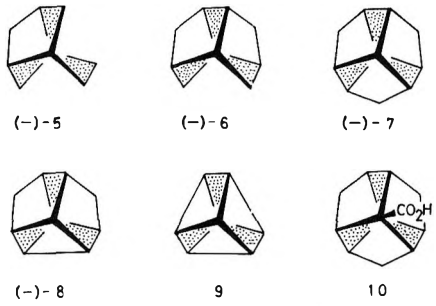
(−)-Ditwist-brendane (tetracyclo[5.2.1.$0^{2,6}$.$0^{4,8}$]decane) (**6**) was prepared by hydrogenolysis of optically active (−)-C_2-bishomocubane (**8**) with known absolute configuration. Synthesis of (+)-D_3-trishomocubane (pentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane) (**27**) is reported, and its absolute configuration is discussed by comparing circular dichroism spectra of the closely related pair of ketones (+)-D_3-trishomocuban-4-one (**26**) and (−)-(1*R*,2*R*,4*S*,6*S*,7*R*,8*S*)-ditwist-brendan-5-one (**14**).

Symmetry number 4 inherent to the molecule of (−)-twistane (D_2 symmetry) (**1**)[1] indicates the presence of four identical twist-boat cyclohexane moieties with a $(MPM)_2$ conformation being disposed around its three C_2 axes. Although this structural feature of **1** can be constructed by bridging the 1,4 and 2,5 positions of the twist-boat cyclohexane (**2**) with two ethano bridges, the twisted bicyclo[2.2.2]octane (**3**) with D_3 symmetry can be regarded as its other generatrix.



Freezing the chiral conformation of the bicyclo[2.2.2]octane system (**3**) with either an ethano or methano bridge spanning the 3,6 position gives (−)-twistane (**4**), $[\alpha]_D$ −414°,[1a] or (−)-twist-brendane (C_2 symmetry) (**5**), $[\alpha]_D$ −235°,[2] respectively.



Successive diagonal bridging of **5** with CH_2 furnishes ditwist-brendane (C_2 symmetry) (**6**)[3] followed by D_3-trishomocubane (D_3 symmetry) (**7**),[5] which can be regarded as a higher homologue of (−)-C_2-bishomocubane (**8**)[6] whose preparation and absolute configuration have been recently reported from our laboratory.

Among nine theoretically possible trishomocubanes [symmetry (number of members)], C_{3v} (1), C_{2v} (1), C_s (3), D_3 (1), C_2 (1), C_1 (2), generated from cubane (**9**)[7], D_3-trishomocubane (**7**) has the highest chiral symmetry, and its symmetry number 6 necessitates that this molecule is constructed from six identical twist-cyclopentane structural units.

The unique stereochemistry of **7** as well as its rather small size ($C_{11}H_{14}$) appear to render **7** as an attractive C_3 building block (**10**) for constructing high-symmetry chiral molecules with *T*, *O*, and *I* symmetries.[8]

We have been interested in syntheses and chiroptical properties of various high-symmetry chiral (gyrochiral[9]) molecules, and this paper reports syntheses of (−)-ditwist-brendane (**6**) and (+)-D_3-trishomocubane (**27**) as well as their absolute configurations.

Results and Discussion

Synthesis of (−)-Ditwist-brendane (6). Smooth conversion of the C_2-bishomocubane framework into the ditwist-brendane framework via hydrogenolysis of the 8,9 bond has been reported,[4b,c] and this procedure was carried out on (−)-(1*S*,2*S*,3*S*,4*S*,5*R*,7*S*,8*S*,9*R*)-C_2-bishomocubane (**8**) with 5% Pd on carbon, furnishing a 25% yield of (−)-(1*R*,2*R*,4*R*,6*R*,7*R*,8*R*)-ditwist-brendane (**6**): mp 164.5–165.5 °C; $[\alpha]_D$ −233°. Since we desired optically active ditwist-brendan-5-one (**14**) of known absolute configuration as a reference substance for deducing the absolute configuration of (+)-D_3-trishomocubane (**27**), an attempt was made to obtain optically active ditwist-brendane (**6**) via **14** obtained from (+)-C_2-bishomocubane-5,10-dione ethylene ketal (**11**) whose absolute configuration was recently reported from our laboratory.[6] Facile hydrogenolysis with 5% Pd on carbon converted (+)-**11**, $[\alpha]_D$ + 95.9°, into (−)-**13**, and removal of the keto group by Wolff–Kishner reduction followed by hydrolysis of the ethylene ketal protective group afforded (−)-**14**, mp 165–167 °C; $[\alpha]_D$ −181°, Wolff–Kishner reduction of which gave another route to (−)-ditwist-brendane (**6**). (See Scheme I.)

Synthesis of (+)-D_3-Trishomocubane (27). Among various synthetic routes reported for the preparation of trishomocubane (**7**), Barborak's procedure[5e] was our choice because its intermediates appeared to promise facile optical resolution. Rearrangement of Barborak's intermediate **15** afforded (±)-D_3-trishomocubane-4,7-diol, mp 200–203 °C, as a single product, to which the cis configuration **16** was assigned by Barborak for mechanistic reasons. Our observation of two well-resolved equal intensity singlets at δ 1.93 and 1.96 (CH_3CO) exhibited by diacetate **19** supports the cis stereochemistry (C_1 symmetry) of the diol **16** and excludes the two other trans diastereomers **17** and **18** both with C_2 symmetry.

Our various efforts toward optical resolution of diol **16**

Scheme I

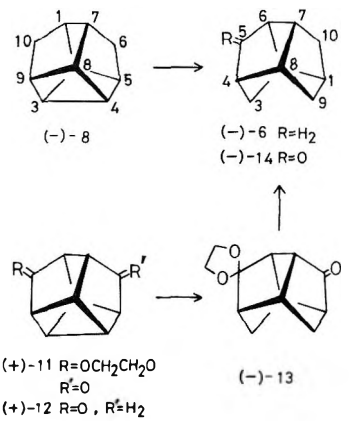


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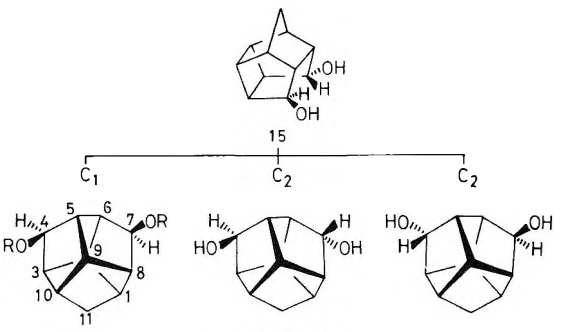
Table I. CD Spectra of (−)-Ditwist-brendan-5-one (14), (+)-D_3-Trishomocuban-4-one (26), and (+)-C_2-Bishomocuban-6-one (12) (in isooctane)

(−)-14		(+)-26		(+)-12	
[θ]	nm	[θ]	nm	[θ]	nm
+6.67 × 10^3 (sh)	289	−5.37 × 10^3 (sh)	289.3	+1.22 × 10^3 (sh)	298
+7.04 × 10^3	293	−5.60 × 10^3	292.5	+1.29 × 10^3	301.5
+6.82 × 10^3 (sh)	296.5	−5.27 × 10^3 (sh)	296.8	+1.23 × 10^3 (sh)	304
+5.66 × 10^3 (sh)	302.5	−4.06 × 10^3 (sh)	303	+9.48 × 10^2 (sh)	312
+4.21 × 10^3 (sh)	307.5	−2.85 × 10^3 (sh)	307.5		

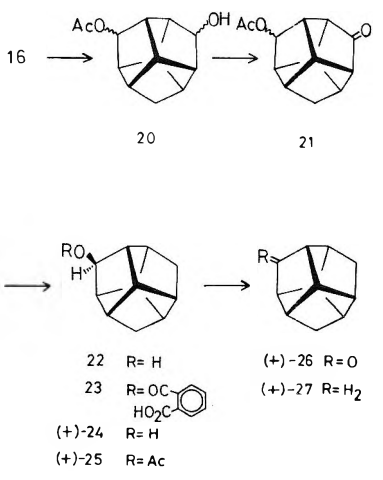


failed, and monoalcohol **22** was chosen as our next candidate for the optical resolution. An equimolar amount of acetyl chloride was added to a pyridine solution of **16**, and chromatography of the reaction mixture afforded, besides the diacetate **19** (28%), a mixture of the diastereomeric cis monoacetates **20** (43%) which was directly oxidized with Jones reagent to the keto acetate **21**. (See Scheme II.)

Although two acetyl signals (δ 2.00 and 2.07; ratio 4:1) observed in the NMR spectrum of **21** indicated its heterogeneity, Wolff–Kishner reduction of **21** was carried out without isolation of the diastereomers and furnished (±)-D_3-trishomocubanol (**22**), mp 165–166 °C. Optical resolution of the alcohol **22** was accomplished via the hydrogen phthalate (**23**) with (+)-2-(1-aminoethyl)naphthalene as the resolving agent. Fractional recrystallization from acetone gave a sparingly soluble salt, $[\alpha]_D$ +65.7°, from which the (+)-alcohol **24**, mp 168.5–169.5 °C, $[\alpha]_D$ +143°, was obtained. Collins oxidation converted **24** into (+)-D_3-trishomocubanone (**26**), mp 163–163.5 °C; $[\alpha]_D$ +83.2°, whose carbonyl group was removed by Wolff–Kishner reduction to give (+)-D_3-trishomocubane (**27**), mp 148–149 °C; $[\alpha]_D$ +155°.[10]

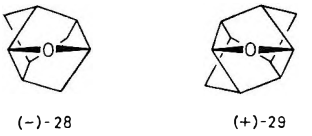
Chiroptical Properties and Absolute Configurations. Before discussing the absolute configuration of (+)-D_3-trishomocubane (**27**), it appears pertinent to describe here some of our efforts made to examine its optical purity. To a $CDCl_3$ solution of (+)-D_3-trishomocubanol acetate (**25**), $[\alpha]_D$ +110°, obtained from the (+)-alcohol **24**, $[\alpha]_D$ +143°, tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) [Eu(facam)$_3$][11] was added to give a molar ratio of (+)-**25**/Eu(facam)$_3$ = 1.0:0.15. Observed intensities of the anisochronous CH_3CO signals (ΔΔδ 0.068 ppm) gave a 34:1 enantiomer ratio, which eventually furnishes $[\alpha]_D$ +88.5° and $[\alpha]_D$ +165° as the absolute rotations of **26** and (+)-D_3-trishomocubane (**27**), respectively.

Scheme II



Coupled with the synthetic route (Scheme I), the *1S,2S,3S,4S,5R,7S,8S,9R* configuration of (−)-C_2-bishomocubane (**8**) reported in our preceding paper[6] permits us to assign the *1R,2R,4R,6R,7R,8R* configuration to (−)-ditwist-brendane (**6**) and *1R,2R,4S,6S,7R,8S* configuration to (−)-ditwist-brendan-5-one (**14**). From almost exact antipodal *n*–π* Cotton curves at 293 nm (Table I) exhibited by (−)-ditwist-brendan-5-one (**14**) and (+)-D_3-trishomocuban-4-one (**26**), the enantiomeric environments around these carbonyl groups can be reasonably deduced and indicate the *1R,3R,5R,6S,8R,10S* configuration for (+)-D_3-trishomocuban-4-one (**26**) and *1R,3R,5R,6R,8R,10R* for (+)-D_3-trishomocubane (**27**).[10]

These conclusions are further supported by the octant projections (**28** and **29**) of these ketones which predict a (−)-Cotton effect for (−)-ditwist-brendan-5-one (**28**) and a (+)-Cotton effect for (+)-D_3-trishomocuban-6-one (**29**).



Also included in Table I is the CD data for (+)-C_2-bishomocuban-6-one (**12**), which shares the same optically active precursor (+)-**11** with (−)-ditwist-brendan-5-one (**14**). Since this indicates that **12** and **14** must have almost the same optical purity, it is rather surprising to note a Cotton effect of markedly lower intensity for **12** as compared to **14**. We tentatively attribute this effect to the presence of the strained bicyclo[2.2.2]octane moiety in **12**, and this effect also seems to be reflected in the small optical rotation shown by its parent hydrocarbon, (−)-C_2-bishomocubane (**8**), relative to closely related cage-shaped hydrocarbons all possessing the twisted bicyclo[2.2.2]octane system as their characteristic feature (See Table II).

Experimental Section

Infrared spectral data were obtained with a Hitachi EPI-S2 spectrophotometer. Nuclear magnetic resonance spectra were obtained with a JNM-MH-100 spectrometer. Ultraviolet spectra were recorded on a Beckman DB spectrometer. Optical rotations were measured with a JASCO-DIP-SL automatic polarimeter. Circular dichroism data were measured on a JASCO J-40 spectropolarimeter. Elemental analyses were determined on a Yanagimoto CHN-Corder Type II. All melting and boiling points are uncorrected.

(−)-Ditwist-brendane-5,10-dione 5-Ethylene Ketal (13). A solution of (+)-**11** (750 mg, 3.67 mmol), $[\alpha]^{14}_D$ + 95.9°,[6] in 75 mL of

Table II. Optical Rotations of (−)-Twist-brendane (5), (−)-Ditwist-brendane (6), (−)-D_3-Trishomocubane (7), and (−)-C_2-Bishomocubane (8)

	(−)-5	(−)-6	(−)-7	(−)-8
$[\alpha]_D$	−235° [a]	−233° [b]	−155° [b]	−33.8° [b]

[a] In ethanol. [b] In chloroform.

methanol was shaken at room temperature in a hydrogenation flask with 370 mg of 5% Pd on carbon at 1 atm of hydrogen. After hydrogen uptake had ceased, the catalyst was removed by filtration. The filtrate was concentrated and the residue was chromatographed on silica gel. Elution with benzene gave a solid which was sublimed at 85 °C (bath temperature, at 5 mm) to yield 316 mg of (−)-**13** (42% yield): mp 53–54 °C; $[\alpha]^{24}_D$ −148° (*c* 0.340, $CHCl_3$); IR (KBr) 1750, 1325, 1100, 1055, 1042, and 1010 cm^{-1}; CD (*c* 2.66 × 10^{-2}, isooctane) [θ] (nm) 0 (240), +1.03 × 10^4 (sh) (287.5), +1.11 × 10^4 (292), +1.08 × 10^4 (sh) (295), +8.89 × 10^3 (sh) (301.5), +6.40 × 10^3 (sh) (306.5), 0 (332).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.67; H, 6.84.

(−)-Ditwist-brendan-5-one (14). A mixture of (−)-**13** (250 mg, 1.21 mmol), 80% hydrazine hydrate (0.2 mL), KOH (0.105 g), and triethylene glycol (2 mL) was heated in an oil bath. During 1.5 h the bath temperature was gradually raised to 190 °C, and this temperature was kept for an additional 3 h. After cooling, a white solid which had formed on the inner wall of the condenser was washed with ether into the flask. The reaction mixture was diluted with water and extracted with ether. The combined ethereal solution was washed with water and dried over $MgSO_4$. The solvent was evaporated to give 0.24 g of an oily product, to which 5 mL of 10% sulfuric acid was added. The mixture was stirred for 24 h at room temperature and extracted with pentane. The extract was washed with saturated $NaHCO_3$ solution and water and dried over $MgSO_4$. Evaporation of the solvent gave a solid which was purified by sublimation at 80–90 °C (bath temperature, at 20 mm) to yield 120 mg of (−)-**14** (67% yield based on **13**); mp 165–167 °C (in a sealed tube); $[\alpha]^{27}_D$ −181° (*c* 0.170, $CHCl_3$); IR (KBr) 1760, 1300, 1142, 872, 860, and 745 cm^{-1}; CD (*c* 3.18 × 10^{-2}, isooctane) [θ] (nm) 0 (243), +6.67 × 10^3 (sh) (289), +7.04 × 10^3 (293), +6.82 × 10^3 (sh) (296.5), +5.66 × 10^3 (sh) (302.5), +4.21 × 10^3 (sh) (307.5), 0 (335); UV λ_{max} (isooctane) 291 nm (ε 19.2); NMR ($CDCl_3$) δ 1.00–1.35 (m, 1 H), 1.45–1.55 (m, 3 H), 1.75–2.02 (m, 4 H), 2.1–2.6 (m, 4 H).

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.81; H, 8.07.

(−)-Ditwist-brendane (6). From (−)-ditwist-brendan-5-one (14). To a mixture of KOH (30 mg), 80% hydrazine hydrate (0.1 mL), and triethylene glycol (1 mL) was added (−)-**14** (70 mg, 0.473 mmol). The mixture was heated in an oil bath. During 1.5 h, the bath temperature was gradually raised to 200 °C. When the temperature reached at 160 °C, a white solid was observed to condense on the inner wall of the condenser. After further heating for 3 h at 200 °C, the reaction mixture was cooled to room temperature and the condensed white solid was rinsed with pentane. The reaction mixture was diluted with water and extracted with pentane. The combined pentane extracts were washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a solid which was sublimed at 50 °C (bath temperature, at 20 mm) to yield 28 mg of (−)-**6** (44% yield): mp 164.5–165.5 °C (in a sealed tube); $[\alpha]^{27}_D$ −233° (*c* 0.096, $CHCl_3$); IR (KBr) 2920, 1380, 1255, and 810 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.25; H, 10.31.

From (−)-C_2-Bishomocubane (8). A solution of (−)-**8** (70 mg, 0.530 mmol), $[\alpha]^{19}_D$ − 33.8°,[6] in 5 mL of methanol was shaken at room temperature in a hydrogenation flask with 30 mg of 5% Pd on carbon at 1 atm of hydrogen. After hydrogen uptake had ceased, the catalyst was filtered off. After the solvent was removed, the residue was sublimed at 50 °C (bath temperature, at 20 mm) to afford 18 mg of **6** (25% yield), $[\alpha]^{27}_D$ −232° (*c* 0.101, $CHCl_3$).

The IR spectrum was completely superimposable on the spectrum of (−)-**6** prepared from (−)-**14**.

(±)-D_3-Trishomocubane-4,7-diol (16). (±)-D_3-Trishomocubane-4,7-diol (**16**) was prepared according to Smith and Barborak's procedure.[5e] Recrystallization of the crude diol from acetone gave colorless platelets, mp 200–203 °C (lit.[5e] mp 203–205 °C).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.01; H, 7.88.

(±)-4,7-Diacetoxy-D_3-trishomocubane (19). To a solution of (±)-**16** (800 mg, 4.49 mmol) in pyridine (3 mL) was added acetic anhydride (1.08 g, 10.8 mmol) at 0–5 °C, and the mixture was stirred for 8 h at room temperature and was then allowed to stand overnight at room temperature. After pouring onto ice, it was acidified with HCl and extracted with ether. The extract was washed successively with 10% HCl, saturated $NaHCO_3$ solution, and water and was dried over $MgSO_4$. After evaporation of the solvent, the residue was distilled to yield 900 mg of **19** (77% yield): bp 165–170 °C (4 mm); IR (neat film) 1732, 1363, 1238, 1041, 942, and 781 cm^{-1}; NMR (CCl_4) δ 1.42 (s, 2 H), 1.93 (s, 3 H), 1.96 (s, 3 H), 2.18 (br s, 6 H), 2.42 (br s, 1 H), 2.53 (br s, 1 H), 4.79 (s, 2 H).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.67; H, 6.97. Found: C, 68.91; H, 6.93.

(±)-4-Acetoxy-D_3-trishomocuban-7-one (21). To a solution of (±)-**16** (21.3 g, 0.120 mol) in 100 mL of pyridine was added acetyl chloride (12.2 g, 0.155 mol) and the mixture was kept overnight at room temperature. After pouring onto ice, it was made acidic with HCl and extracted with ether. The extract was washed successively with 10% HCl, saturated $NaHCO_3$ solution, and water and was dried over $MgSO_4$. Evaporation of the solvent gave 41.0 g of an oily product, which was chromatographed on neutral alumina (Woelm, acitivity II). Elutions with benzene gave 8.70 g of diacetate **19** (28% yield), and elutions with ether afforded 11.2 g of monoacetate **20** (43% yield). Final elution with ether–methanol (93:7 volume) gave 4.3 g of recovered diol **16** (20%). Monoacetate **20** (11.2 g, 0.0509 mol) was dissolved in 10 mL of acetone and excess of Jones reagent[12] (19 mL), which was prepared from 5.34 g of chromic trioxide, 4.6 mL of concentrated sulfuric acid, and 15 mL of water, was added slowly to the solution at 0–5 °C. After stirring for 1.5 h at this temperature, the reaction mixture was diluted with water and extracted with ether. The extract was washed with saturated $NaHCO_3$ solution and water and was dried over $MgSO_4$. Evaporation of the solvent gave an oily product which was distilled to afford 10.3 g of **21** (93% yield): bp 115–120 °C (0.25 mm); IR (neat film) 1755, 1730, 1240, and 1050 cm^{-1}; NMR ($CDCl_3$) δ 1.52–1.68 (m, 2 H), 1.8–2.0 (m, 1 H), 2.01 (s, 3 H), 2.0–2.3 (m, 2 H), 2.64 (br s, 5 H), 5.11 (br s, 1 H).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.84; H, 6.63.

(±)-D_3-Trishomocuban-4-ol (22). A mixture of **21** (4.70 g, 0.0215 mol), KOH (4.30 g), 80% hydrazine hydrate (5.4 mL), and triethylene glycol (30 mL) was heated in an oil bath. During 1 h, the bath temperature was gradually raised to 200 °C and this temperature was then kept for an additional 4.5 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ether. The extract was washed successively with 10% HCl, saturated $NaHCO_3$ solution, and water and was then dried over $MgSO_4$. Evaporation of the solvent gave a solid which was recrystallized from *n*-hexane to afford 2.80 g of **22** (80% yield): mp 165–166 °C (in a sealed tube); IR (KBr) 3300, 1348, 1298, 1275, 1078, and 1065 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.22; H, 8.72.

Optical Resolution of D_3-Trishomocuban-4-ol (22). Phthalic anhydride (18.7 g, 0.126 mol) was added to a solution of **22** (20.4 g, 0.126 mol) in 150 mL of pyridine and the mixture was stirred for 4 h with ice cooling. After standing overnight at room temperature, the reaction mixture was poured onto ice and made acidic with HCl. It was extracted with ether, and the extract was washed with 10% HCl and water. Drying over $MgSO_4$, followed by removal of the solvent, gave 37.3 g of viscous oily hydrogen phthalate (**23**), which was dissolved in 1.5 L of acetone without further purification. To this solution was added slowly a solution of (+)-2-(1-aminoethyl)naphthalene (20.5 g, 0.120 mol) in 200 mL of acetone. After boiling for 2 h, acetone (~1 L) was removed and the residual solution was allowed to stand overnight at room temperature. The deposited solid was collected by filtration to give 29.4 g of the hydrogen phthalate salt with (+)-amine, $[\alpha]^{25}_D$ +32.3° (*c* 0.510, EtOH), and the filtrate was reserved for isolation of (−)-hydrogen phthalate (**23**) (vide infra).

(+)-Hydrogen Phthalate (23). Several fractional recrystallizations of the salt from acetone yielded 12.5 g of the dextrorotatory salt: mp 188–189 °C; $[\alpha]^{26}_D$ +65.7° (*c* 0.347, EtOH). This salt was mixed with 250 mL of 5% HCl and the mixture was stirred for 6 h at room temperature. After drying over $MgSO_4$, the solvent was evaporated to give 7.96 g of the dextrorotatory hydrogen phthalate (**23**) [21% from (±)-hydrogen phthalate (**23**)], $[\alpha]^{23}_D$ +84.5° (*c* 0.638, $CHCl_3$), which was recrystallized from benzene to yield 6.88 g of **23**: mp 151–152 °C; $[\alpha]^{24}_D$ +86.5° (*c* 0.600, $CHCl_3$).

Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.68; H, 5.82.

(−)-Hydrogen Phthalate (23). The filtrate separated from the salt of (+)-hydrogen phthalate was concentrated and the crystalline product was recrystallized from acetone to give the levorotatory salt (3.60 g), $[\alpha]^{24}_D$ −16.2° (*c* 0.320, EtOH), which was treated with 5% HCl

to yield 2.31 g of (−)-hydrogen phthalate (**23**), $[\alpha]^{20}_D$ −35.3° (*c* 0.533, $CHCl_3$).

(+)-D_3-Trishomocuban-4-ol (24). (+)-Hydrogen phthalate (**23**) (6.88 g, 0.0222 mol), $[\alpha]^{24}_D$ +86.5°, was stirred for 5 h at room temperature with 5% KOH aqueous solution (200 mL), and the reaction mixture was then extracted with ether. The extract was washed successively with 10% HCl, saturated $NaHCO_3$ solution, and water and was dried over $MgSO_4$. Evaporation of the solvent gave 3.40 g of **24**, $[\alpha]^{20}_D$ +139° (*c* 0.364, EtOH), which was recrystallized five times from *n*-hexane to afford 2.68 g of (+)-**24** (74% yield): mp 168.5–169.5 °C (in a sealed tube); $[\alpha]^{25}_D$ +143° (*c* 0.590, EtOH); IR (KBr) 3300, 1348, 1298, 1280, 1078, and 1065 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.30; H, 8.73.

(+)-4-Acetoxy-D_3-trishomocubane (25). To a solution of (+)-**24** (400 mg, 2.46 mmol) in 1.5 mL of pyridine was added acetyl chloride (290 mg, 3.67 mmol) with ice cooling, and the mixture was stirred for 5 h at this temperature. After standing overnight at room temperature, the reaction mixture was poured onto ice. It was made acidic with HCl and extracted with ether. The extract was washed successively with 10% HCl, saturated $NaHCO_3$ solution, and water and was dried over $MgSO_4$. The solvent was evaporated and the residue was distilled to yield 402 mg of (+)-**25** (80% yield): bp 108–109 °C (4 mm); $[\alpha]^{24}_D$ +110° (*c* 0.797, $CHCl_3$); IR (neat film) 1735, 1245, and 1048 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (s, 4 H), 1.92 (s, 3 H), 2.07 (br s, 7 H), 2.42 (br s, 1 H), 4.75 (s, 1 H).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 46.44; H, 7.90. Found: C, 46.47; H, 7.89.

(+)-D_3-Trishomocuban-4-one (26). To a suspension of pyridinium chlorochromate[13] (2.80 g, 13.1 mmol) in dry methylene chloride (8 mL) was added a solution of (+)-**24** (1.00 g, 6.17 mmol) in dry methylene chloride (17 mL) and the mixture was stirred for 1.5 h at room temperature. The organic solution was separated by decantation and the inorganic residue was rinsed with ether. Combined extracts were washed successively with 10% HCl, saturated $NaHCO_3$ solution, and water and was dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on neutral alumina (Woelm, activity II). Elutions with pentane–ether (9:1 v/v) gave a solid which was sublimed at 70–80 °C (bath temperature, at 25 mm) to afford 770 mg of (+)-**26** (78% yield): mp 163–163.5 °C (lit.[5c] racemate mp 163–164 °C); $[\alpha]^{25}_D$ +83.2° (*c* 0.650, EtOH); IR (KBr) 1768, 1748, 1160, and 890 cm^{-1}; NMR ($CDCl_3$) δ 1.46 (s, 2 H), 1.61 (s, 2 H), 1.78 (br s, 2 H), 2.40 (br s, 6 H); CD (*c* 3.30 × 10^{-2}, isooctane) [θ] (nm) 0 (239), −5.37 × 10^3 (sh) (289.3), −5.60 × 10^3 (292.5), −5.27 × 10^3 (sh) (296.8), −4.06 × 10^3 (sh) (303), −2.85 × 10^3 (sh) (307.5), 0 (334); UV λ_{max} (isooctane) 272 nm (sh) (ε 12.7), 285.5 (ε 17.5).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.25; H, 7.54.

(+)-D_3-Trishomocubane (27). A mixture of (+)-**26** (250 mg, 1.56 mmol), KOH (300 mg), 80% hydrazine hydrate (420 mg), and triethylene glycol (1.5 mL) was heated in an oil bath. During 100 min, the bath temperature was gradually raised to 200 °C and this temperature was kept for an additional 3 h. A white solid was observed to condense on the inner wall of the condenser during this time. After cooling to room temperature, the white solid was washed with ether and the reaction mixture was poured into ice water. After extraction with ether, combined ethereal solutions were washed with 10% HCl, saturated $NaHCO_3$ solution, and water and was dried over $MgSO_4$. Evaporation of the solvent gave a semisolid which was chromatographed on neutral alumina (Woelm, activity II). Elution with pentane afforded a solid which was sublimed at 130 °C (bath temperature, at 30 mm) to yield 150 mg of (+)-**27** (66% yield): mp 148–149 °C (in a sealed tube) (lit.[5c] mp 149–151 °C; lit.[10] mp 149 °C); $[\alpha]^{24}_D$ +155° (*c* 0.760, $CHCl_3$); IR (KBr) 2940, 2860, 1460, 1295, 1275, 965, and 765 cm^{-1}; NMR ($CDCl_3$) δ 1.32 (s, 6 H), 1.94 (br s, 8 H).

Anal. Calcd for $C_{11}H_{14}$: C, 90.35; H, 9.65. Found: C, 90.11; H, 9.57.

Registry No.—**5**, 42070-69-9; **6**, 64727-80-6; **7**, 61473-77-6; **8**, 62928-75-0; **11**, 62928-73-8; **12**, 62928-74-9; **13**, 64706-11-2; **14**, 64753-80-6; **16**, 64727-81-7; **19**, 64727-82-8; **20**, isomer I, 64706-12-3; **20** isomer II, 64727-83-9; **21**, 64706-13-4; **22**, 64706-14-5; (+)-**23**, 64706-15-6; (+)-**23** (+)-2-(1-aminoethyl)naphthalene salt, 64727-84-0; (−)-**23**, 64727-85-1; (−)-**23** (+)-2-(1-aminoethyl)naphthalene salt, 64783-67-1; **24**, 61473-81-2; **25**, 64706-16-7; **26**, 61473-82-3; **27**, 61473-83-4; acetic anhydride, 108-24-7; acetyl chloride, 75-36-5; (+)-2-(1-aminoethyl)naphthalene, 3906-16-9; phthalic anhydride, 85-44-9.

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Silane Reductions in Acidic Media. 10. Ionic Hydrogenation of Cycloalkenes. Stereoselectivity and Mechanism[1a]

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Stereochemical results from reductions of $\Delta^{9(10)}$-octalin and 4-*tert*-butylmethylenecyclohexane in trifluoroacetic acid by sterically disparate organosilanes, ranging from *n*-butylsilane to tri-*tert*-butylsilane, are reported. Addition of trifluoroacetic acid to the carbon–carbon double bond of these alkenes results in the formation of an equilibrium mixture of isomeric tertiary trifluoroacetates and precedes organosilane reduction. Results are described which indicate that hydride transfer to a symmetrically solvated carbenium ion occurs in ionic hydrogenations of alkenes. Steric factors govern the stereochemical outcome of silane reductions of symmetrically solvated carbenium ions; both the number of substituents bonded to silicon and the steric bulk of these substituents are important determinants of stereoselectivity.

Ionic hydrogenation of alkenes by organosilanes in acidic media is reported to occur in two stages: proton addition followed by hydride transfer to the intermediate carbenium ion (eq 1).[2] Alcohols are likewise reduced by organosilanes

$$R_2C{=}CR_2 + H^+ \longrightarrow R_2\overset{+}{C}{-}CR_2(H) \xrightarrow{R'_3SiH} R_2C(H){-}CR_2(H) \quad (1)$$

through an ionic mechanism.[3] The effectiveness of hydride transfer from organosilanes is intimately associated with the electrophilic character of the cationic intermediate so that in protic acid media only carbenium ions generated from tri- or tetrasubstituted ethylenes and tertiary or certain benzylic alcohols abstract hydride from organosilanes.[2–5] Despite this limitation,[6] however, there continues to be considerable interest in the uses of organosilanes as selective reducing agents[2,4,7] and as efficient scavengers for carbenium ions.[8]

The stereoselectivity in organosilane reductions of alkenes and alcohols has been studied in limited detail.[2,3c,9] Carey and Tremper have reported that the ratio of isomeric hydrocarbons from the reduction of 4-*tert*-butyl-1-phenylcyclohexanols is independent of the geometry of the reactant alcohol and, because the trans-substituted cycloalkane is the dominant reduction product in reactions with organosilanes that possess different steric requirements, propose that the stereoselectivity of hydride transfer is determined by product development control.[3c] However, recent developments in the stereochemical understanding of carbocations under solvolytic conditions[8a,10] and of organosilane reductions in acidic media[1a,7d,11] suggest that the primary determinant of stereoselectivity in reductions of alkenes and alcohols by organosilanes may be more complex than previously imagined. Indeed, Fort and co-workers have found that the triethylsilane reduction of *cis*- or *trans*-9-decalol occurs with nearly complete retention of configuration in the formation of the isomeric decalins.[8a] The present study was undertaken to thoroughly examine the stepwise mechanism for ionic hydrogenation and to delineate those factors that influence stereoselectivity in organosilane reductions that occur in acidic media.

Results and Discussion

Representative model compounds for tri- and tetrasubstituted ethylenes, $\Delta^{9(10)}$-octalin and 4-*tert*-butylmethylenecyclohexane, were chosen for this investigation. Treatment of these alkenes in trifluoroacetic acid at 25 °C with a series of organosilanes that have widely different steric requirements produced the corresponding cycloalkanes in isolated yields of 80–95% (from $\Delta^{9(10)}$-octalin) and 60–85% (from 4-*tert*-butylmethylenecyclohexane). The relative yields of the less stable cycloalkane isomers and their corresponding isomeric ratios are presented in Table I. Clearly, steric factors are important determinants of the stereoselectivity in organosilane reductions.

The compound that is actually reduced in these reactions is unclear from previous studies of organosilane reductions. Kursanov and co-workers have reported, for example, that 1-methylcyclohexene is reduced in methylene chloride solutions of trifluoroacetic acid by triethylsilane at a rate that is from two to five times slower than is the addition product, 1-methylcyclohexyl trifluoroacetate.[7a] The implication from this and related experiments[12] is that simultaneous reduction of the alkene and trifluoroacetate occur, conceivably through the same or distinctly different[8a,10] carbenium ion intermediates. However, trifluoroacetic acid undergoes rapid addition to the carbon–carbon double bonds of both $\Delta^{9(10)}$-octalin and 4-*tert*-butylmethylenecyclohexane under the reaction conditions that we have employed; complete addition occurs within 5 min after mixing the olefin and trifluoroacetic acid. Reduction by triethylsilane, the most reactive organosilane employed in this study, is considerably slower: the time required for 50% conversion to cycloalkane is approximately 20 min with $\Delta^{9(10)}$-octalin and nearly 90 min with 4-*tert*-butylmethylenecyclohexane. With the exception of triethylsilane, reductions by the organosilanes that are listed in Table I are less than 10% complete within the first 5 min following mixing of trifluoroacetic acid with the alkene in the presence of the organosilane.[13] Thus trifluoroacetic acid addition to the reactant alkene is sufficiently more rapid than direct organosilane reduction of the alkene (eq 1) that the trifluoroacetate addition products must be considered to be the effective reactants in hydride transfer reactions with organosilanes (eq 2).[16]

$$R_2C{=}CR_2 \xrightarrow{CF_3COOH} R_2C(H){-}CR_2(OOCCF_3) \xrightarrow{R'_3SiH} R_2C(H){-}CR_2(H) \quad (2)$$

Addition of trifluoroacetic acid to $\Delta^{9(10)}$-octalin produced an isomeric mixture of 9-decalyl trifluoroacetates (67% trans, 33% cis). The isomeric trifluoroacetate ratio (67:33) remained constant during organosilane reduction. Similarly, 4-*tert*-butyl-1-methylcyclohexyl trifluoroacetate was formed from 4-*tert*-butylmethylenecyclohexane and trifluoroacetic acid in the isomeric proportion of 72% axial trifluoroacetate/28% equatorial trifluoroacetate. This trifluoroacetate ratio was also constant throughout the time required for organosilane reduction. Since the axial derivative has been demonstrated to be more reactive than the equatorial derivative in solvolysis reactions of similar cyclohexyl substrates,[8a,10,17] and since identical rates for reduction of the isomeric forms of the trifluoroacetates would be unlikely, the constancy in the isomeric

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Table I. Stereoselectivities of Organosilane Reductions of Representative Cycloalkenes in Trifluoroacetic Acid[a]

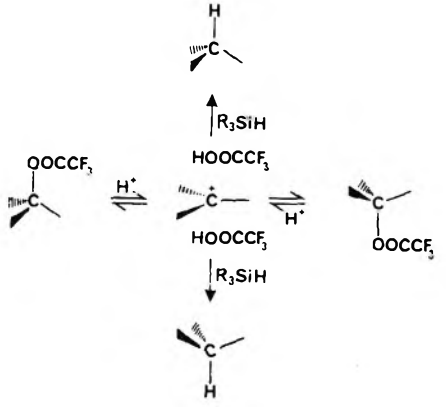
Silane	Registry no.	[Silane] [Alkene]	Decahydronaphthalene		4-*tert*-Butyl-1-methylcyclohexane	
			% cis[b]	% cis/% trans	% cis[b]	% cis/% trans
n-$BuSiH_3$	1600-29-9	2.0	22	0.28		
		1.1	27	0.37	4	0.04
		0.36	37	0.59		
Et_2SiH_2	542-91-6	0.60	40	0.67	8	0.09
Et_3SiH	617-86-7	1.1	42	0.72	10	0.11
i-$Pent_3SiH$	17922-08-6	1.1	35	0.54	9	0.10
c-$Pent_3SiH$	33729-87-2	1.1	54	1.17		
Ph_3SiH	789-25-3	1.1	58[c]	1.38		
sec-Bu_3SiH	6531-11-9	1.1	72	2.57	16	0.19
t-Bu_2SiH_2	30736-07-3	0.55	77	3.35	16	0.19
t-Bu_2MeSiH	56310-20-4	1.1	83	4.88		
t-Bu_3SiH	18159-55-2	1.1	93	13.3		

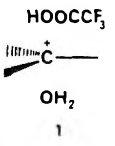
[a] Trifluoroacetic acid (5 molar equiv based on alkene) was added to the combined silane and alkene at 25 °C. [b] Relative product yield based on the average of at least two determinations. Precision of analyses is within ±1%. [c] Carey and Tremper report 61% of the cis isomer for reduction in methylene chloride solutions of trifluoroacetic acid.[3b]

ratio of trifluoroacetates during hydride transfer indicates that the trifluoroacetates are in isomeric equilibrium.

If the trifluoroacetate derivatives of alkenes are the effective reactants in organosilane reductions and if these derivatives are in isomeric equilibrium, the stereoselectivity for hydride transfer will be independent of the olefinic source of the isomeric trifluoroacetates. To test this hypothesis a mixture composed of 60% $\Delta^{9(10)}$-, 32% $\Delta^{1(9)}$-, and 8% $\Delta^{1(2)}$- plus $\Delta^{2(3)}$-octalin was reduced by triethylsilane in trifluoroacetic acid under the same conditions as those for the reactions in Table I. The relative yield of *cis*-decahydronaphthalene (42%) was identical with that reported in Table I.[18] In addition, reduction of *trans*-1-decalone by an equivalent molar amount of *n*-butylsilane in trifluoroacetic acid yielded the by-product decahydronaphthalene (3% yield) with essentially the same isomeric composition (29% *cis*-decahydronaphthalene) as that reported for ionic hydrogenation of $\Delta^{9(10)}$-octalin (27% *cis*-decahydronaphthalene). Similarly, triethylsilane reduction of 4-*tert*-butyl-1-methylcyclohexene in trifluoroacetic acid produced the same relative yield of *cis*-4-*tert*-butyl-1-methylcyclohexane (10%) as did 4-*tert*-butylmethylenecyclohexane. The combined results suggest that ionic hydrogenation of alkenes occurs by hydride transfer to a symmetrically solvated carbenium ion that is common to both isomeric trifluoroacetates and that stereoselectivity in this reduction process results from steric influences between the organosilane and the symmetrically solvated cation (Scheme I). This interpretation fully conforms with the observation by Fort and co-workers[8a] of predominant retention at carbon for reductions of *cis*- and *trans*-1-decalol by triethylsilane in methylene chloride solutions of trifluoroacetic acid. The cationic intermediate formed by trifluoroacetolysis of the isomeric 9-decalols is unsymmetrically solvated (1), and since the nucleophilicity of water is predictably greater than that of trifluoroacetic acid for replacement of hydride on silicon,[19] hydride transfer preferentially occurs from the water-solvated side of 1.[20,22] Organosilane reductions of *cis*- and *trans*-4-*tert*-butyl-1-phenylcyclohexanols[3c] apparently involve a symmetrically solvated cationic intermediate.

Scheme I





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The dramatic increase in the yield of the less stable alkane isomer with the increasing size of the organosilane in reductions of $\Delta^{9(10)}$-decalin (Table I) and the absence of a correlation between the isomeric product ratio and the rate for hydride transfer indicate that stereoselectivity in reductions of symmetrically solvated carbenium ions are governed by steric factors. As was observed for reductions of cyclic ketones by organosilanes,[7d,11b] the number of substituents bonded to silicon and the steric bulk of these substituents are important determinants of stereoselectivity. The relative insensitivity of the percentage of the less stable cis isomer from ionic hydrogenation of 4-*tert*-butylmethylenecyclohexane to the steric bulk of the organosilane does, however, indicate that steric approach control[1a,23] may not be the sole factor responsible for the stereoselectivity that is observed in these reductions. The rate for reduction of 4-*tert*-butylmethylenecyclohexane is between 4 and 5 times slower than that for reduction of $\Delta^{9(10)}$-octalin by the organosilanes included in Table I. This same factor of between 4 and 5 also constitutes the ratio of percentage *cis*-decahydronaphthalene to *cis*-4-*tert*-butyl-1-methylcyclohexane.[24] Although steric factors are important in the ionic hydrogenation of alkenes, the data obtained in this study do not limit stereoselective control solely to the steric bulk of the organosilane. Additional stereochemical data are required to fully extract the intimate details of other factors that influence stereoselectivity in organosilane reductions of carbenium ions, particularly those that are related to the solvolytic behavior of tertiary alkyl substrates.

The stereoselectivities that are observed in organosilane reductions of carbenium ions provide a valuable reference for similar reductions by hydrocarbon reducing agents[25] and serve to characterize ionic hydrogenation processes. Comparison of the data in Table I with similar results for hydrogenation catalyzed by chloroplatinic acid–stannous chloride,[26] for example, indicates that this latter process operates as an ionic

hydrogenation; stereochemical results obtained for hydrogenations with platinum oxide[27] and soluble osmium, rhodium, iridium, or ruthenium catalysts[26] are distinctly different.

Experimental Section

General. Instrumentation has been previously described.[7d] Peak areas in GLC analyses were determined using the Varian Model 485 digital integrator and the Varian CDS 101 data system. Diethyl-, triethyl-, and triphenylsilane were commercially available and were used without further purification. *n*-Butylsilane was prepared from *n*-butyltrichlorosilane by reduction with lithium aluminum hydride.[7c] The syntheses of triisopentyl-, tri-*sec*-butyl-, and tricyclopentylsilane from trichlorosilane and the appropriate Grignard or organolithium reagent have been reported.[7d] Methods for the preparation of di-*tert*-butyl- and di-*tert*-butylmethylsilane have also been described.[28] Tri-*tert*-butylsilane was prepared from di-*tert*-butyldifluorosilane and *tert*-butyllithium in 81% yield.[29] The isomeric mixture of octalins (64% $\Delta^{9(10)}$-, 29% $\Delta^{1(9)}$-, and 7% $\Delta^{1(2)}$- and $\Delta^{2(3)}$-octalin) produced from commercial 2-decalol through dehydration with polyphosphoric acid[30] was isomerized over Amberlyst 15 (0.8 g/g of octalin) to an isomeric composition of 92% $\Delta^{9(10)}$, 4% $\Delta^{1(9)}$-, and 4% $\Delta^{1(2)}$-, $\Delta^{2(3)}$-octalin by refluxing the octalin mixture in a solution of 2:1 acetic acid–benzene (4 mL/mL of octalin) for 3 h under nitrogen.[31] 4-*tert*-Butylmethylenecyclohexane was synthesized from 4-*tert*-butylcyclohexanone and methylenetriphenylphosphine.[32] 4-*tert*-Butyl-1-methylcyclohexene was prepared by dehydration of 4-*tert*-butyl-1-methylcyclohexanol[33] using catalytic amounts of *p*-toluenesulfonic acid in refluxing benzene. Hydrogenation of 4-*tert*-butylmethylenecyclohexane in glacial acetic acid using a platinum oxide catalyst and 3 atm pressure gave 4-*tert*-butyl-1-methylcyclohexane (75% cis isomer) in 63% yield: lit.[34] 75% cis isomer.

General Procedure for Organosilane Reductions in Trifluoroacetic Acid. The olefin (generally 5.0 mmol) and a 10% molar excess of the organosilane were weighed into a round-bottom flask which was fitted with a condenser and placed in a water bath at 25 °C. Precautions were taken to avoid the introduction of water into the reaction system. Addition of trifluoroacetic acid (5.0 molar equiv) in one portion to the rapidly stirred solution effected an exothermic reaction that was independent of the organosilane. The extent of reaction was determined by ^{1}H NMR analyses through observation of the change in the characteristic absorption patterns for the organosilane (Si–*H*) and cycloalkene or trifluoroacetate addition product. Analysis of the reaction solution at 5 min after the addition of trifluoroacetic acid gave no evidence for the alkene reactant and showed only the trifluoroacetate derivative and, if reduction had occurred, the alkane product in addition to the organosilane reactant and product. 9-Decalyl trifluoroacetate: ^{1}H NMR (CF_3COOH): δ 2.85–2.40 (10 H, m, trans isomer) and 2.25–1.85 (10 H, m, cis isomer).[35] 4-*tert*-Butyl-1-methylcyclohexyl trifluoroacetate: ^{1}H NMR (CF_3COOH): δ 1.65 (s, axial-CH_3), and 1.58 (s, equatorial-CH_3). Organosilane reductions of $\Delta^{9(10)}$-octalin were complete within 5 d even when tri-*tert*-butylsilane was employed as the hydride donor; reductions of 4-*tert*-butylmethylenecyclohexane were between 4 and 5 times slower. After reduction was complete the reaction mixture was diluted with ether and the acidic ether solution was washed with saturated aqueous sodium bicarbonate until gas evolution ceased. The ether solution was then dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure to give the isomeric hydrocarbons and organosilane products which were analyzed by GLC. The composition of *cis*- and *trans*-decahydronaphthalenes was determined on a 6-ft column of 20% Carbowax 20M on Chromosorb P (120 °C) and on an 8-ft column of 20% SE-30 on Chromosorb W (95 °C); the 4-*tert*-butyl-1-methylcyclohexanes were analyzed on an 8-ft column of 20% SE-30 on Chromosorb W (75 °C). Silyl trifluoroacetates were identified as the sole silane product from these reductions by ^{1}H NMR and GLC analyses through comparison with authentic samples. The stereoselectivity observed for reductions of 4-*tert*-butylmethylenecyclohexane (Table I) was independent of temperature over the range −15 to 50 °C with both triethylsilane and *n*-butylsilane.

Reductions by *n*-Butylsilane. The extent of reactions of $\Delta^{9(10)}$-octalin and 4-*tert*-butylmethylenecyclohexane with various molar equivalents of *n*-butylsilane (Table I) in trifluoroacetic acid was followed by ^{1}H NMR spectroscopic analysis. Only two of the three available silane hydrogens of *n*-butylsilane were reactive hydrides. Transfer of the first hydride was rapid and resulted in the formation of *n*-butylsilyl trifluoroacetate (δ 4.77, t, J = 2.7 Hz, Si–*H*). The rate of loss of the first hydride was more than 10 times faster than the rate for hydride transfer from *n*-butylsilyl trifluoroacetate. *n*-Butylsilyl ditrifluoroacetate was not detected in these reaction solutions. Similar stepwise reductions were observed in ionic hydrogenations that employed diethylsilane and di-*tert*-butylsilane; ^{1}H NMR (CF_3COOH): $Et_2SiHO_2CCF_3$ (δ 4.77, m, Si–*H*); *t*-$Bu_2SiHO_2CCF_3$ (δ 4.54, s, Si–*H*, δ 1.12, s, t-Bu).

Equilibration of Isomeric 4-*tert*-Butyl-1-methylcyclohexyl Trifluoroacetates in Trifluoroacetic Acid. 4-*tert*-Butyl-1-methylcyclohexanol was prepared from 4-*tert*-butylcyclohexanone and methylmagnesium bromide by the method of House and Respess.[33] The isomeric cis/trans alcohol ratio was determined by GLC analysis on a 10-ft column of 10% FFAP on Chromosorb P (190 °C) to be 1.48 (lit.[33] 1.50). The corresponding isomeric mixture of trifluoroacetate esters was prepared by the reaction of 4-*tert*-butyl-1-methylcyclohexanol with trifluoroacetic anhydride using a catalytic amount of trifluoroacetic acid; ^{1}H NMR (CCl_4): δ 0.88 (s, 9 H), 1.15–1.46 (m, 6 H), 1.56 (s, equatorial-CH_3), 1.60 (s, axial-CH_3), and 1.75–2.50 (m, 3 H). The isomeric cis/trans trifluoroacetate ratio (eq-CH_3/ax-CH_3) was 1.9. This mixture was dissolved in carbon tetrachloride and trifluoroacetic acid was added at regular intervals. The isomeric ratio changed from 1.9 to 2.57 within 15 min after 2 molar equiv of trifluoroacetic acid was added to the reaction solution. No further change in the isomeric trifluoroacetate ratio occurred upon subsequent additions of trifluoroacetic acid over a 21-h period or during organosilane reductions in separate experiments.

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Registry No.—Trifluoroacetic acid, 76-05-1; $\Delta^{9(10)}$-octalin, 493-03-8; 4-*tert*-butylmethylenecyclohexane, 13294-73-0; *trans*-9-decalyl trifluoroacetate, 64252-68-2; *cis*-9-decalyl trifluoroacetate, 64252-69-3; *cis*-4-*tert*-butyl-1-methylcyclohexyl trifluoroacetate, 64252-70-6; *trans*-4-*tert*-butyl-1-methylcyclohexyl trifluoroacetate, 64252-71-7; butylsilyl trifluoroacetate, 64252-72-8; $Et_2SiHO_2CCF_3$, 64252-73-9; *t*-$Bu_2SiHO_2CCF_3$, 64265-08-3; *cis*-4-*tert*-butyl-1-methylcyclohexanol, 10601-39-5; *trans*-4-*tert*-butyl-1-methylcyclohexanol, 13004-06-3.

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Fluorination with Xenon Difluoride. Stereochemistry of Fluorine Addition to Phenyl-Substituted Cycloalkenes

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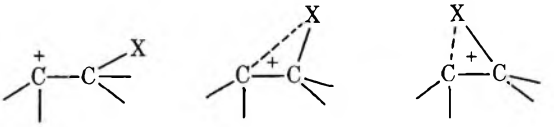
Acid-catalyzed liquid-phase fluorine addition with xenon difluoride to some phenyl-substituted cycloalkenes, i.e., 1-phenylcyclopentene, 1-phenylcyclohexene, and 1-phenylcycloheptene, results in the formation of vincinal difluorides in high yield. The ratio of syn and anti addition depends on ring magnitude. The stereochemistry of fluorine addition to aryl-substituted cyclohexenes also depends on the substituent in the phenyl ring.

The mechanisms of electrophilic addition of halogens have been widely investigated, both from the kinetic and stereochemical points of view.[1] Apart from the relative importance of the various kinetically significant processes, it is now known that the nature of the intermediates of the addition depends on the structure of the substrate, on the halogen, and on the reaction medium, ranging from strongly bridged ions (type C), to weakly bridged species (type B), or to open ions like A (Scheme I). If the cation is of the open structure A (X = F), a mixture of cis and trans adducts is generally expected. However, ion-pairing phenomena can cause preferential formation of the cis adduct and electronic, steric, or conformational effects can cause attack at one or the other side of the carbonium p orbital of A to be favored. On the other hand, the intermediate can have a bridged structure (C, X = Br), which will be presumably opened stereospecifically to form a trans adduct.

Recently we have observed that xenon difluoride readily adds fluorine to phenyl-substituted olefins to give the corresponding 1,2-difluorophenylalkanes in high yield and under mild conditions.[2] The ratios of *dl*-erythro and *dl*-threo difluorides formed by fluorination of alkyl- or phenyl-substituted olefins are nearly independent of the starting olefin, and in the trans series anti addition of fluorine predominates. We have suggested the formation of an open β-fluorocarbonium ion intermediate.[3] The intermediate from the trans olefin collapses preferentially to an anti adduct, while the cis olefin intermediate can freely rotate about the newly formed single bond, thus assuming a sterically more favorable conformation identical with that of the trans intermediate. As an extension

Scheme I



A B C

of our research, we therefore chose some phenyl-substituted cycloalkenes, i.e., 1-phenylcyclopentene, 1-phenylcyclohexene, and 1-phenylcycloheptene, as substrates in the acid-catalyzed liquid-phase fluorination reaction with xenon difluoride. We extended our studies to cycloolefins so as to eliminate a complexity which exists in an acyclic system, in which there is a possibility of rotation about the carbon–carbon single bond in the β-fluorocarbonium ion, depending on its lifetime and the energy barrier resisting free rotation about the newly formed single bond. From the data obtained it should be possible to get information about the influence of the ring magnitude on the stereochemistry of the fluorine addition. The variation of the substituent on the phenyl ring (X = H, *p*-OCH_3, *m*-Cl) in 1-phenylcyclohexene will give us further information about the effect of the stability of β-fluorocarbonium ions on the stereochemistry of fluorine addition.

Results and Discussion

The preparation of fluoroalkanes presents a different problem from that of other haloalkanes and necessitates a specific method of fluorination.[4] The acid-catalyzed liquid-phase fluorination of organic substrates with XeF_2 avoids some experimental difficulties, e.g., low temperature, high-

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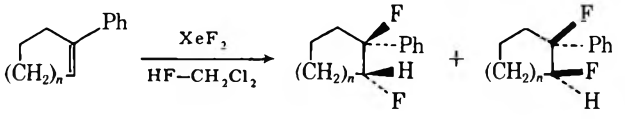
Table I

2 3

	2			3		
	$n = 1$	$n = 2$	$n = 3$	$n = 1$	$n = 2$	$n = 3$
δ_{F_b}	−157.9	−178.4	−159.4	−172.5	−197.5	181.1
δ_{F_a}	−186.4	−212.0	−189.4	−207.0	−205.5	
δ_{H_a}	4.8	4.81	4.63	4.8	4.9	4.63
$^2J_{F_aH_a}$	52	49.5	45	54	48	45
$^3J_{F_bH_a}$	7.5	<1	6	18	25	27
$^3J_{H_bH}$	5	<1	6	7.5	7.5	9

Scheme II



1 2 3

relative yields, %

n	2	3
1	79	21
2	50	50
3	35	65

pressure equipment, only a catalytic amount of hydrogen fluoride, which prevents the polymerization of alkenes and products.

We now report the reaction of xenon difluoride with some phenyl-substituted cycloalkenes. In a typical experiment, we dissolved 1 mmol of compound in methylene chloride; anhydrous hydrogen fluoride (1 mmol) was introduced into the reaction mixture and, under stirring, 1 mmol of xenon difluoride was added at room temperature. The colorless solution turned dark blue and xenon gas quickly evolved. After 10–40 min, when gas evolution has ceased, the crude, reaction mixture was isolated by the usual work-up procedure, analyzed by NMR, and separated by preparative GLC and TLC. The crude reaction mixture formed by fluorination of 1-phenylcyclopentene (1) (Scheme II) showed four multiplets in its ^{19}F NMR spectrum corresponding to two products in relative yields of 79:21% (2:3). Products were separated by preparative TLC. The major product formed (2) showed two multiplets in its ^{19}F NMR at δ −157.9 and −186.4 and in its ^1H NMR a ddd signal at δ 4.8, corresponding to one proton with coupling constants of J = 52, 7.5, and 5 Hz, while the minor product formed (3) showed two multiplets in its ^{19}F NMR at δ −172.5 and −207.0 and in its ^1H NMR a ddd signal at δ 4.8, corresponding to one proton with coupling constants of J = 54, 18, and 7.5 Hz. On the basis of the differences in NMR data, we have established that the major product was formed after trans addition of fluorine and that the minor product corresponds to cis addition. The results are parallel to those observed by fluorination of indene with xenon difluoride.[3]

The fluorination of 1-phenylcyclohexene resulted in the formation of two products in equal amounts (Scheme II). The products were separated by preparative GLC and their NMR spectra are presented in Figure 1. On the basis of the differences in NMR spectra, which are listed in Table I, and on the basis of the fact that the coupling constant between fluorine and the proton ($^3J_{F_bH_a}$) is greater when the atoms are in a diaxial position (J = 25 Hz) than in the case of an axial–equatorial position (J < 1 Hz), we have established that syn and anti addition took place in equal proportions.

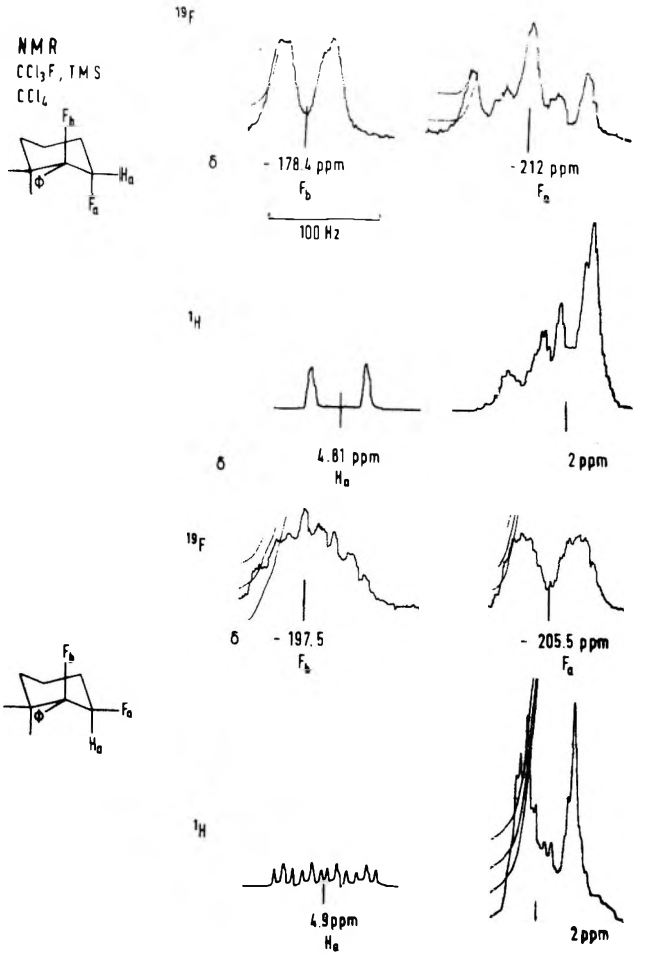
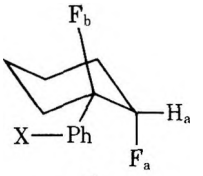


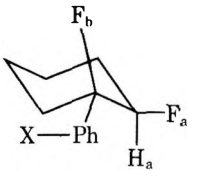
Figure 1. NMR spectra of compounds 2 and 3.

The acid-catalyzed liquid-phase fluorination of 1-phenylcycloheptene (Scheme II) also resulted in the formation of two products. The crude reaction mixture showed only three multiplets in its ^{19}F NMR spectrum. By separation using preparative TLC we have isolated two products. The major product formed showed one multiplet signal at δ −181.1 in its ^{19}F NMR and in ^1H NMR a ddd signal at δ 4.63 with coupling constants of J = 45, 27, and 9 Hz, while the minor product formed showed two multiplets in its ^{19}F NMR at δ −159.4 and −189.4 and in ^1H NMR a ddd signal at δ 4.63 with coupling constants of J = 45, 6, and 6 Hz. A comparison of the NMR data to those of the products formed by fluorination of 1-phenylcyclopentene and 1-phenylcyclohexene (Table I) enabled us to establish that the major product formed (3) arose from syn addition of fluorine, while the minor product formed (2) corresponded to anti addition.

Table II



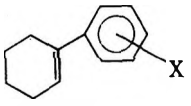
6



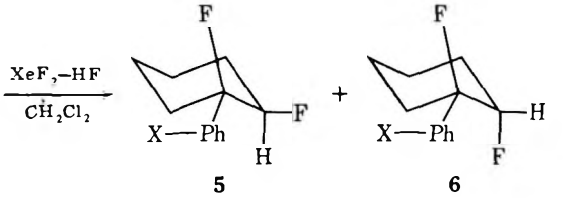
5

	6			5		
	X = H	X = *m*-Cl	X = *p*-OCH_3	X = H	X = *m*-Cl	X = *p*-OCH_3
δ_{F_a}	−212	−211	−211	−205.5	−204	−205
δ_{F_b}	−178.4	−178.5	−178	−197.5	−198	−197
δ_{H_a}	4.81	4.8	4.8	4.9	4.9	4.9
$^2J_{F_aH_a}$	49.5	48	48	48	48	48
$^3J_{F_bH_a}$	<1	<1	<1	25	25	24.5
$^3J_{H_aH}$	<1	<1	<1	7.5	7	8

Scheme III



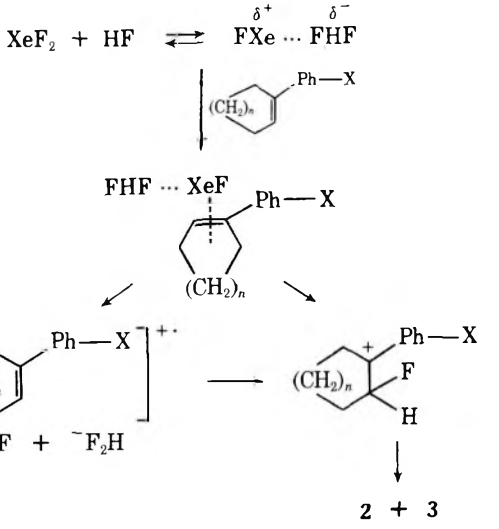
4a, X = H
b, X = *m*-Cl
c, X = *p*-OCH_3



5 6

X	% 5	% 6
H	50	50
m-Cl	55	45
p-OCH_3	75	25

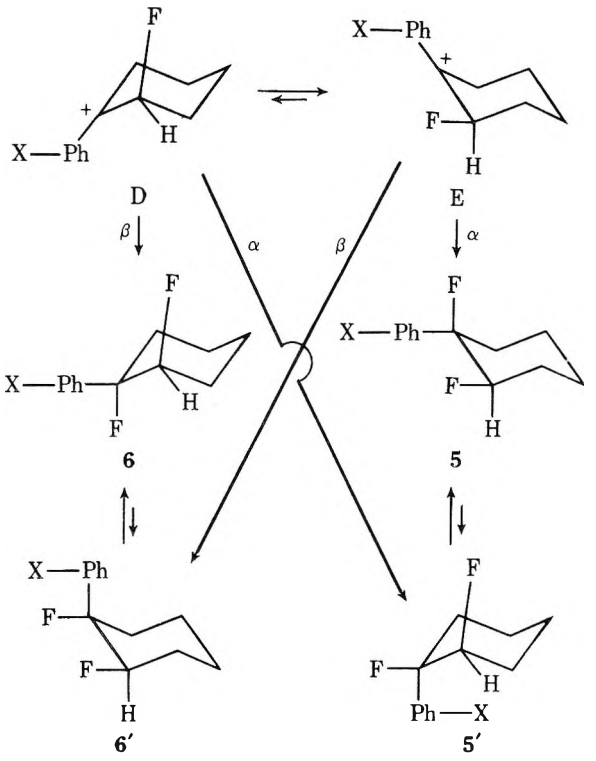
Scheme IV



Dependence of the steric course of fluorine addition to phenyl-substituted cycloalkenes on ring magnitude, which could be ascribed to flexibility of the intermediates, stimulated us to study the effect of the group bonded to the phenyl ring on the stereochemistry of fluorine addition to the cyclohexene ring. The addition of fluorine with xenon difluoride to 1-phenylcyclohexene yielded equal amounts of syn and anti adducts as already mentioned above, while the fluorination of the *m*-chlorophenyl derivative **4b** resulted in the formation of 55% of **5** and 45% of **6** (Scheme III). The NMR data of the adducts are very similar to those observed by fluorination of 1-phenylcyclohexene and are listed in Table II. The fluorination of the *p*-methoxyphenyl derivative **4c** also resulted in the formation of two products with the cis adduct being the major product (the NMR data are very similar to those observed for products resulting from fluorination of unsubstituted 1-phenylcyclohexene). The acid-catalyzed liquid-phase fluorination of 1-phenylcyclohexene with xenon difluoride in the presence of a free-radical inhibitor (oxygen) had no significant effect on the product distribution.

On the basis of earlier observations of the addition of fluorine with xenon difluoride in the liquid-phase acid-catalyzed reaction to phenyl-substituted olefins,[3] and the observations already made in this paper, the following reaction mechanism (Scheme IV) could be suggested. The mechanism must involve catalysis by hydrogen fluoride, since the reaction proved to be very slow without it. It might be expected that in the presence of hydrogen fluoride xenon difluoride behaves as an electrophile. Previously this has been suggested by Filler et al.[5] for the fluorination of aromatic compounds. In the next step a π complex is probably formed between this electrophilic species and the olefin, which could be transformed by a heterolytic Xe–F bond cleavage into an open β-fluorocarbonium ion intermediate, which then, after fluoride ion attack, results in the formation of cis and trans difluorides. Furthermore, another possibility is the formation of an ion radical which has already been observed in the fluorination of benzene and its derivatives,[5] transforming in the next step by XeF· or XeF_2 into an open carbonium ion. The lower oxidation potentials of olefins (in comparison to those of benzo derivatives) make the suggested path quite reasonable. It is very interesting that the stereochemistry of addition depends on ring magnitude. The situation resembles that already observed in the fluorination of various 1-phenyl-2-alkyl-substituted ethenes, where the ratios of *dl*-erythro and *dl*-threo difluorides are independent of the starting olefin and trans addition of fluorine predominates.[3] The higher amounts of syn adducts formed by fluorination of cis alkenes were explained by rotation about the newly formed C–C single bond in the β-fluorocarbonium ion. The stereochemistry of fluorine addition to 1-phenylcyclopentene is very similar to that of indene.[3] The addition is preferentially anti. The lower anti stereoselectivity in the case of 1-phenylcyclohexene could be explained by isomerization of the initially formed ion D (Scheme V), in which fluorine is in an axial position, into the more stable ion E, in which fluorine is in an equatorial position. Ion E is more stable, because there are smaller interactions between the fluorine atom and the p orbital of the carbocation than in the primarily formed ion D, while the steric interactions become

Scheme V[a]



[a] α = syn attack; β = anti attack.

less important than in substituted cyclohexanes. Initially formed ion D could undergo preferential anti attack by a fluoride ion, thus forming difluoride **6**, or the less favored syn attack, thus resulting in the nonstable conformation of cis difluoride **5′** with the phenyl group in an axial position, which then transformed into preferential conformation **5** with the phenyl group in the equatorial position.[6] The more stable ion E could undergo preferential syn fluoride ion attack, thus forming defluoride **5**, or anti attack, thus forming the unfavored conformation **6′**, which transforms into the more stable conformation **6**. On the basis of the literature data,[6] conformations **5′** and **6′** could be practically excluded. Isomerization of initially formed ion D into ion E becomes more important in the case of the *p*-methoxy (*p*-OCH_3) substituent, which is then reflected in the preferential formation of difluoride **5**. The formation of greater amounts of syn adduct in the fluorination of 1-phenylcycloheptene could also be ascribed to the secondary isomerization of the primarily formed β-fluorocarbonium ion, in which interaction between the p orbital of the carbocation and fluorine atom becomes smaller, and also to the high flexibility of the cycloheptane ring. However, limited data are available about the conformation of the β-halonium ions of cycloheptanes.

Experimental Section

IR spectra were recorded using a Perkin-Elmer 257 spectrometer and ^1H and ^{19}F NMR spectra by a Jeol JNM-PS-100 from CCl_4 solution with Me_4Si or CCl_3F as internal reference. Mass spectra and high-resolution measurements were taken on a CEC-21-110 spectrometer. Gas–liquid partition chromatography was carried out on a Varian Aerograph Model 1800 and TLC on Merck PSC-Fertigplatten silica gel F-254 (activated for 3 h at 120 °C before use).

Materials. Pure samples of olefins were prepared by known methods: 1-phenylcyclopentene,[7] 1-phenylcyclohexene,[7] 1-phenylcycloheptene,[7] 1-(3-chlorophenyl)cyclohexene,[7] and 1-(4′-methoxyphenyl)cyclohexene.[7] Hydrogen fluoride of Fluka Purum quality was used without further purification. Methylene chloride was purified[8] and stored over molecular sieves. Xenon difluoride was prepared by a photosynthetic method[9] and its purity was better than 99.5%.

Addition and Isolation Procedures. To a solution of 1 mmol of olefin in methylene chloride (5 mL) in a Kel-F vessel, 1 mmol of xenon difluoride was added at T = 25 °C and under stirring anhydrous hydrogen fluoride (trace amounts) was introduced into the reaction mixture. After a few seconds the colorless solution turned dark blue and xenon gas was evolved. After 10–40 min xenon gas evolution ceased and the reaction appeared to be complete. The reaction mixture was diluted with methylene chloride (15 mL), washed with 10 mL of 5% $NaHCO_3$ and water, and dried over anhydrous sodium sulfate. The crude reaction mixture was separated by preparative TLC or GLC.

Fluorination of 1-phenylcyclopentene: yield, 94% of crude products; separation by preparative TLC.

1-Fluoro-1-phenyl-*trans*-2-fluorocyclopentane (2): yield, 54% of liquid product; NMR data are stated in Table I; mass spectra (mol wt calcd for $C_{11}H_{12}F_2$, 182.0920; found, 182.0902) *m/e* 182 (M^+, 77), 161 (12), 150 (12), 147 (18), 142 (22), 136 (24), 135 (100), 133 (22), 122 (25), 121 (26), 115 (30), 109 (32), 105 (15), 91 (15), 77 (15), 51 (14).

1-Fluoro-1-phenyl-*cis*-2-fluorocyclopentane (3): yield, 13% of liquid product; NMR data are stated in Table I; mass spectra (mol wt calcd for $C_{11}H_{12}F_2$, 182.0920; found, 182.0912) *m/e* 182 (M^+, 31), 142 (23), 141 (13), 136 (10), 135 (77), 133 (8), 123 (10), 121 (100), 109 (13).

Fluorination of 1-phenylcyclohexene: yield, 81% of crude products; separation by preparative GLC [Carbowax 20M/Varaport 30 (70:80), 10%, T = 250 °C].

1-Fluoro-1-phenyl-*trans*-2-fluorocyclohexane (2): yield, 27% of oily products; NMR data are stated in Table I; mass spectra (mol wt calcd for $C_{12}H_{14}F_2$, 196.1064; found, 196.1062) *m/e* 196 (M^+, 40), 135 (100), 122 (21).

1-Fluoro-1-phenyl-*cis*-2-fluorocyclohexane (3): yield, 30% of liquid products; NMR data are stated in Table I; mass spectra (mol wt calcd for $C_{12}H_{14}F_2$, 196.1064; found, 196.1054) *m/e* 196 (M^+, 39), 135 (100), 122 (20).

Fluorination of 1-phenylcycloheptene: yield, 91% of crude products; separation by preparative TLC.

1-Fluoro-1-phenyl-*trans*-2-fluorocycloheptane (2): yield, 20% of solid product; mp 55–57 °C; NMR data are stated in Table I; mass spectra (mol wt calcd for $C_{13}H_{16}F_2$, 210.1238; found, 210.1236) *m/e* 210 (M^+, 77), 136 (19), 135 (100), 122 (77), 115 (19), 109 (28), 91 (15).

1-Fluoro-1-phenyl-*cis*-2-fluorocycloheptane (3): yield, 51% of solid product; mp 49–51 °C; NMR data are stated in Table I; mass spectra (mol wt calcd for $C_{13}H_{16}F_2$, 210.1238; found, 210.1238) *m/e* 210 (M^+, 79), 136 (23), 135 (100), 122 (78), 115 (15), 109 (30), 91 (10).

Fluorination of 1-(3′-chlorophenyl)cyclohexene: yield, 79% of crude products; separation by prepative TLC.

1-fluoro-1-(3′-chlorophenyl)-*trans*-2-fluorocyclohexane (6b): yield, 22% of oily product; NMR data are stated in Table II; mass spectra (mol wt calcd for $C_{12}H_{13}F_2Cl$, 230.0674; found, 230.0667) *m/e* 230 (M^+, 31), 169 (58), 86 (61), 28 (100).

1-Fluoro-1-(3′-chlorophenyl)-*cis*-2-fluorocyclohexane (5b): yield, 31% of oily product; NMR data are stated in Table II; mass spectra (mol wt calcd for $C_{12}H_{13}F_2Cl$, 230.0674; found, 230.0678) *m/e* 230 (M^+, 29), 169 (59), 86 (63), 28 (100).

Fluorination of 1-(4′-methoxyphenyl)cyclohexene: yield, 94% of crude products; separation by preparative TLC.

1-Fluoro-1-(4′-methoxyphenyl)-*trans*-2-fluorocyclohexane (6c): yield, 15% of oily product; NMR data are stated in Table II; mass spectra (mol wt calcd for $C_{13}H_{16}OF_2$, 226.1169; found, 226.1159) *m/e* 226 (M^+, 42), 165 (100), 84 (28), 66 (36).

1-Fluoro-1-(4′-methoxyphenyl)-*cis*-2-fluorocyclohexane (5c): yield, 37% of oil product; NMR data are stated in Table II; mass spectra (mol wt calcd for $C_{13}H_{16}OF_2$, 226.1169; found, 226.1162) *m/e* 226 (M^+, 40), 165 (100, 84 (30), 66 (35).

Fluorination in the Presence of Oxygen. 1-Phenylcyclohexene (1 mmol) was dissolved in 5 mL of methylene chloride, 1 mmol of xenon difluoride was added at 25 °C, and, under stirring, a mixture of anhydrous hydrogen fluoride and oxygen was introduced into the reaction mixture for 30 min. After workup, the residue was analyzed by NMR spectroscopy; the product distribution was 50% of **2** and 50% of **3**. It can be seen that the free-radical inhibitor had no effect on the product distribution.

Acknowledgments. We thank Professor J. Slivnik for xenon fluoride. The financial assistance of the Boris Kidrič Foundation is acknowledged.

Registry No.—**1** (*n* = 1), 825-54-7; **1** (*n* = 2), 771-93-2; **1** (*n* = 3), 25308-75-2; **2** (*n* = 1), 64332-84-9; **2** (*n* = 2), 64332-83-8; **2** (*n* = 3), 64332-82-7; **3** (*n* = 1), 64332-81-6; **3** (*n* = 2), 64332-80-5; **3** (*n* = 3),

64332-79-2; **4b**, 27163-65-1; **4c**, 20758-60-5; **5** (X = *m*-Cl), 64332-78-1; **5** (X = *p*-OCH_3), 64332-77-0; **6** (X = *m*-Cl), 64332-76-9; **6** (X = *p*-OCH_3), 64332-75-8; xenon difluoride, 13709-36-9.

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Chemistry of Carbanions. 31. Cyclization of the Metal Enolates from ω-Bromo Ketones[1]

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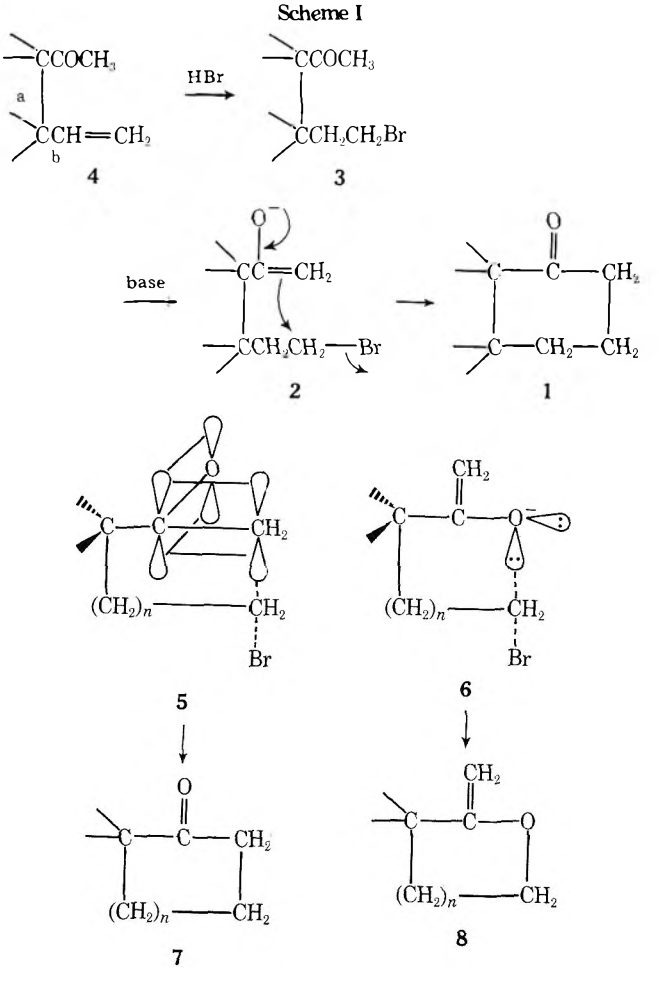
Utilizing *stable solutions* of *i*-Pr_2NLi in hexane, a convenient procedure is described for the conversion of methyl ω-bromoalkyl ketones **9–12**, **32**, **42**, **50**, and **67** to mixtures of Li^+ enolates containing predominantly the terminal enolates. Although solutions of these Li^+ enolates in Et_2O–hexane mixtures are stable at 0 °C, when activating ligands such as 4 molar equiv of HMP [$(Me_2N)_3PO$], 1 molar equiv of triglyme (**15**) or the 14-crown-4 ether **16**, or excess DME are added these Li^+ enolates undergo intramolecular cyclization reactions. In the absence of serious geometrical constraints (cf. bromo ketone **32**), the enolates of bromo ketones **9–12** underwent intramolecular C-alkylation to form the corresponding cyclohexanone derivatives in 60–80% yield. Similar intramolecular cyclization by bromo ketone **67** produced a mixture of five-membered and seven-membered C-alkylated products, but intramolecular cyclization of the bromo ketone **42** yielded only the five-membered O-alkylated product **43**. The Li^+ enolate of bromo ketone **50** underwent a very slow intramolecular cyclization to produce a mixture of O-alkylated and C-alkylated four-membered ring products. Thus, the method described constitutes a useful synthetic route to cyclohexanone derivatives and, with limitations, is also applicable to the synthesis of cycloheptanone derivatives.

The most common synthetic routes to cyclohexane derivatives involve the reduction of benzene derivatives, use of the Diels–Alder reaction to form intermediate cyclohexenes, or use of the Robinson annulation technique (or related procedures) to form intermediate cyclohexenones. It seemed to us that another rather general synthetic route to cyclohexanone derivatives **1** (Scheme I) could be based on the cyclization of a regiospecifically generated metal enolate **2** derived from an ω-bromo ketone **3**. We have noted elsewhere[2] that the requisite ω-bromo ketones **3** can readily be obtained by addition of HBr to the vinyl ketones **4** in a free-radical chain process. The vinyl ketone precursors **4** can generally be assembled either by addition of a $(vinyl)_2CuLi$ reagent to an enone to form bond b in **4** or by allylation of a regiospecifically generated metal enolate to form bond a in **4**.

Superficially the intramolecular C-alkylation reaction (arrows in structure **2**) would appear to be straightforward. However, when one imposes the geometrical constraints that the nucleophile (the enolate α-carbon atom) attack along a path collinear with the C–Br bond[3] and that the electron density at the α carbon of the enolate is concentrated in orbitals perpendicular to the plane of the enolate anion, then the transition state required for this intramolecular C-alkylation is represented by structure **5**. In this transition state **5** three of the carbon atoms lie in a plane perpendicular to the forming C–C bond. Study of molecular models indicates that this transition state **5** can be attained without excessive distortion of normal carbon bond angles when *n* has values of two or larger to form cyclic ketones **7** with six or more ring members. However, substantial distortion of normal carbon bond angles is required to attain the transition state **5** when *n* has values one or zero. In such cases an alternative transition state **6** in which the forming C–O bond lies in the plane of the enolate anion with a nonbonded electron pair on the oxygen atom

Scheme I



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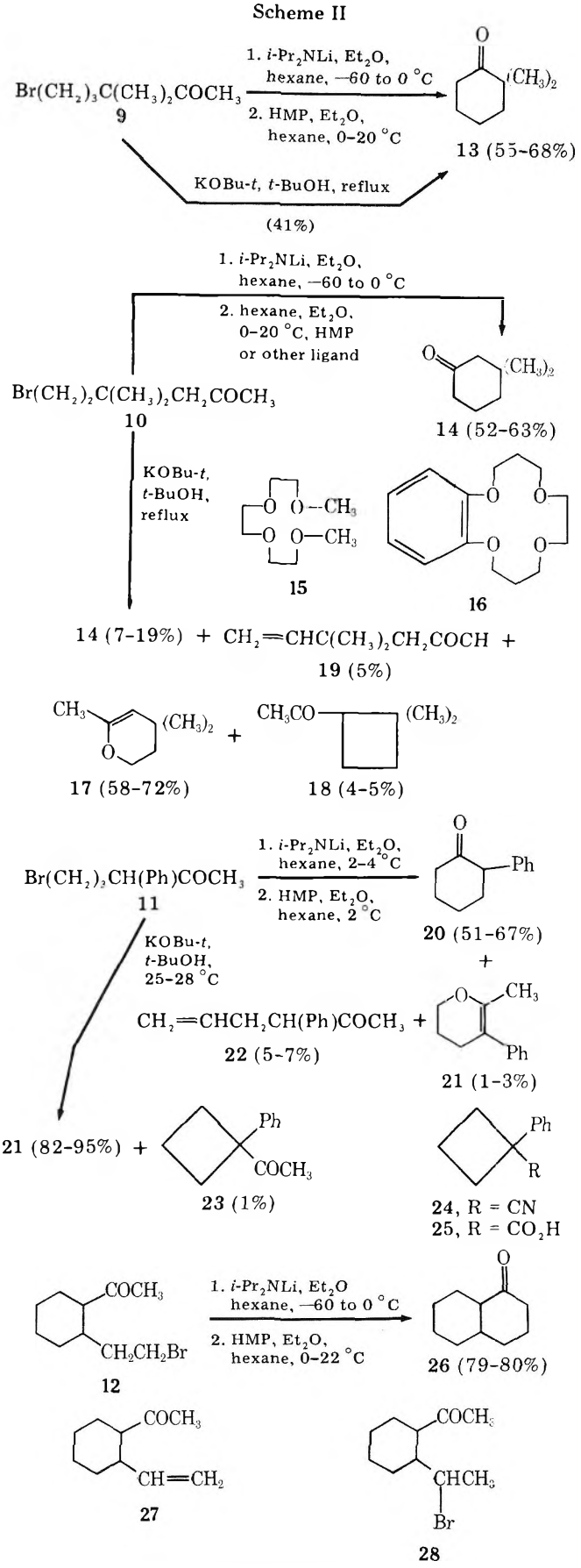
Scheme II



serving as the nucleophile seems much more attractive. In short, these geometrical considerations suggest that these intramolecular alkylation reactions **5** → **7** should be favorable (or at least feasible) when ketones with six or more ring members (**7**, n = 2, 3, etc.) are being formed, but should be unfavorable for the formation of four- and five-membered ketones (**7**, n = 0, 1). In these latter cases either intramolecular O-alkylation **6** → **8** or intermolecular reactions might be expected.

Generation of Enolates and the Formation of Six-Membered Rings. To explore these considerations experimentally, we have examined the behavior of various metal enolates derived from the previously described[2] bromo ketones. Scheme II summarizes our study of bromo ketones **9**–**12** that could be converted to six-membered cyclic ketones. The bromo ketones **3** were converted to the intermediate terminal enolates **2** by the slow addition of the ketones to a slight excess of the strong, sterically hindered base, *i*-Pr_2NLi, dissolved in a cold (−60 to 0 °C) mixture of Et_2O and hexane (typically 9:1 v/v). This kinetically controlled deprotonation procedure is known[4] to convert methyl *n*-alkyl ketones to mixtures of lithium enolates in which the terminal enolate predominates (typically 85% of the enolate mixture) and the proportion of the terminal enolate is even larger (typically 95%) when branching is present at the α-carbon atom of the alkyl group. The regiospecificity of this enolate generation procedure is illustrated by the conversion of the ketone **11** to its terminal enolate (and subsequently to the ketone **20**) in spite of the fact that the internal enolate, stabilized by a phenyl substituent, is substantially more stable at equilibrium. Note that conversion of ketone **11** to its enolates under equilibrating conditions (KOBu-*t* in *t*-BuOH) yielded only products **21** and **23** derived from the more stable internal enolate.

Since *i*-Pr_2NLi is a sufficiently strong base to deprotonate and cleave solvents such as Et_2O, THF, and especially DME and HMP [$(Me_2N)_3PO$] at temperatures above 0 °C, it is not practical to prepare stock solutions of *i*-Pr_2NLi in these solvents. However, we have found that if commercial solutions of *n*-BuLi in hexane are diluted with additional hexane or pentane and then treated with 1 molar equiv of *i*-Pr_2NH, *stable solutions* of *i*-Pr_2NLi (0.5–0.6 M) in hexane or hexane–pentane mixtures are formed. Provided that these hexane solutions are not cooled or concentrated to induce the irreversible separation of solid *i*-Pr_2NLi, they may be standardized (titration with 2,2′-bipyridyl indicator) and stored at 25 °C without deterioration for weeks. Thus, it is especially convenient to prepare solutions of *i*-Pr_2NLi for reactions by adding a known volume of the stable hexane solution to the desired volume of cold (<0 °C) ethereal solvent such as Et_2O or THF.

Utilizing the above procedures, we were able to generate 0.05 M solutions (dilute solutions were used to disfavor intermolecular reactions) of the lithium bromoenolates **2** from each of the various bromo ketones studied. At 0 °C in Et_2O–hexane solution these lithium bromoenolates (which are presumably aggregated as dimers, trimers, tetramers, etc.) were stable to further change for at least 1 h, allowing us first to prepare solutions of the lithium bromoenolates **2** and then to activate these bromoenolates for further reactions by adding ligands such as HMP (4 molar equiv/Li^+), DME (excess), triglyme (**15**, 1 molar equiv/Li^+), or the 14-crown-4 ether **16** (1 mol equiv/Li^+).[5] Among these activating ligands, stoichiometric amounts of HMP appeared to be most effective with stoichiometric amounts of either triglyme (**15**) or the crown **16**, affording slightly lower yields in the conversion of bromo ketone **10** to ketone **14**. In reactions where the polyethers **15** or **16** were used, as the reaction proceeded the LiBr produced formed Et_2O-insoluble complexes with these polyethers, facilitating the separation of these materials from the remaining reaction products.

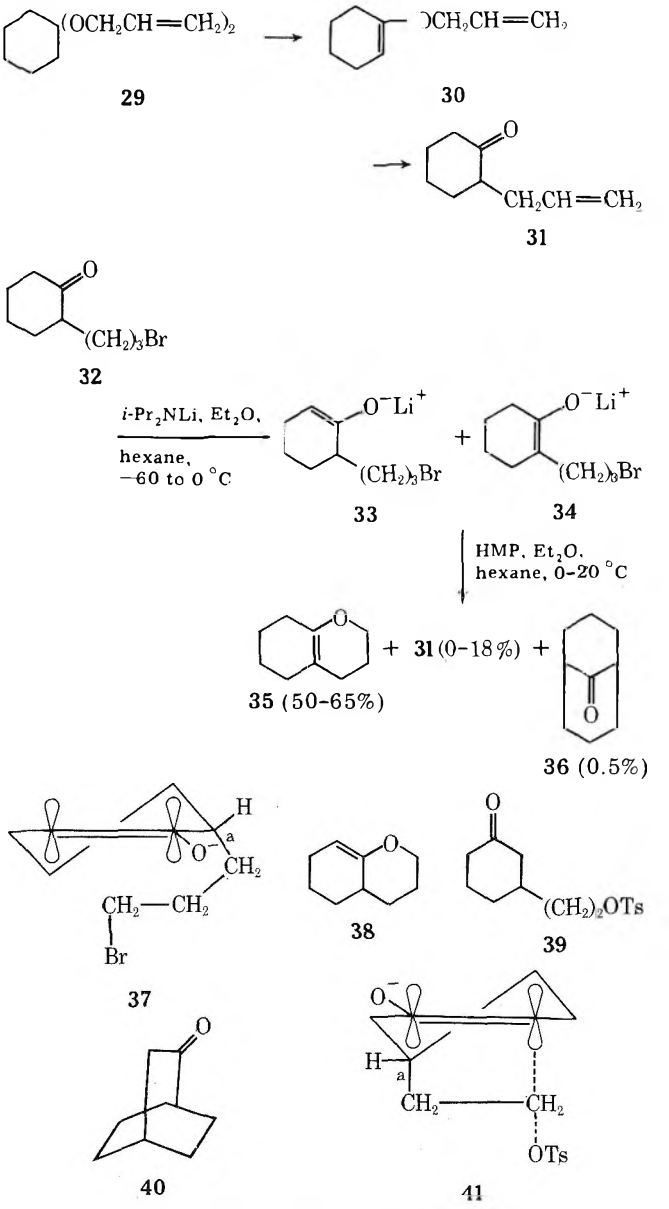
Utilizing the above procedures to generate and activate the lithium bromoenolates **2**, each of the acyclic bromo ketones **9**,[6] **10**, and **11** could be converted to the corresponding six-membered cyclic ketone **13**, **14**, or **20** in 60–70% by reaction at 0–20 °C for 1 h. Even with bromo ketones **10** and **11**, where

two structurally isomeric enolates could be formed, by-products derived from the internal enolate (e.g., **21**) were minor. In each of these cyclizations (**9**–**11**), the main by-product was a complex mixture of higher molecular weight compounds that was apparently derived from intermolecular reaction of the bromoenolate **2** either with itself or with the reaction product. When the bromo ketones **10** and **11** were converted to their enolates with KOBu-*t* in *t*-BuOH (conditions that allow enolate equilibration), the major products **17**, **18**, **21**, and **23** were derived from the internal enolates and the typical preference for forming a six-membered ring by O-alkylation (**17** and **21**) rather than a four-membered ring by C-alkylation (**18** and **23**) was observed. When one considers the relative rates of ring closure of the enolates derived from KOBu-*t* and the malonates $(Cl)Br(CH_2)_nCH(CO_2Et)_2$ [3-ring > 5-ring > 6-ring > 4-ring],[7] where incorporation of the entire planar enolate system into the cyclic transition state (i.e., structure **5**) is not required, the fact that we observe relatively little 6-ring C-alkylation with bromo ketones **10** and **11** under equilibrating conditions suggests that the transition state **5** (n = 2), although attainable, must still possess significant strain. The formation of appreciable quantities of by-product from intermolecular reaction, even at relatively low enolate concentrations, is also in keeping with this idea.

When we turned our attention to the cyclization of the bromo ketone **12**, a compound in which the derived terminal enolate and the C–Br bond are held in positions favorable for attaining the transition state **5** (n = 2), the yield of intramolecularly cyclized product **26** was significantly improved. We have observed this phenomenon with other cyclizations of bromo ketones to form bicyclic products that will be reported elsewhere.

The foregoing results demonstrate that the projected cyclization **3** → **2** → **1** can be a viable synthetic route to six-membered cyclic ketones, although there is an indication of strain in the six-membered transition state **5** (n = 2) leading to products. One can then anticipate that adding other structural features that would be unfavorable to attaining this transition state **5** (n = 2) would prevent formation of a cyclohexanone derivative. This idea is illustrated by the behavior of the bromo ketone **32** (Scheme III). In an earlier study,[8] reaction of this ketone **32** with KOBu-*t* (equilibrating conditions) in PhH was found to yield the O-alkylated product **35** that would be derived from the *more stable* enolate **34**. We have now treated this bromo ketone **32** with *i*-Pr_2NLi under conditions that will clearly favor formation of the less stable, but kinetically favored, enolate **33**.[4] After activation with HMP, this mixture of enolates **33** and **34** underwent a relatively slow reaction (accompanied by enolate equilibration) to form the same enol ether **35** observed earlier with only a very minor product corresponding to the cyclohexanone derivative **36**. Although we found no indication of the presence of the isomeric enol ether **38**, we cannot exclude the possibility that this substance **38** was destroyed or isomerized during our isolation procedure. We attribute the failure of enolate **33** to form the cyclohexanone **36** to the geometrical problem illustrated in structure **37**. Since the enolate **33** can at best only adopt a conformation with the bromoalkyl side chain on a pseudoaxial bond (bond a in structure **37**) which is not perpendicular to the plane of the enolate, considerable distortion would be required to obtain the collinear arrangement C···C···Br needed in the transition state **5** for C-alkylation. In contrast, reaction of the related keto tosylate **39** with NaH in DME produced the bicyclic ketone **40** in good yield.[8] As indicated in structure **41**, the enolate derived from ketone **39** can adopt a conformation with the tosyloxyalkyl side chain on a normal axial bond (bond a in structure **41**) allowing the collinear arrangement needed for C-alkylation. Further support for this explanation is found in the successful C-alkylations performed with enolates similar to enolate **33**, but possessing four-carbon ω-haloalkyl side chains.[9]

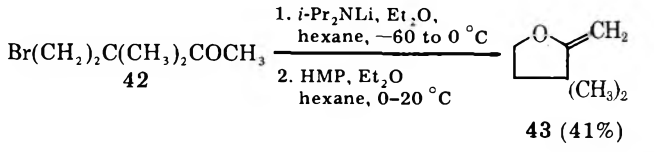
Scheme III



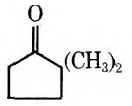
The Formation of Five- and Four-Membered Rings. Application of the previously discussed procedure for the formation and activation of the enolate to the bromo ketone **42**[6] (Scheme IV) resulted in the formation of the enol ether **43** and a complex mixture of higher molecular weight products (presumably formed by intermolecular reactions). However, none of the C-alkylated product **44** was detected, supporting the earlier hypothesis that it would be very difficult to attain the geometry required for the transition state **5** (n = 1). Earlier examples of bromocarbonyl compounds that have reacted with bases to form enol ethers (O-alkylation) rather than five-membered carbonyl compounds (C-alkylation) include the bromo ester **45**[10] and bromo ketones **46**[11] and **47**.[12] Related phenomena include the reaction of the chloro ketone **48** with base to form only methyl cyclopropyl ketone and no cyclopentanone[13] and the cyclization of the bromo amide **49** to form an O-alkylated imino ether rather than an N-alkylated lactam.[14] All of these examples support the general idea that the synthetic sequence **5** → **7** is unlikely to be a satisfactory route to cyclopentanone derivatives **7** (n = 1).

Conversion of the bromo ketone **50** (Scheme V) to its Li^+ enolate followed by activation with HMP resulted in a very slow reaction (part of the bromo ketone **50** was recovered after

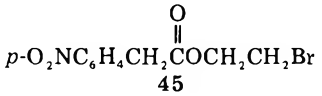
Scheme IV



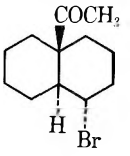
42 → 43 (41%)



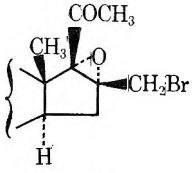
44



45



46



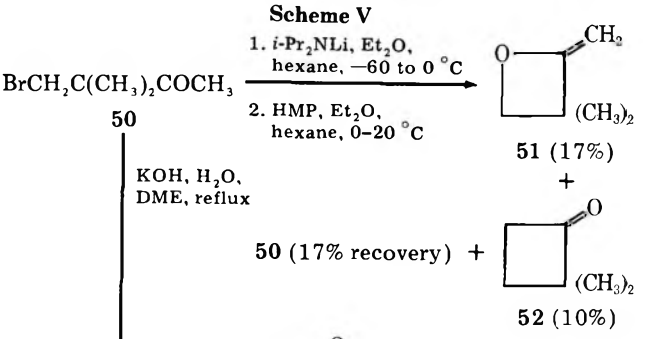
47

$CH_3COCH_2CH_2CH_2Cl$
48

$Br(CH_2)_3CONHC_6H_{11}$
49

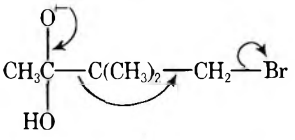
reaction for 2.5 h) to form a mixture of comparable amounts of the enol ether **51** and the cyclobutanone **52** as well as a mixture of higher molecular weight materials. A similar mixture of O-alkylated and C-alkylated products was reported[15] from the reaction of the tosyloxy ketone **55** with NaH or KH in THF. Although the formation of O-alkylated products such as **51** by way of a transition state of the type **6** (n = 0) is reasonable, the formation of the cyclobutanone products (e.g., **52**) by a normal S_N2 displacement (structure **5**, n = 0) seems most improbable. A further indication that a different pathway may be involved in cyclobutanone formation is provided by earlier studies of the reactions of the related bromo (or tosyloxy) ketones **56**.[16] The reaction of this ketone **56** with KOH or NaOH in a polar, partially aqueous solvent (H_2O–dioxane, H_2O–MeOH) produced a mixture of the "expected" cyclobutanone **57**, the rearranged cyclobutanone **58** (frequently the major product), and the acid **59** resulting from fragmentation. When we subjected the bromo ketone **50** to similar reaction conditions (KOH in refluxing H_2O–DME), the major product was NaOAc from fragmentation (see structure **54**) accompanied by lesser amounts of the "expected" cyclobutanone **52** and the rearranged cyclobutanone **53**.

Scheme V



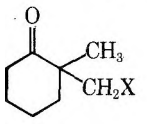
50 → 51 (17%) + 50 (17% recovery) + 52 (10%)

CH_3CO_2H + **52** (6%) + **53** (<1%)
(93% as the Me ester)

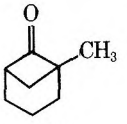


54

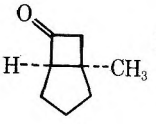
$TsOCH_2C(CH_3)_2COCH_2Ph$
55



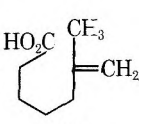
56 (X = Br or OTs)



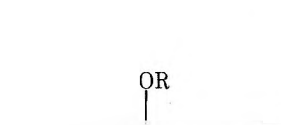
57



58



59



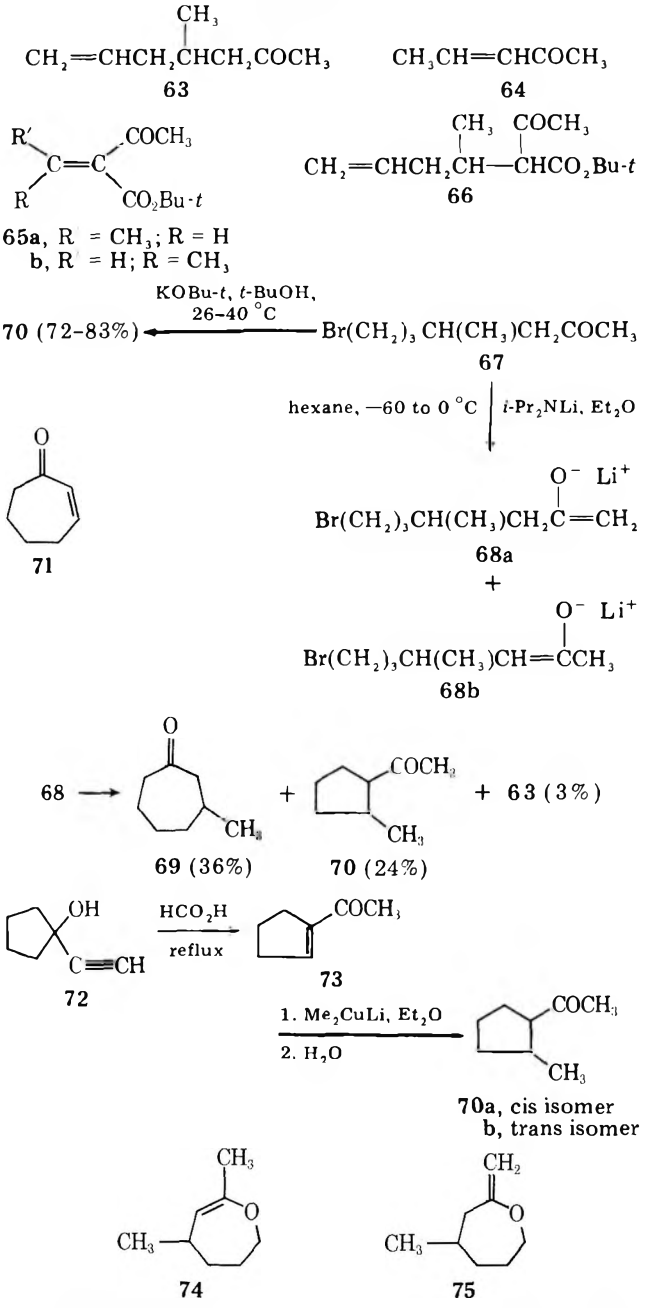
60 (R = H or metal cation) → 61 (R = H or metal cation) → 52 + 53 → 62

A possible interpretation of these results would involve the initial solvolytic rearrangement of the bromoenol (or enolate) **60** to the cyclopropanol derivative **61** (or the related cyclopropylcarbinyl cation, cf. ref 16d). This rearrangement **60** → **61** is, of course, an example of the homoallyl → cyclopropylcarbinyl rearrangement. Further base-catalyzed rearrangement of this intermediate (arrows in **61**) or conversion to the oxaspiropentane **62** followed by rearrangement would provide pathways to the cyclobutanones **52** and **53**. Since the oxaspiropentane **62** is known[17] to rearrange to a mixture of ketones **52** (minor) and **53** (major) when treated with various Lewis acids including Li^+ salts, the fact that the rearranged cyclobutanone **53** was, at most, the minor product in our reaction indicates that the oxaspiropentane **62** is not an important intermediate in the reactions we have studied.

The Formation of a Seven-Membered Ring. We had previously obtained the olefinic precursor **63** (Scheme VI) for the bromo ketone **67** by a rather inefficient oxy-Cope rearrangement.[2] Although this precursor **63** can also be obtained by the reaction of the enone **64** with $(CH_2{=}CHCH_2)_2CuLi$,[18] use of the more readily accessible organometallic reagent, $CH_2{=}CHCH_2MgBr$, with the enone **64** gave primarily the 1,2-addition product even in the presence of added Me_2SCuBr catalyst. To explore the possibility that Cu-catalyzed conjugate addition of $CH_2{=}CHCH_2MgBr$ would be more efficient with a substrate having a less negative reduction potential than enone **64** (E_{red} = −2.08 V vs. SCE), we prepared the enones **65** (E_{red} = −1.80 and −1.79 V vs. SCE). The Cu-catalyzed addition of $CH_2{=}CHCH_2MgBr$ to the enone **65** produced cleanly the conjugate adduct **66** that could be cleaved and decarboxylated to form the unsaturated ketone **63**.

The usual reaction of the bromo ketone **67** with i-Pr_2NLi followed by activation of the resulting enolate with HMP resulted in a slow reaction (about 2 h at 0 °C was required for complete reaction) to form a mixture of comparable amounts of the five- and seven-membered ring products **70** and **69**. Authentic samples of these products were obtained by addition of Me_2CuLi to the enones **71** and **73**. Conversion of the bromo ketone **67** to its enolates under equilibrating conditions (KOBu-t in t-BuOH or KH in DME) resulted in the formation of only the five-membered ring C-alkylated product **70** accompanied by minor amounts of two by-products that may be the enol ethers **74** and **75**. This result indicates that cyclization of the enolate **68b** to **70** is more rapid than cyclization of enolate **68a** to **69**. The formation of comparable amounts of five-membered (**70**) and seven-membered (**69**) C-alkylated products from cyclization of the kinetically generated mixture of Li^+ enolates **68** (mainly **68a**) is thus attributable to a combination of three factors: (1) cyclization **68b** → **70** is faster than cyclization **68a** → **69**; (2) terminal enolates such as **68a** are

Scheme VI



typically less reactive (and presumably more highly aggregated) than internal enolates of the type **68b**;[4] (3) the relatively slow cyclization **68a** → **70** allows time for enolate equilibration (**68a** ⇌ **68b**) to compete with the desired cyclization process. By varying the temperature used for this cyclization from the usual range 0–20 °C to 25 °C we were able to shorten the time required for the cyclization from 2 h to 1 h and to increase the ratio of seven-membered (**69**) to five-membered (**70**) products from 44:56 to 60:40. However, it appears that the best way to increase substantially the proportion of seven-member cyclization product is to utilize systems with an alkyl substituent at the α carbon of the ω-bromoalkyl methyl ketone (which will diminish both the equilibrium concentration and the reactivity of the internal enolate)[4] and to use more rigid bromo ketone substrates analogous to **12** in order to increase the rate of the desired cyclization to a seven-membered ring product. Bromo ketone substrates incorporating these features are being prepared and the study of their cyclization will be reported subsequently.

Experimental Section[19]

Preparation of *i*-Pr_2NLi. After 22.8 mL of a hexane solution containing[20] 34.2 mmol of *n*-BuLi (Foote Mineral Co.) had been diluted with 30 mL of anhydrous pentane, 4.15 g (41.5 mmol) of *i*-Pr_2NH was added dropwise and with stirring during 45 min. Titration[20] of the resulting colorless solution of *i*-Pr_2NLi with a 2,2′-bipyridyl indicator indicated the concentration of the amide to be 0.53 M; at the end point of this titration the color of the solution changed from dark brown to pale yellow green. Such solutions of *i*-Pr_2NLi in pentane–hexane mixtures were stable for weeks at 25 °C provided that they were not cooled or concentrated to induce the irreversible separation of solid *i*-Pr_2NLi.

Preparation of Starting Materials. A. Known Bromo Ketones. Previously described procedures[2] were used to obtain samples of bromo ketones **9**, **10**, **11**, **42**, and **50**.

B. Bromo Ketone 12. The previously described[2] light-catalyzed addition of HBr to 1.500 g (9.87 mmol) of the vinyl ketone **27** in 300 mL of anhydrous pentane yielded 2.22 g (96.5%) of the crude bromo ketone **12** as a pale yellow liquid. Low-pressure liquid chromatography on silica gel (Woelm 0.032–0.064 mm) with an EtOAc–hexane eluent (7:93 v/v) separated 101 mg (4.5%) of early liquid fractions containing (NMR analysis) mainly the secondary bromo ketone **28** accompanied by ~33% of the primary bromo ketone **12**: IR (CCl_4) 1712 cm^{-1} (C=O); NMR (CCl_4) δ 4.23 (q, J = 7 Hz, additional splitting not resolved, CHBr of **28**), 3.38 (m, CH_2Br of **12**), and a multiplet in the region 0.9–2.8 upon which were superimposed singlets at 2.13 (CH_3CO of **28**) and 2.08 (CH_3CO of **12**) and a doublet (J = 7 Hz) at 1.67 (CH_3 of **28**). Later chromatographic fractions contained (NMR analysis) 1.802 g of the primary bromide **12** not contaminated with the isomer **28**. Distillation afforded 1.398 g (60.8%) of the pure bromide **12** as a colorless liquid, bp 76.5–77 °C (0.02 mm), $n^{25}D$ 1.4988–1.4992, as well as 166 mg of less pure bromide in the forerun, bp 76–77 °C (0.02 mm), $n^{25}D$ 1.4990. The spectral properties of the pure bromo ketone **12** were: IR (CCl_4) 1708 cm^{-1} (C=O); NMR (CCl_4) δ 3.2–3.6 (2 H, m, CH_2Br) and 0.9–2.4 (15 H, m, aliphatic CH including a CH_3 singlet at 2.08); mass spectrum *m/e* (rel intensity) 234 (M^+, <1), 232 (M^+, <1), 153 (20), 109 (21), 81 (11), 67 (19), 55 (13), 43 (100), and 41 (17).

Anal. Calcd for $C_{10}H_{17}BrO$: C, 51.52; H, 7.36; Br, 34.27. Found: C, 51.59; H, 7.37; Br, 34.30.

C. Bromo Ketone 32. Use of a previously described procedure[21a] formed the acetal **29**, bp 96–98 °C (10 mm), $n^{25}D$ 1.4597 [lit.[21a] bp 98 °C (10 mm), $n^{25}D$ 1.4600], in 67% yield. Conversion of the acetal **29** to the enol ether **30** accompanied by rearrangement[21b] formed the ketone **31** in 90% yield: bp 86–88 °C (15 mm); $n^{25}D$ 1.4672 [lit.[21b] bp 86–88 °C (15 mm); $n^{25}D$ 1.4670]; IR (CCl_4) 1715 (C=O), 1640 (C=C), and 920 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 4.7–6.0 (3 H, m, vinyl CH) and 1.2–2.7 (11 H, m, aliphatic CH). The previously described[2] light-catalyzed addition of HBr to 1.38 g (10 mmol) of the unsaturated ketone **31** in 300 mL of anhydrous pentane yielded 2.02 g (92%) of the crude bromo ketone **32** as a pink liquid. Distillation afforded 1.87 g (85%) of the pure bromo ketone **32** as a colorless liquid: bp 99–100 °C (0.3 mm); $n^{25}D$ 1.5035 [lit.[22] bp 74–76 °C (0.05 mm)]; IR (CCl_4) 1712 cm^{-1} (C=O); NMR (CCl_4) δ 3.37 (2 H, t, J = 7 Hz, CH_2Br) and 1.1–2.6 (13 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 220 (M^+, <1), 218 (M^+, <1), 139 (100), 138 (28), 111 (20), 110 (34), 109 (20), 98 (24), 95 (44), 81 (31), 69 (34), 67 (28), 55 (56), 41 (41), and 39 (23).

Anal. Calcd for $C_9H_{15}BrO$: C, 49.32; H, 6.85; Br, 36.53. Found: C, 49.35; H, 6.91; Br, 36.39.

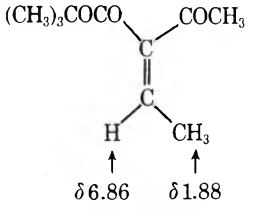
D. Enone 65. To a cold (−6 °C) mixture of 79.0 g (500 mmol) of the keto ester $CH_3COCH_2CO_2Bu$-*t* and 26.4 g (600 mmol) of CH_3CHO was added, dropwise with stirring and cooling (−6 to −1 °C) during 10 min, a solution of 2.2 g (26 mmol) of piperidine in 10 mL of EtOH. After the resulting mixture had been stirred at −6 to −1 °C for 30 min, it was allowed to stand at −22 °C for 45 h and then partitioned between Et_2O and aqueous NH_4Cl. The ethereal layer was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl and then dried, concentrated, and distilled to separate 66.23 g (70%) of the enone **65**, bp 83–105 °C (4.3 mm), $n^{25}D$ 1.4415–1.4434 [lit.[23] bp 95–96 °C (9 mm), $n^{20}D$ 1.4457]. This product contained (TLC, silica gel coating with an Et_2O–pentane eluent, 1:1 v/v) a mixture of isomer **65a** (R_f 0.58) and isomer **65b** (R_f 0.43). A 1.132-g aliquot was subjected to low-pressure liquid chromatography on silica gel with an Et_2O–hexane eluent (2:3 v/v) to separate early fractions containing 244 mg of isomer **65a**, $n^{25}D$ 1.4408, 542 mg of intermediate fractions containing (TLC) mixtures, and finally fractions containing 80 mg of isomer **65b**, $n^{25}D$ 1.4466. The spectral properties of isomer **65a** follow: IR (CCl_4) 1722 (ester C=O), 1708 (C=O), and 1640 cm^{-1} (weak, C=C); UV (95% EtOH) end absorption with ϵ 6900 at 210 nm; NMR (CCl_4) δ 6.86 (1 H, q, J = 7 Hz, vinyl CH), 2.28 (3 H, s, $COCH_3$), 1.88 (3 H, d, J = 7 Hz, CH_3), and 1.52 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 169 (1), 128 (32), 111 (44), 69 (45), 57 (100), 43 (56), and 41 (59).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.92; H, 8.81.

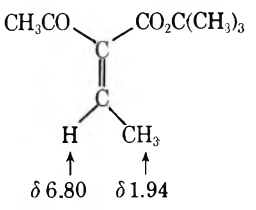
The spectral properties of isomer **65b** follow: IR (CCl_4) 1725 (ester C=O), 1700, 1682 (C=O), 1645, and 1628 cm^{-1} (C=C); UV max (95% EtOH) 217 nm (ε 8400); NMR (CCl_4) δ 6.80 (1 H, q, J = 7 Hz, vinyl CH), 2.21 (3 H, s, CH_3CO), 1.94 (3 H, d, J = 7 Hz, CH_3), and 1.54 (9 H, s, t-Bu); mass spectrum m/e (rel intensity), 169 (2), 129 (60), 128 (43), 113 (23), 111 (94), 74 (43), 69 (73), 57 (100), 43 (80), 41 (56), and 39 (40).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.22; H, 8.78.

We have tentatively assigned the stereochemistry indicated in structures **65a** and **65b** to these two geometrical isomers based upon

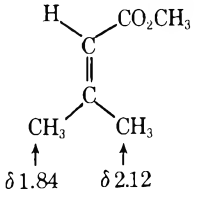


65a [UV end absorption with ε 6900 at 210 nm]



65b [UV max 217 nm (ε 8400)]

the differences in their ^1H NMR (CCl_4) and UV (95% EtOH) spectra. It has been noted that a carboalkoxy group (see structure **76**) will normally cause a larger downfield shift than an acetyl group (see structure **77**) on the NMR signal of a *cis*-methyl group.[24] This cor-



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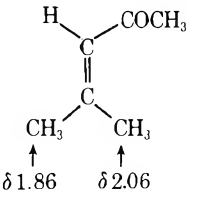
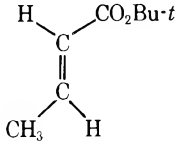
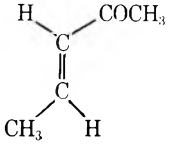


77

relation would argue that the isomer with the lower field allylic CH_3 group should be assigned structure **65b**. Also based on the expectation that the group cis to the methyl group is more likely to be twisted away from coplanarity with the remainder of the π system, it is reasonable to assume that the UV spectrum of isomer **65a** will resemble the spectrum of ester **78** [UV max (95% EtOH) 205 nm (ε 11 600)[25a]] while the spectrum of isomer **65b** should resemble enone **79** [UV max (95%



78



79

EtOH) 220 nm (ε 10 800)[25b]]. These stereochemical assignments must be regarded as tentative both because of the small differences in the spectra and because of uncertainty about the predominant conformations of the two carbonyl functions in each isomer.

Polarographic measurments[26] of the enones **65** employed a custom-made polarographic module utilizing solid-state amplifiers that followed the typical three-electrode design. Descriptions of the cell, working electrodes, reference electrode, reagent purification, and measurement procedures have been published previously.[27] Solutions in anhydrous DMF containing 0.5 M n-Bu_4NBF_4 and 1.2–2.3 × 10^{-3} M enone **65a** exhibited a polarographic $E_{1/2}$ value of −1.80 V vs. SCE (n = 1.4, i_d = 6–18 μA). A comparable measurement of solutions in anhydrous DMF containing 0.5 M n-Bu_4NBF_4 and 1.9–2.1 × 10^{-3} M enone **65b** gave a polarographic $E_{1/2}$ value of −1.79 V vs. SCE (n = 1.3, i_d = 12–13 μA).

E. Keto Ester 66. To a cold (−74 °C) solution of 8.40 g (40.8 mmol) of Me_2SCuBr[28] and 25.00 g (136 mmol) of the enone **65** (a mixture of stereoisomers) in 35 mL of Me_2S and 450 mL of Et_2O was added, dropwise with stirring and cooling (−73 to −74 °C) during 130 min, 170 mL of an ethereal solution containing 151 mmol of CH_2=$CHCH_2MgBr$. The reaction mixture, a pale yellow suspension that became brownish red in color as the last of the Grignard reagent was added, was stirred at −73 to −74 °C for 30 min and then allowed to warm to 20 °C with stirring during 135 min. The reaction solution was siphoned into a stirred aqueous solution of aqueous NH_3 and NH_4Cl and then extracted with Et_2O. After the ethereal solution had been washed successively with aqueous NH_4Cl and with aqueous NaCl, it was dried and concentrated to leave 36.6 g of crude yellow liquid product. Distillation separated 1.13 g of forerun, bp 84–87 °C (1.6 mm), n^{25}_D 1.4379, and 23.16 g (75%) of the keto ester **66**, bp 88–89 °C (1.6 mm), n^{25}_D 1.4396–1.4402, that contained (TLC, silica gel coating with an Et_2O–hexane eluent, 3:7 v/v) the keto ester **66** (R_f 0.38) and several very minor impurities. A portion of this product was chromatographed on silica gel with Et_2O–hexane mixtures as the eluent to separate the pure (TLC) keto ester **66** as a colorless liquid: n^{25}_D 1.4400; IR (CCl_4) 1750 (shoulder, ester C=O), 1716 (C=O), 1642 (C=C), and 922 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 4.8–6.0 (3 H, m, vinyl CH), 3.0–3.2 (1 H. m, COCHCO of two diastereoisomers), 1.5–2.6 (6 H, m, aliphatic CH including a CH_3CO singlet at 2.11), 1.42 (9 H, s, t-Bu), and 0.8–1.1 (3 H, m, CH_3 of two diastereoisomers); mass spectrum m/e (rel intensity) 170 (7), 153 (7), 111 (22), 69 (48), 68 (100), 59 (20), 57 (71), 43 (88), and 41 (48).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.02; H, 9.84.

Although the same keto ester **66** was formed by the reaction of the enone **65** with CH_2=$CHCH_2MgBr$ in the absence of Me_2SCuBr, the crude reaction product contained (TLC) additional products not present in the copper-catalyzed reactions.

F. Unsaturated Ketone 63 and Bromo Ketone 67. To a warm (72 °C) solution of 4.70 g (24.8 mmol) of p-TsOH in 275 mL of PhH was added rapidly a solution of 13.6 g (60.2 mmol) of the keto ester **66** in 50 mL of PhH. The resulting solution, from which gas evolution was vigorous at temperatures above 70 °C, was heated to 72–74 °C[29] for 45 min and then cooled rapidly, diluted with Et_2O, and washed successively with aqueous $NaHCO_3$ and with aqueous NaCl. After the organic solution had been dried and concentrated, fractional distillation separated 5.09 g (65%) of the pure (GLC, IR, and NMR analyses) ketone **63**: bp 79 °C (43 mm), n^{25}_D 1.4272–1.4277 [lit.[2] bp 85 °C (56 mm), n^{25}_D 1.4251–1.4254]. The unsaturated ketone **63** was converted to the bromo ketone **67** by the previously described procedure.[2]

Cyclization Studies. A. General Procedure for Bromo Ketone 9 with *i*-Pr_2NLi. To a cold (−60 °C) solution of 10.5 mmol of *i*-Pr_2NLi, 19.8 mL of a pentane–hexane mixture, and several milligrams of 2,2′-bipyridyl (an indicator) in 155 mL of Et_2O was added, dropwise and with stirring at −60 °C during 30 min, a solution of 2.07 g (10.0 mmol) of the bromo ketone **9** in 20 mL of Et_2O. The resulting pale yellow (excess *i*-Pr_2NLi) solution of the lithium enolate (~0.05 M) was warmed to 0 °C, treated with 7.53 g (42 mmol, 4 equiv/Li^+) of HMP [bp 70–71 °C (1.5 mm), freshly distilled from a blue solution of Na], and then stirred at 0 °C for 30 min and at 0–20 °C for 30 min. A white precipitate separated from the pale yellow solution during the reaction period. After the reaction mixture had been partitioned between Et_2O and aqueous $NaHCO_3$, the organic phase was dried and concentrated to leave 1.221 g of yellow liquid product. After an aliquot of this crude product had been mixed with a known amount of internal standard (n-$C_{12}H_{26}$), GLC analysis (silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of n-$C_{12}H_{26}$ (retention time 21.1 min), the ketone **13** (28.8 min, 68% yield), and several minor, rapidly eluted impurities; none of the unchanged bromo ketone **9** was detected by NMR or GLC analysis. A 960-mg aliquot of the crude product was chromatographed on silica gel (Et_2O–hexane eluent, 1:9 v/v) to separate in the early fractions 2.0 mg of liquid believed to be the enol ether [IR (CCl_4) 1680 cm^{-1} (enol ether C=C)] and 5.0 mg of the crude known[2] unsaturated ketone CH_2=$CHCH_2C(CH_3)_2COCH_3$. Subsequent fractions contained 557 mg (58%) of the ketone **13**; distillation gave 524 mg (55%) of the ketone **13** as a colorless liquid, bp 89.5–90 °C (55 mm), n^{25}_D 1.4458 [lit.[30b] bp 170–170.5 °C (761 mm)], that was identified with an authentic sample[30a] by comparison of IR, NMR, and mass spectra.

Subsequent chromatographic fractions, eluted with Et_2O–hexane mixtures, contained a total of 186 mg of viscous colorless to yellow liquids. The fractions were complex mixtures exhibiting IR absorption (CCl_4) attributable to both OH (3600, 3420 cm^{-1}) and C=O functions (1710 cm^{-1}). Thus, these by-products are apparently higher molecular weight products formed from the bromo ketone **9** and/or ketone product **13**. When a comparable cyclization was performed employing a higher concentration of enolate (ca. 0.12 M) from bromo ketone **9**, the yield of the ketone **13** (62%, GLC analysis) was lower.

B. General Procedure for Bromo Ketone 9 with KOBu-*t*.[31] To a solution of 5.0 mmol of KOBu-t in 10 mL of t-BuOH was added, dropwise and with stirring at 25 °C during 10 min, a solution of 1.012 g (4.9 mmol) of the bromo ketone **9** in 10 mL of pentane. During this addition the solution changed from colorless to yellow to dark tan in color with separation of a white precipitate. After the resulting mixture had been stirred at 25–28 °C for 15 min, it was refluxed for 45 min

and then partitioned between H_2O and pentane. The organic phase was dried and concentrated to leave 611 mg of crude product as a red liquid. After an aliquot of the crude product had been mixed with an internal standard (n-$C_{12}H_{26}$), GLC analysis indicated that all of the bromo ketone **9** was gone and the yield of ketone **13** was 41%. A collected (GLC) sample of product **13** was identified with an authentic sample[30a] by comparison of IR, NMR, and mass spectra. When an analogous reaction was performed employing a total reaction time of 40 min at 25–28 °C, the reaction was incomplete and the crude product contained (GLC analysis) both ketones **9** and **13**.

C. Bromo Ketone 10 with i-Pr_2NLi. A cold (−60 °C) solution of the enolate (0.05 M), from 10.5 mmol of i-Pr_2NLi in 19.8 mL of a hexane–pentane mixture and 155 mL of Et_2O and 2.07 g (10.0 mmol) of the bromo ketone **10** in 20 mL of Et_2O, was warmed to 0 °C and treated with 7.53 g (42 mmol, 4 equiv/Li^+) of HMP. After the resulting colorless solution had been stirred at 0 °C for 30 min and at 20 °C for 30 min (during which time a precipitate separated), the previously described isolation procedure separated 1.286 g of crude product as a pale yellow liquid. An aliquot of the crude product was mixed with a known weight of n-$C_{12}H_{26}$ (internal standard) and analyzed by GLC (silicone XE-30 on Chromosorb P, apparatus calibrated with known mixtures): the crude product contained n-$C_{12}H_{26}$ (retention time 13.8 min), ketone **14** (27.4 min, 63% yield), and several minor unidentified rapidly eluted components (1.8, 3.7, and 4.5 min), but no unchanged bromo ketone **10** was observed (GLC and NMR analysis). An 834-mg aliquot of the crude product was chromatographed on silica gel with an Et_2O–hexane eluent (1:9 v/v) to separate 511 mg (61%) of the ketone **14**; distillation afforded 492 mg of the pure ketone **14**, bp 61–61.5 °C (10 mm), n^{25}_D 1.4454 [lit. bp 47–49 °C (5 mm),[32a] 74–74.5 °C (16 mm),[32b] n^{25}_D 1.4454,[32a] 1.4458[32b]], that was identified with an authentic sample[32] by comparison of IR, NMR, and mass spectra and GLC retention times.

Later fractions from the chromatography column (eluted with Et_2O) amounted to 212 mg of viscous yellow liquid containing a complex mixture of higher molecular weight components with IR absorption (CCl_4) at 3580, 3420, 1705, 1675, and 1610 cm^{-1}, suggesting the presence of OH, C=O, and C=C groups. The mass spectrum of the material exhibited relatively abundant high-mass peaks at m/e 252, 234, and 219.

Several additional experiments were performed to examine the effect on the Li^+ enolate of activating ligands other than HMP. Following the previously described procedure, a series of cold (0 °C) solutions of the Li^+ enolate (0.05 M) were prepared from 1.03 g (5.0 mmol) of the bromo ketone **10** and 5.25 mmol of i-Pr_2NLi in 88 mL of Et_2O and 10 mL of a pentane–hexane mixture. To one of these enolate solutions was added, dropwise and with stirring during 1 min, a solution of 1.30 g (5.2 mmol) of the crown ether **16**[5] in 10 mL of Et_2O. The resulting pink solution, from which a heavy white precipitate (the complex of LiBr with the crown ether **16**) rapidly separated, was stirred and allowed to warm from 0 to 20 °C during 30 min. After the resulting mixture had been partitioned between Et_2O and aqueous $NaHCO_3$, the organic layer was dried and concentrated. A solution of the residual yellow liquid in 20 mL of anhydrous ether was treated, dropwise and with stirring, with a solution of 1.00 g (11.5 mmol) of anhydrous LiBr in 20 mL of anhydrous DME until no further precipitate (LiBr–crown ether **16** complex) separated and then filtered to remove the crown ether **16**. The filtrate was concentrated and a portion of the residual yellow liquid (1.46 g, NMR analysis indicated residual DME but no crown ether **16**) was mixed with a known weight of n-$C_{12}H_{26}$. The calculated (GLC analysis) yield of ketone **14** was 56% and no other monomeric product was detected. A collected (GLC) sample of the ketone **14** was identified with an authentic sample by comparison of GLC retention times and IR and mass spectra. The crude product was distilled to separate 312 mg (50%) of the ketone **14**, bp 61–61.5 °C (10 mm), leaving 262 mg of viscous pot residue containing a complex mixture of higher molecular weight materials.

A second cold (0 °C) solution of the Li^+ enolate was treated, dropwise and with stirring during 2 min, with 50 mL of cold (0 °C) DME and the resulting solution was stirred, allowed to warm from 0 to 20 °C during 30 min, and then partitioned between Et_2O and aqueous $NaHCO_3$. After the organic solution had been dried and concentrated, analysis (GLC with added internal standard) of the crude liquid product (2.09 g) indicated a 52% yield of the ketone **14** with no other monomeric product being detected. Distillation separated 272 mg (43%) of the ketone **14**, bp 61–61.5 °C (10 mm), leaving 322 mg of a viscous higher molecular weight pot residue.

A third cold (0 °C) solution of the Li^+ enolate was treated, dropwise and with stirring during 1 min, with 986 mg (5.53 mmol) of triglyme [**15**, freshly distilled from $LiAlH_4$, bp 74–74.5 °C (1.2 mm)]. The resulting mixture, from which a white precipitate began to separate, was stirred at 0 °C for 30 min and then allowed to warm to 20 °C during 30 min. After the mixture had been partitioned between Et_2O and aqueous $NaHCO_3$, the organic layer was dried and concentrated to leave 1.505 g of crude product as a yellow liquid containing (GLC analysis with added internal standard) the ketone **14** (54% yield) with no other monomeric products being detected. A 1.416-g aliquot of the crude product was distilled to separate 305 mg (48%) of the ketone **14**, bp 63–64.5 °C (12 mm), that was identified with an authentic sample by comparison of GLC retention times and IR spectra. A subsequent distillation fraction, bp 102–103.5 °C (12 mm), contained 695 mg of triglyme and the residual brown viscous pot residue amounted to 230 mg.

D. Bromo Ketone 10 with KOBu-t. After mixing 1.66 g (8.0 mmol) of the bromo ketone **10** in 20 mL of pentane with a solution of KOBu-t from 312 mg (8.0 mg-atom) of K and 18 mL of t-BuOH, the resulting pale yellow solution, from which a precipitate gradually separated, was stirred at 25 °C for 30 min and at reflux for 45 min. After a portion of the crude liquid product (1.582 g, isolated in the usual way) had been mixed with a known weight of 1,3,5-(i-Pr)$_3$C$_6$H$_3$ (an internal standard), analysis (GLC, silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of the enol ether **17** (retention time 3.1 min, 69% yield), the unsaturated ketone **19** (7.1 min, 4.6% yield), the ketone **18** (9.0 min, 3.5% yield), the ketone **14** (18.3 min, 11% yield), and 1,3,5-(i-Pr)$_3$C$_6$H$_3$ (25.9 min). In a second comparable reaction the calculated product yields (GLC analysis) were: **17**, 72%; **19**, 5.4%; **18**, 4.8%; and **14**, 19%. The crude product was chromatographed on basic alumina with pentane and ether–pentane mixtures as eluents. The early fractions, eluted with pentane, contained 610 mg (60%) of the enol ether **17**. Distillation afforded 580 mg (58%) of the pure (GLC) enol ether **17** as a colorless liquid: bp 108–109 °C; n^{25}_D 1.4415; IR (CCl_4) 1680 (shoulder) and 1668 cm^{-1} (enol ether C=C); NMR (CCl_4) δ 4.08 (1 H, br, vinyl CH), 3.6–3.9 (2 H, m, CH_2O), 1.57 (3 H, d, J = 1 Hz, allylic CH_3), 1.3–1.6 (2 H, m, CH_2), and 0.93 (6 H, s, CH_3); mass spectrum, m/e (rel intensity) 126 (M^+, 45), 111 (100), 83 (23), 55 (25), and 43 (42).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.10; H, 11.19.

Continued elution from the chromatography column separated 69 mg (7%) of the ketone **14**. This sample and a sample collected by GLC were identified with an authentic sample of ketone **14** by comparison of GLC retention times and IR and mass spectra. A collected (GLC) sample of the unsaturated ketone **19** was identified with an authentic sample[2] by comparison of GLC retention times and IR and mass spectra. A collected (GLC) sample of the ketone **18** was obtained as a colorless liquid that was tentatively identified from the following spectral properties: IR (CCl_4) 1710 cm^{-1} (C=O); NMR (CCl_4) δ 2.91 (1 H, t, J = 7 Hz, CHCO), 1.95 (3 H, s, CH_3CO), 1.4–1.9 (4 H, m, CH_2), 1.30 (3 H, s, CH_3), and 1.00 (3 H, s, CH_3); mass spectrum m/e (rel intensity) 126 (M^+, 14), 111 (48), 83 (73), 71 (100), 56 (48), 55 (53), 43 (51), and 41 (28). Anal. Calcd for $C_8H_{14}O$: 126.1045. Found. 126.1022.

E. Bromo Ketone 11 with i-Pr_2NLi. A cold (3 °C) solution of the enolate from 15.5 mmol of i-Pr_2NLi in 32.5 mL of hexane and 90 mL of Et_2O and 3.031 g (11.9 mmol) of the bromo ketone **11** in 30 mL of Et_2O was treated with 11.1 g (61.8 mmol or 4 equiv) of HMP. The solution was stirred at 2 °C for 30 min, during which time a precipitate separated, and then was subjected to the usual isolation procedure. After an aliquot of the crude product (1.956 g of liquid) had been mixed with a known amount of phenanthrene (an internal standard), analysis (GLC, silicone QF_1 on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of the enol ether **21** (retention time, 4.2 min, 3% yield), the unsaturated ketone **22** (5.4 min, 5% yield), and the ketone **20** (19.5 min, 67% yield); none of the cyclobutyl ketone **23** (6.9 min) was detected. Also none of the starting bromo ketone **11** was detected in the crude product (NMR analysis). The crude product was chromatographed on silica gel with a hexane–Et_2O mixture as the eluent. The first fraction eluted (64 mg) was further purified by preparative TLC (silica gel, Et_2O–hexane eluent 3:7 v/v) to separate 22 mg (1%) of the enol ether **21**. The next fraction (201 mg) was also subjected to preparative TLC to separate 139 mg (7%) of the unsaturated ketone **22**. Subsequent chromatographic fractions contained 1.219 g (59%) of the crude ketone **20**; recrystallization from hexane separated 1.052 g (51%) of the pure ketone **20**, mp 56.5–58.5 °C. Each of the components **21**, **22**, and **20** was identified with an authentic sample by comparison of IR and NMR spectra. The final fractions eluted from the chromatography column (347 mg) contained a complex mixture of materials with IR absorption attributable to OH and C=O functions.

F. Bromo Ketone 11 with KOBu-t. The bromo ketone **11**, pre-

pared as previously described,[2] was purified by chromatography and subsequent distillation to separate the bromo ketone **11** as a colorless liquid, bp 95–96 °C (0.006 mm), n^{25}_D 1.5384–1.5386 [lit. bp 123–125 °C (0.5 mm),[33] n^{20}_D 1.5412,[33] n^{25}_D 1.5392[2]]. A solution of *t*-BuOK, from 0.84 g (21.5 mg-atom) of K and 75 mL of *t*-BuOH, and 2.64 g (10.4 mmol) of the bromo ketone **11** in 15 mL of *t*-BuOH was stirred at 25–28 °C for 2 h and then subjected to the usual isolation procedure to give 1.69 g of crude product as a pale yellow liquid containing (IR and NMR analysis) mainly the enol ether **21**. After an aliquot of the crude product had been mixed with a known amount of phenanthrene (an internal standard), GLC analysis (silicone QF_1 on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of the enol ether **21** (retention time 4.2 min, 95% yield), the ketone **23** 7.1 min, 1% yield), and phenanthrene (27.7 min). A collected (GLC) sample of the ketone **23** was identified with an authentic sample by comparison of GLC retention times and IR and mass spectra. The remainder of the crude product (1.665 g) was distilled to separate 1.472 g (82%) of the enol ether **21** as a colorless liquid, bp 71–72 °C (0.7 mm), n^{25}_D 1.5483–1.5522, containing (GLC) 99% of the enol ether **21** and 1% of the ketone **23**. A collected (GLC) sample of the enol ether **21**, n^{25}_D 1.5532, was identified with an authentic sample by comparison of GLC retention times and IR, NMR, and mass spectra.

G. Bromo Ketone 12 with *i*-Pr_2NLi. A cold (−60 °C) solution of the enolate (0.053 M), from 5.94 mmol of *i*-Pr_2NLi in 11.9 mL of a hexane–pentane mixture and 87.5 mL of Et_2O and 1.318 g (5.66 mmol) of the bromo ketone **12** in 7.5 mL of Et_2O, was warmed to 0 °C, treated with 4.25 g (23.7 mmol) of HMP, stirred at 0–3 °C for 20 min, and then allowed to warm to 22 °C during 20 min. The usual isolation procedure separated 1.257 g of yellow liquid product (contained some HMP). After an aliquot of the crude product had been mixed with a known amount of 2-methylnaphthalene (an internal standard), GLC analysis (silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of 2-methylnaphthalene (retention time 15.0 min), decalone **26** (80% yield, 19.1 min, cis and trans isomers not resolved), and three minor unidentified impurities (5.2, 10, and 43.3 min). A 1.018-g aliquot of the crude product was chromatographed on silica gel with an EtOAc–hexane eluent to separate 586 mg (84%) of decalone **26**; distillation of this material gave 550 mg (79%) of decalone **26**, bp 68–69 °C (1.0 mm), n^{25}_D 1.4844, that was identified with an authentic sample (an equilibrium mixture of cis and trans isomers) by comparison of GLC retention times and IR, NMR, and mass spectra. The later fractions from the liquid chromatograph contained 62 mg of a crude mixture of higher molecular weight products with IR absorption at 3400 and 1710 cm^{-1}.

H. Bromo Ketone 32 with *i*-Pr_2NLi. A cold (−60 °C) solution of the enolate (0.05 M), from 10.5 mmol of *i*-Pr_2NLi in 22 mL of a hexane–pentane mixture and 155 mL of Et_2O and 2.20 g (10.0 mmol) of the bromo ketone **32** in 20 mL of Et_2O, was warmed to 0 °C, treated with 7.53 g (42 mmol, 4 equiv/Li^+) of HMP, and stirred at 0 °C for 30 min and at 20 °C for 30 min. The usual isolation procedure separated 2.67 g of crude product as a yellow liquid. An aliquot of crude product was mixed with a known weight of 1,3,5-triisopropylbenzene for GLC analysis (silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures). The mixture contained the enol ether **35** (retention time 8.8 min, 59% yield), 1,3,5-triisopropylbenzene (13.2 min), the unsaturated ketone **31** (17.4 min, 18% yield), and a very small peak corresponding in retention time to the bicyclic ketone **36** (36.6 min, area corresponds to a 0.5% yield). From a second comparable reaction, GLC analysis indicated the yield of the enol ether **35** to be 65% and none of the unsaturated ketone **31** was observed. The remaining crude reaction product (2.467 g) was chromatographed on Merck basic alumina with pentane as an eluent to separate 721 mg (52%) of early fractions containing the enol ether **35**. Distillation gave 681 mg (50%) of the pure enol ether **35** as a colorless liquid: bp 104–104.5 °C (45 mm); n^{25}_D 1.4861 [lit.[22] bp 80–90 °C (14 mm)]; IR (CCl_4) 1691 cm^{-1} (enol ether C=C); NMR (CCl_4) δ 3.7–4.0 (2 H, m, CH_2O) and 1.3–2.4 (12 H, m, CH_2); mass spectrum *m/e* (relative intensity) 138 (M^+, 41), 110 (63), 109 (36), and 67 (39).

We did not find evidence for the presence of the isomeric enol ether **38** in either fractions collected by GLC or fractions collected from chromatography on basic alumina. Consequently, any of this isomeric enol ether **38** formed in the alkylation reaction must have been either isomerized or destroyed during the isolation procedures.

Fractions eluted from the chromatography column with Et_2O–pentane (1:9 v/v) contained 210 mg (15%) of the unsaturated ketone **31** that was identified with an authentic sample by comparison of GLC retention times and IR spectra. The final fractions eluted from the column with Et_2O amounted to 1.496 g of yellow liquid containing (IR and NMR analysis) a mixture of HMP and higher molecular weight material.

An authentic sample of the ketone **36** (Aldrich Chemical Co.) was recrystallized from hexane to separate the pure ketone **36** as colorless needles: mp 155–157 °C (sealed capillary) [lit.[34] mp 151–152 °C]; IR (CCl_4) 1722 cm^{-1} (C=O); NMR (CCl_4) δ 1.3–2.6 (m, aliphatic CH); mass spectrum *m/e* (rel intensity) 138 (M^+, 100), 82 (65), 81 (41), 68 (46), 67 (94), 54 (46), and 41 (46).

I. Bromo Ketone 42 with *i*-Pr_2NLi. A cold (−60 °C) solution of the enolate (0.05 M), from 10.5 mmol of *i*-Pr_2NLi in 20.2 mL of a hexane–pentane mixture and 155 mL of Et_2O and 1.93 g (10 mmol) of the bromo ketone **42** in 20 mL of Et_2O, was warmed to 0 °C, treated with 7.53 g (42 mmol, 4 equiv/Li^+) of HMP, and stirred at 0 °C for 30 min and at 20 °C for 30 min. After the usual isolation procedure, the crude product (1.26 g of yellow liquid) exhibited one major GLC peak (silicone XE-60 on Chromosorb P) corresponding to the enol ether **43** (retention time 5.8 min), but no peak corresponding to the ketone **44** (12.2 min). The crude product was chromatographed on basic alumina to separate 521 mg (46%) of the enol ether **43** in early fractions eluted with pentane. Distillation afforded 462 mg (41%) of the enol ether **43** as a colorless liquid: bp 125–125.5 °C; n^{25}_D 1.4375; IR (CCl_4) 1672 (enol ether C=C) and 895 cm^{-1} (C=CH_2); NMR (CCl_4) δ 3.8–4.2 [3 H, m, overlapping triplet (J = 7 Hz) at 4.00 (CH_2O) and a partially obscured doublet (vinyl CH)], 3.61 (1 H, d, J = 1.7 Hz, vinyl CH), 1.81 (2 H, t, J = 7 Hz, CH_2), and 1.18 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 112 (M^+, 42), 97 (100), 69 (37), 67 (27), 57 (28), 55 (42), 43 (73), 42 (32), 41 (97), and 39 (34).

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 74.91; H, 10.80.

Later fractions from the chromatography column, eluted with Et_2O, contained 732 mg of viscous red liquid with IR absorption (CCl_4) at 3670, 3460 (OH), and 1709 cm^{-1} (weak, C=O). The mass spectrum of this crude mixture exhibited abundant fragment peaks at *m/e* 179, 135, 45, and 44.

J. Bromo Ketone 50 with *i*-Pr_2NLi. A cold (−60 °C) solution of the enolate (0.05 M), from 5.25 mmol of *i*-Pr_2NLi in 78 mL of Et_2O and 10 mL of a pentane–hexane mixture and 895 mg (5.0 mmol) of the bromo ketone **50** in 10 mL of Et_2O, was warmed to 0 °C, treated with 3.77 g (21 mmol, 4 equiv/Li^+) of HMP, and stirred at 0 °C for 30 min and then at 20 °C for 2 h. The usual isolation procedure separated 1.67 g of crude yellow liquid product. After an aliquot of this crude product had been mixed with an internal standard (n-$C_{11}H_{24}$), GLC analysis (silicone XE-60 on Chromosorb P at 100 °C, apparatus calibrated with known mixtures) indicated the presence of the enol ether **51** (retention time 8.8 min, 17% yield), the ketone **52** (15.8 min, 10% yield), and n-$C_{11}H_{24}$ (26.2 min). When the temperature of the GLC column was raised to 120 °C, peaks corresponding to the unchanged bromo ketone **50** (retention time 19.2 min, 17% recovery) and the internal standard n-$C_{11}H_{24}$ (6.6 min) were observed. A 923-mg aliquot of the crude product was chromatographed on Merck basic alumina with an Et_2O–pentane eluent to separate successive fractions containing 41 mg (8% yield) of the cyclobutanone **52** (IR analysis), 62 mg (13% recovery) of the bromo ketone **50** (IR analysis), and 732 mg of final fractions of yellow viscous liquid containing mixtures of HMP and components with IR absorption at 3320 (br), 1775, and 1685 cm^{-1} attributable to OH and C=O functions.

The crude product from a second comparable reaction was used to collect (GLC) samples of the monomeric products. The enol ether **51** was obtained as a very volatile colorless liquid: IR (CCl_4) 1689 (C=C), 1375, 1392 (geminal CH_3 groups), 1212, 1158 (COC), and 895 cm^{-1} (C=CH_2); NMR (CCl_4) δ 4.31 (2 H, s, CH_2O), 3.90 (1 H, d, J = 4 Hz, vinyl CH), 3.60 (1 H, d, J = 4 Hz, vinyl CH), and 1.33 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 98 (M^+, 73), 68 (100), 67 (86), 56 (34), 53 (45), 43 (22), 41 (62), 40 (25), and 39 (34). Anal. Calcd for $C_6H_{10}O$: 98.0731. Found: 98.0729.

The ketone **52** was obtained as a colorless liquid: n^{25}_D 1.4130 (lit. bp 113.5–114 °C,[35] n^{20}_D 1.4150[36b]); IR (CCl_4) 1781 cm^{-1} (C=O); NMR (CCl_4), δ 3.02 (2 H, t, J = 8.5 Hz, further partially resolved splitting apparent, CH_2CO), 1.80 (2 H, t, J = 8.5 Hz, further partially resolved splitting apparent, CH_2), and 1.18 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 98 (M^+, 13), 70 (63), 56 (88), 55 (50), 42 (59), 41 (100), and 39 (35). These spectral features correspond to those previously reported[36] for the ketone **52** and the NMR spectrum of our product clearly excludes the presence of any appreciable amount of the isomeric ketone **53**.[36b]

K. Bromo Ketone 50 with KOH in H_2O–DME. To a refluxing solution of 323 mg (5.8 mmol) of KOH in 10 mL of H_2O and 10 mL of DME was added, dropwise and with stirring during 2 h, a solution of 301 mg (1.68 mmol) of the bromo ketone **50** in 5 mL of DME. The resulting colorless solution was refluxed for an additional 2 h and then cooled and partitioned between H_2O and Et_2O. After the Et_2O solution had been dried and concentrated to leave 128 mg of crude liquid

product, an aliquot of the crude product was mixed with an internal standard (n-$C_{11}H_{24}$) and subjected to the previously described GLC analysis. Although neither the enol ether **51** nor the unchanged bromo ketone **50** were detected, the crude product contained the ketone **52** (16.8 min, 5.5% yield), n-$C_{11}H_{24}$ (27.5 min), and a minor component (19.9 min, yield <1%) believed to be the isomeric cyclobutanone **53**. A collected (GLC) sample of the ketone **52** was identified with the previously described sample by comparison of IR, NMR, and mass spectra and a collected (GLC) sample of the minor product **53** exhibited IR absorption (CCl_4) at 1780 and 1788 cm^{-1} (cyclobutanone C=O); mass spectrum m/e (relative intensity) 98 (M^+, 10), 70 (61), 56 (99), 55 (41), 42 (46), 41 (100), and 39 (23). These spectral properties correspond to those reported[36b] for the ketone **53**.

The basic aqueous phase from the above reaction was acidified, saturated with NaCl, and extracted with Et_2O. After the Et_2O solution had been concentrated, the crude acidic product (212 mg) was esterfied with excess ethereal CH_2N_2. The resulting solution contained (GLC, silicone XE-60 on Chromosorb P) Et_2O (retention time 3.0 min), $CH_3CO_2CH_3$ (5.0 min), and DME (8.4 min), but none of the ester $(CH_3)_3CCH_2CO_2CH_3$ (17.4 min, the product that could be obtanied by cleavage of ketone **53**) was detected. After an aliquot of this solution had been mixed with an internal standard (n-$C_{11}H_{24}$), GLC analysis indicated the yield of $CH_3CO_2CH_3$ to be 93% (based on the starting bromo ketone **50**). An authentic sample of the ester $(CH_3)_3CCH_2CO_2CH_3$ was obtained by esterification of the acid $(CH_3)_3CCH_2CO_2H$[37] with ethereal CH_2N_2. The product was distilled to separate the ester $(CH_3)_3CCH_2CO_2CH_3$ as a colorless liquid: bp 127–127.5 °C; $n^{25}D$ 1.4001 [lit.[38] bp 126.5 °C (739 mm); $n^{20}D$ 1.3981]; IR (CCl_4) 1740 cm^{-1} (ester C=O); NMR (CCl_4), δ 3.60 (3 H, s, OCH_3), 2.15 (2 H, s, CH_2), and 1.02 (9 H, s, t-Bu); mass spectrum m/e (rel intensity) 115 (5), 99 (40), 74 (100), 73 (95), 59 (37), 57 (95), 55 (58), 43 (54), 41 (78), and 39 (43).

L. Bromo Ketone 67 with i-Pr_2NLi. A cold (−60 °C) solution of the enolate (0.05 M), from 12.6 mmol of i-Pr_2NLi in 188 mL of Et_2O and 24 mL of a hexane–pentane mixture and 2.48 g (12.0 mmol) of the bromo ketone **67** in 10 mL of Et_2O, was warmed to 25 °C and 9.03 g (50.4 mmol, 4 equiv) of HMP was added. The solution, from which a fine precipitate slowly separated, was stirred at 25 °C for 75 min and subjected to the usual isolation procedure to separate 2.75 g of crude product as a yellow liquid. An aliquot of this crude product was mixed with a known weight of n-$C_{14}H_{30}$ (an internal standard) for GLC analysis (UCON 50HB280X on Chromosorb P, apparatus calibrated with known mixtures). The crude product contained (GLC) the unsaturated ketone **63** (2.9% yield, retention time 5.0 min), the ketone **70** [24% yield, mainly **70b** (6.4 min) plus **70a** (7.4 min)], the ketone **69** (36% yield, 13.8 min), and n-$C_{14}H_{30}$ (29.2 min). A 2.654-g aliquot of the crude product was distilled in a short-path still to separate 1.190 g of a volatile fraction, bp 60–110 °C (25 mm), containing (GLC) a mixture of ketones **63**, **69**, and **70**. The pot residue from the distillation contained a mixture of HMP and higher molecular weight products. The distillate (1.190 g) was chromatographed on silica gel with an Et_2O–hexane eluent (1:9 v/v) to separate 398 mg (26%) of early fractions containing (GLC) a mixture of ketones **63** and **70** followed by 536 mg (35%) of fractions containing (GLC) the ketone **69**. Distillation of these later fractions afforded 510 mg (34%) of the ketone **69**: bp 70–71 °C (13 mm); $n^{25}D$ 1.4558. The early chromatographic fractions (398 mg) were rechromatographed on silica gel coated with 5% $AgNO_3$ and eluted with Et_2O–hexane (1:9 v/v). The fractions eluted first (310 mg or 21%) contained the ketone **70**; these fractions were distilled to separate 300 mg (20%) of the ketone **70** (mainly **70b**): bp 70–71 °C (23 mm); $n^{25}D$ 1.4410. The final fraction from the second chromatography contained 31 mg (2%) of the unsaturated ketone **63** (GLC analyses). The isolated samples of ketones **63**, **69**, and **70** were identified with authentic samples by comparisons of IR spectra and GLC retention times.

A series of comparable small-scale experiments were performed in which 2.5 mmol of the bromo ketone **67** was added to a cold (−60 °C) solution of 2.65 mmol of i-Pr_2NLi and the resulting enolate solution (0.05 M) was activated with 10.5 mmol of HMP and allowed to react at various temperatures. The product yields after various times and temperatures were: 2 h at 0 °C, 3.9% of **63**, 28% of **70**, and 22% of **69**; 1.75 h at 25 °C, 3.5% of **63**, 21% of **70**, and 31% of **69**; 2 h at 35 °C, 2.6% of **63**, 35% of **70**, and 26% of **69**. When excess i-Pr_2NLi (5.0 mmol) was used with 2.5 mmol of bromo ketone **67** and 10.5 mmol of HMP at 25 °C for 2 h dehydrohalogenation became the major reaction with the yields being 33% of **63**, 2% of **70**, and 10% of **69**. Activation of the enolate with excess DME rather than with HMP followed by reaction at 40 °C for 2 h gave the following yields: 40% of **70** and 10% of **69**. Activation of the enolate **68** with 1 molar equiv of triglyme (**15**) followed by reaction at 0 °C for 2 h resulted in recovery of most of the starting bromo ketone **67**. Thus, the most favorable ratio of seven-membered (**69**) to five-membered (**70**) product (60:40) was obtained when a solution of the enolate at 25 °C was activated with HMP and allowed to react at 25 °C for 1–2 h.

M. Bromo Ketone 67 with KOBu-t. A solution of KOBu-t, from 0.33 g (10.3 mg atom) of K and 18 mL of t-BuOH, and 2.05 g (9.9 mmol) of the bromo ketone **67** in 20 mL of pentane was stirred at 26 °C for 30 min and at 40 °C for 45 min. The usual isolation procedure separated 6.21 g (contains t-BuOH) of crude product as a yellow liquid. After an aliquot of the crude product had been mixed with a known weight of n-$C_{14}H_{30}$ (an internal standard), GLC analysis (UCON 50 HB280X on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of the isomeric cyclopentyl ketones **70** (83% yield, retention times 7.3 min for **70b** and 9.0 min for **70a**), n-$C_{14}H_{30}$ (34.7 min), and two minor by-products (2.9 and 5.2 min), but no peak corresponding to the cycloheptanone **69** (15.6 min). A 5.57-g aliquot of the crude reaction product was distilled to separate low-boiling materials (mainly t-BuOH) from 789 mg (72%) of fractions, bp 78 °C (40 mm), $n^{25}D$ 1.4376–1.4392, containing (GLC) the stereoisomeric ketones **70**. A collected (GLC) sample of the ketone **70** (mainly **70b**), $n^{25}D$ 1.4392, was identified with an authentic sample by comparison of IR and NMR spectra and GLC retention times. Collected (GLC) samples of the minor, more rapidly eluted by-products (2.9 and 5.2 min) had IR and mass spectral peaks suggesting that they may be the structurally isomeric enol ethers **74** and **75**. The spectral properties of the more rapidly eluted component (2.9 min) were: IR (CCl_4) 1715, 1380, 1100, and 900 cm^{-1}; mass spectrum m/e (rel intensity) 126 (M^+, 17), 111 (36), 69 (34), 58 (27), 55 (25), 43 (100), and 41 (28). Anal. Calcd for $C_8H_{14}O$: 126.1045. Found: 126.1022. The corresponding properties for the less rapidly eluted component (5.2 min) were: IR (CCl_4) 1695, 1380, 1182, and 1170 cm^{-1}; mass spectrum m/e (rel intensity) 126 (M^+, 6), 111 (32), 55 (40), 43 (100), and 41 (29). Anal. Calcd for $C_8H_{14}O$: 126.1045. Found: 126.1051.

In a similar experiment, a cold (4 °C) mixture of 460 mg (11.5 mmol) of KH (prewashed with pentane) and 140 mg (1.4 mmol) of i-Pr_2NH in 10 mL of DME was treated, dropwise and with stirring during 8 min, with a solution of 61.1 mg (0.295 mmol) of the bromo ketone **67** and 33.3 mg of n-$C_{14}H_{30}$ in 3 mL of DME. After the mixture, from which a precipitate began to separate immediately, had been stirred at 25 °C for 1 h, the previously described isolation and analysis procedures indicated the yield of ketone **70** to be 52%.

Preparation of Authentic Samples of Products. A. Ketone 44. A previously described procedure[39] was used to obtain a sample of the ketone **44**: bp 143 °C; $n^{25}D$ 1.4320; IR (CCl_4) 1740 cm^{-1} (C=O); NMR (CCl_4) δ 1.2–2.4 (6 H, m, CH_2) and 1.02 (6 H, s, CH_3); mass spectrum m/e (rel intensity) 112 (M^+, 19), 69 (14), 56 (100), 55 (14), 41 (34), and 39 (13).

B. Enol Ether 21. To a solution of NaOEt, from 1.5 g (67 mg-atom) of Na and 40 mL of EtOH, was added, dropwise and with stirring, a solution of 8.48 g (33.3 mmol) of the bromo ketone **11** in 7 mL of EtOH. The resulting mixture was stirred at 27–33 °C for 45 min and then partitioned between hexane and aqueous $NaHCO_3$. The organic solution was washed with H_2O, dried, and concentrated to leave 5.61 g of yellow liquid that contained (TLC, silica gel, eluent 3:7 v/v Et_2O–hexane) the enol ether **21** (R_f 0.50) accompanied by several minor unidentified components (R_f 0.13, 0.27, and 0.34). The crude product was chromatographed on silica gel to separate 1.47 g (26%) of fractions (1:10 to 1:6 v/v Et_2O–hexane eluent) containing (GLC, TLC) the pure enol ether **21** as well as 1.38 g of earlier fractions containing **21** with unidentified impurities and 2.59 g of later fractions containing various mixtures of **21** and the bromo ketone **11**. The pure enol ether **21** was obtained as a colorless liquid: $n^{25}D$ 1.5533 [lit. bp 128–133 °C (18 mm);[33] $n^{25}D$ 1.5530[40]]; IR (CCl_4) 1660 cm^{-1} (enol ether C=C); UV max (95% EtOH) 256 nm (ϵ 5760); NMR (CCl_4) δ 6.9–7.3 (5 H, m, aryl CH), 3.8–4.1 (2 H, m, CH_2O), 1.8–2.5 (4 H, m, CH_2), and 1.67 (3 H, t, J = 1.8 Hz, allylic CH_3); mass spectrum m/e (rel intensity) 174 (M^+, 59), 131 (46), 104 (23), 103 (100), 77 (32), 51 (20), and 43 (94).

C. Ketone 20. A commercial sample of the ketone **20** (Pfaltz and Bauer, Inc.) was recrystallized from EtOH and then from hexane to separate the pure ketone **20** as colorless prisms: mp 57–59 °C [lit. mp 62 °C,[41] 51.5–54 °C,[42] bp 148–152 °C (15 mm)[42]]; IR (CCl_4) 1720 cm^{-1} (C=O); UV (95% EtOH) series of weak maxima (ϵ 280–618) in the region 242–264 nm with a maximum at 288 nm (ϵ 131); NMR (CCl_4) δ 6.9–7.4 (5 H, m, aryl CH), 3.2–3.7 (1 H, m, benzylic CH), and 1.4–2.6 (8 H, m, aliphatic CH); mass spectrum m/e (rel intensity) 174 (M^+, 39), 130 (100), 117 (55), 104 (43), 91 (37), 77 (19), and 39 (17).

D. Ketone 23. To obtain an authentic sample of ketone **23**, a previously described procedure[43] was used to alkylate 50.0 g (426 mmol) of $PhCH_2CN$ by adding a solution of this nitrile and 94.74 g (469

mmol) of $Br(CH_2)_3Br$ in 165 mL of Et_2O to the base from 22.5 g (938 mmol) of NaH(washed with pentane) and 330 mL of Me_2SO. After the reaction solution was stirred at 25 °C for 1.5 h and then subjected to the previously described isolation procedure,[43] the nitrile **24** was collected as 28.29 g (42%) of colorless liquid, bp 90–91 °C (0.56 mm), $n^{25}D$ 1.5290 [lit. bp 120–122 °C (7 mm),[43] $n^{20}D$ 1.5351[44]], that exhibited one major GLC peak (silicone SE-30 on Chromosorb P) at 7.5 min: IR (CCl_4) 2240 cm^{-1} (C≡N); UV max (95% EtOH) 259 nm (ε 130); NMR (CCl_4) δ 7.1–7.5 (5 H, m, aryl CH) and 1.8–3.0 (6 H, m, CH_2); mass spectrum *m/e* (rel intensity) 157 (M^+, 10), 130 (15), 129 (100), 120 (11), 77 (7), 51 (11), and 39 (6).

A mixture of 5.00 g (31.8 mmol) of the nitrile **24**, 5 mL of concentrated H_2SO_4, 5 mL of H_2O, and 5 mL of HOAc was refluxed for 1.5 h and then partitioned between Et_2O and H_2O. After the organic layer was extracted with aqueous 5% NaOH, acidification of the alkaline aqueous extract precipitated 4.65 g (83%) of the acid **25** as a white solid, mp 104–106 °C. Recrystallization from hexane afforded the pure acid **25** as white plates: mp 106.5–108 °C (lit.[45] mp 106–107 °C); IR (CCl_4) 3300–2500 (carboxyl OH) and 1698 cm^{-1} (carboxyl C=O); UV max (95% EtOH) 256 (ε 144) and 218 nm (shoulder, ε 4620); NMR (CCl_4) δ 12.14 (1 H, s, OH), 7.0–7.4 (5 H, m, aryl CH), and 1.6–3.1 (6 H, m, CH_2); mass spectrum *m/e* (rel intensity) 176 (M^+, 16), 148 (100), 131 (15), 103 (82), 91 (15), 77 (24), and 51 (17).

To a solution of CH_3MgI, prepared from 1.858 g (76.4 mg-atom) of Mg, 10.84 g (76.4 mmol) of CH_3I, and 100 mL of Et_2O, was added a solution of 10.00 g (63.7 mmol) of the nitrile **24**. The reaction solution, from which a white precipitate separated after 1 h, was stirred overnight at 23–25 °C and then partitioned between Et_2O and aqueous 5% H_2SO_4. The Et_2O extracts were washed successively with aqueous $NaHCO_3$ and with H_2O and then dried and concentrated. Distillation of the residual yellow liquid (10.3 g) separated 8.03 g (73%) of the ketone **23** as a colorless liquid: bp 81 °C (0.4 mm); $n^{25}D$ 1.5274 [lit.[46] bp 56–57 °C (0.2 mm)]; IR (CCl_4) 1708 cm^{-1} (C=O); UV max (95% EtOH) 218 (shoulder, ε 5900), 266 (ε 210), and 291 nm (ε 250); NMR (CCl_4) δ 7.0–7.4 (5 H, m, aryl CH) and 1.7–3.0 (9 H, m, aliphatic CH including an CH_3CO singlet at 1.79); mass spectrum *m/e* (rel intensity) 174 (M^+, 16), 131 (100), 103 (57), 91 (19), 77 (13), and 43 (18).

E. Ketone 69. To a cold (4 °C) solution of $LiCuMe_2$, prepared from 2.81 g (13.6 mmol) of Me_2S–CuBr,[28] 27.3 mmol of MeLi, and 26.5 mL of Et_2O, was added, dropwise with stirring at 4–13 °C during 7 min, a solution of 1.00 g (9.09 mmol) of the enone **71** in 5 mL of Et_2O. The reaction mixture, from which a yellow precipitate of $(MeCu)_n$ began to precipitate almost immediately, was stirred at 10 °C for 10 min and at 25 °C for 3 h and then partitioned between Et_2O and an aqueous solution of NH_3 and NH_4Cl. The organic layer was washed with aqueous NaCl, dried over molecular sieves, no. 4A, and concentrated to leave 1.00 g (88%) of the crude ketone **69** (GLC analyses) as a pale yellow liquid. Distillation afforded 718 mg (63%) of the pure ketone **69** as a colorless liquid: bp 68–72 °C (13 mm); $n^{25}D$ 1.4557–1.4559 [lit.[47] bp 104–105 °C (60 mm); $n^{26.5}D$ 1.4540]; IR (CCl_4) 1701 cm^{-1} (C=O); NMR (CCl_4) δ 2.2–2.6 (4 H, m, CH_2CO), 1.2–2.2 (7 H, m, aliphatic CH), and 1.01 (3 H, d, J = 5.5 Hz, CH_3); mass spectrum *m/e* (rel intensity) 126 (M^+, 11), 82 (65), 69 (100), 56 (44), 55 (57), 42 (26), 41 (56), and 39 (19).

F. Ketone 70. A THF solution containing (by total base titration) 0.88 M HC≡CMgBr was prepared from HC≡CH and a THF solution of EtMgBr as previously described.[48] A solution of 28.0 g (333 mmol) of cyclopentanone in 75 mL of THF was added, dropwise and with stirring during 50 min, to 450 mL of a cold (3–4 °C) THF solution containing 395 mmol of HC≡CMgBr. The resulting pale green mixture was stirred at 25 °C for 20 h and partitioned between Et_2O and aqueous $NaHCO_3$, and the organic layer was washed with aqueous NaCl, dried, and concentrated. Distillation of the residual yellow liquid (41.4 g) separated 25.34 g (69%) of the pure (GLC) alcohol **72** as a colorless liquid: bp 68–75 °C (18–25 mm); $n^{25}D$ 1.4716–1.4717 [lit. bp 65–65.5 °C (16 mm);[49] $n^{20}D$ 1.4741;[49] mp 24 °C[50]]; IR (CCl_4) 3600, 3470 (OH), 3305 (acetylenic CH), and 2115 cm^{-1} (weak, C≡C); NMR (CCl_4) δ 2.83 (1 H, s, OH, exchanged with D_2O), 2.37 (1 H, s, C≡CH), and 1.4–2.2 (8 H, m, CH_2); mass spectrum *m/e* (rel intensity) 110 (M^+, 5), 109 (50), 95 (73), 82 (65), 81 (100), 68 (78), 67 (67), 55 (70), 54 (38), 53 (61), 41 (54), and 39 (55).

A solution of 5.00 g (45.5 mmol) of the alcohol **72** in 50 mL of 92% HCO_2H was refluxed for 80 min and then cooled and partitioned between H_2O and pentane. The organic layer was washed successively with aqueous $NaHCO_3$ and aqueous NaCl and then dried, concentrated, and distilled to separate 1.71 g of the crude enone **73**: bp 69 °C (18 mm); $n^{25}D$ 1.4748–1.4786. The aqueous phase was neutralized with solid $NaHCO_3$ and again extracted with pentane to separate, after drying and distillation, an additional 0.88 g of crude enone **73**: bp 70 °C (20 mm); $n^{25}D$ 1.4788–1.4792 (total yield 2.59 g or 52%). This crude product contained (GLC, UCON 50HB280 X on Chromosorb P) the enone **73** (6.1 min) accompanied by two minor, unidentified impurities (3.1 and 4.0 min). A collected (GLC) sample of the pure enone **73** was obtained as a colorless liquid: $n^{25}D$ 1.4792 [lit.[50] bp 67 °C (16 mm); $n^{23}D$ 1.4776]; IR (CCl_4) 1670 (C=O) and 1615 cm^{-1} (C=C); UV max (95% EtOH) 238.5 (ε 10 000) and 305 nm (ε 46); NMR (CCl_4) δ 6.5–6.7 (1 H, m, vinyl CH) and 1.5–3.1 (9 H, m, aliphatic CH including a CH_3CO singlet at 2.23); mass spectrum *m/e* (rel intensity) 110 (M^+, 57), 95 (100), 67 (90), 65 (24), 43 (71), 41 (47), and 39 (27).

To a cold (3 °C) solution of Me_2CuLi, from 3.08 g (14.9 mmol) of Me_2SCuBr[28] and 29.9 mmol of MeLi in 36 mL of Et_2O, was added, dropwise with stirring and cooling (3–9 °C) during 10 min, a solution of 1.006 g (9.14 mmol) of the enone **73**. After the resulting mixture had been stirred at 3 °C for 15 min, the cooling bath was removed and the mixture was allowed to warm to 25 °C with stirring during 80 min. After the reaction mixture had been partitioned between Et_2O and an aqueous solution of NH_3 and NH_4Cl, the organic layer was washed with aqueous NaCl, dried, concentrated, and distilled to separate 0.87 g (76%) of the ketone **70** as a colorless liquid: bp 70 °C (23 mm); $n^{25}D$ 1.4410–1.4423 [lit.[51] cis-isomer **70a**, bp 53–53.5 °C (14 mm), $n^{25}D$ 1.4418; trans-isomer **70b**, bp 53.5–54 °C (14 mm), $n^{25}D$ 1.4383]. This product contained (GLC, UCON 50HB280 X on Chromosorb P) a mixture of trans-isomer **70b** (retention time 4.1 min, ~65%) and the cis-isomer **70a** (4.8 min, ~35%); IR (CCl_4) 1712 cm^{-1} (C=O); NMR (CCl_4) δ 1.4–2.8 (11 H, m, aliphatic CH including a CH_3CO singlet at 2.08) and two doublets (total 3H) at 1.02 (J = 6 Hz, CH_3 of trans-isomer **70b**[52]) and 0.92 (J = 7 Hz, CH_3 of cis-isomer **70a**[52]); mass spectrum *m/e* (rel intensity) 126 (M^+, 68), 111 (68), 85 (56), 84 (34), 83 (100), 71 (75), 67 (50), 55 (80), 43 (75), 41 (52), and 39 (31). A solution of 545 mg (4.3 mmol) of this mixture of ketones **70** and 0.30 g (2.7 mmol) of *t*-BuOK in 25 mL of *t*-BuOH was stirred at 28 °C for 30 min and then partitioned between pentane and aqueous NaCl. The pentane layer was dried, concentrated, and distilled in a short-path still to separate 254 mg (47% recovery) of the ketone **70**, $n^{25}D$ 1.4388, containing (NMR and GLC analyses) about 94% of the trans-ketone **70b** and about 6% of the cis-ketone **70a**.

Registry No.—**9**, 61675-00-1; **10**, 61675-01-2; **11**, 36307-12-7; **12**, 64507-82-0; **13**, 1193-47-1; **14**, 2979-19-3; **17**, 64507-83-1; **18**, 64507-84-2; **20**, 1444-65-1; **21**, 25252-74-8; **23**, 3972-67-6; **24**, 14377-68-5; **25**, 37828-19-6; **28**, 61675-08-9; **31**, 94-66-6; **32**, 10468-37-8; **35**, 7106-07-2; **36**, 17931-55-4; **42**, 61689-48-3; **43**, 63820-00-8; **44**, 4541-32-6; **50**, 19961-40-1; **51**, 64507-85-3; **52**, 1192-14-9; **53**, 1192-33-2; **63**, 35194-34-4; **65a**, 64507-86-4; **65b**, 64507-87-5; **66** (*R*R**), 64507-88-6; **66** (*R*S**), 64507-89-7; **67**, 61675-02-3; **69**, 933-17-5; **70a**, 3664-69-5; **70b**, 3664-70-8; **71**, 1121-66-0; **72**, 17356-19-3; **73**, 16112-10-0; **74**, 64507-66-0; **75**, 64507-65-9; *i*-Pr_2NLi, 4111-54-0; *n*-BuLi, 109-72-8; *tert*-butyl acetoacetate, 1694-31-1; acetaldehyde, 75-07-0; allyl bromide, 106-95-6; KOBu-*t*, 865-47-4; KOH, 1310-58-3; 3,3-dimethylbutanoic acid methyl ester, 10250-48-3; CH_3I, 74-88-4; $LiCuMe_2$, 15681-48-8; cyclopentanone, 120-92-3; ethynyl bromide, 593-61-3.

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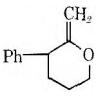

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Mercury in Organic Chemistry. 13.[1] Stereospecific Synthesis of α,β-Unsaturated Ketones via Acylation of Vinylmercurials[2]

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Treatment of vinylmercuric chlorides with acid chlorides and aluminum trichloride for 5 min at room temperature in methylene chloride solvent provides a very mild, convenient method for the synthesis of α,β-unsaturated ketones in excellent yields and high stereochemical purity. The reaction is applicable to the synthesis of functionally substituted enones as well as dienones. Rhodium(I) and palladium(0) reagents also promote the reaction, but in lower yield. The use of titanium tetrachloride instead of aluminum trichloride leads to enones of inverted stereochemistry in some cases, but the reaction is not synthetically useful due to its irreproducibility. Both the aluminum trichloride and titanium tetrachloride reactions appear to proceed through addition of the complexed acid chloride to the carbon–carbon double bond of the vinylmercurial, followed by mercuric chloride elimination. However, direct substitution at the carbon–mercury bond cannot be ruled out in the aluminum trichloride reactions.

A variety of methods presently exist for the synthesis of α,β-unsaturated ketones. The aldol condensation is one important approach to the synthesis of α,β-unsaturated ketones.[6] Another important method employs the Friedel–Crafts reaction of acid chlorides, acids, or anhydrides with olefins.[7] Recently a new procedure involving the hydrozirconation of acetylenes and subsequent aluminum chloride promoted acylation of the resulting vinylzirconium compounds has been added to the list of important methods of preparing α,β-unsaturated ketones.[8] The acylation of vinylmercurials appeared to be an equally promising route to enones since vinylmercurials are readily available directly from acetylenes.[9,10] We wish now to report in detail our studies on the successful development of just such a procedure.

Although a number of reactions of organomercurials which lead to ketones have been reported previously, there are only isolated examples of the direct reaction of acid chlorides with organomercuric chlorides to give ketones.[11] Most of the ex-

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amples involve the reaction of acid halides and activated arylmercuric chlorides, and some of these reactions even require forcing conditions. None of these reactions appear to be very general. However, the use of Lewis acids has been found to promote some of these reactions. Skoldinov and Koschkov used aluminum chloride to promote the reaction of benzoyl chloride and phenylmercuric chloride or diphenylmercury (eq 1 and 2).[12] Reutov and co-workers have used aluminum bromide in dichloromethane to prepare ketones (eq 3).[13] Either dialkyl- or diarylmercury compounds could be used with either aliphatic or aromatic acid halides. The reaction occurs very quickly, often in minutes, and transfers only one aryl or alkyl group from mercury to the acid chloride.

$$(C_6H_5)_2Hg + C_6H_5COCl \xrightarrow[CS_2]{AlCl_3} (C_6H_5)_2C{=}O \qquad (1)$$

$$C_6H_5HgCl + C_6H_5COCl \xrightarrow[neat]{AlCl_3} (C_6H_5)_2C{=}O \qquad (2)$$

$$R_2Hg + R'COCl \xrightarrow[CH_2Cl_2]{AlBr_3} RR'C{=}O + RHgCl \qquad (3)$$

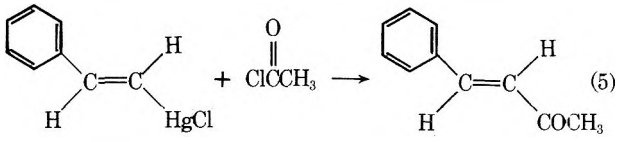
One example of a transition metal catalyzed reaction of dialkyl- or diarylmercurials with acid bromides has also appeared recently. Tetrakis(triphenylphosphine)palladium(0) catalyzes the reaction of acid halides with organomercurials (eq 4).[14] Unfortunately, the reaction requires the use of hexamethylphosphoramide (HMPA) and fails for alkyl- and arylmercuric chlorides.

$$R_2Hg + R'COBr \xrightarrow[HMPA]{Pd(PPh_3)_4} R'RC{=}O + RHgBr \qquad (4)$$

We have developed the first synthesis of α,β-unsaturated ketones from vinylmercuric chlorides and acid chlorides. The reaction proceeds to give high yields of α,β-unsaturated ketones greater than 95% stereochemically pure. The reaction works very well with aliphatic acid chlorides and moderately well with aromatic acid chlorides. Unfortunately, not all functional groups are tolerated, and the reaction conditions, although relatively mild, tend to cause rearrangements in some systems. With these limitations in mind, however, the reaction appears to be fairly general.

Results and Discussion

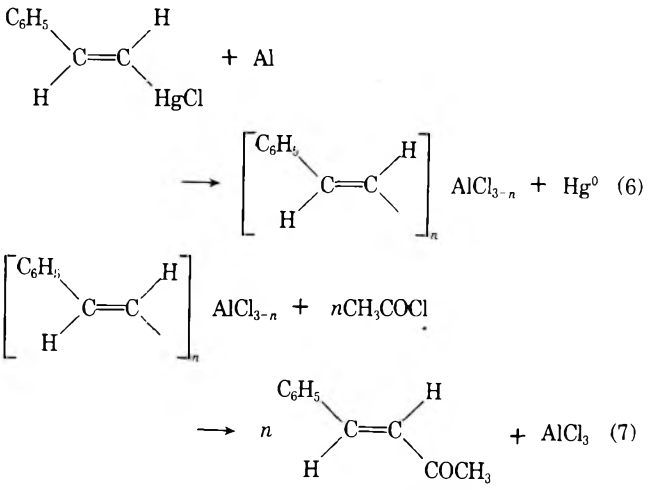
Reaction of Styrylmercuric Chloride with Acetyl Chloride. Reutov's report[13] on the synthesis of ketones from diaryl- or dialkylmercurials prompted us to study the reaction of vinylmercuric chlorides with acid chlorides. Styrylmercuric chloride and acetyl chloride were initially chosen as a model system for study (eq 5). Reutov's reaction conditions, alumi-



(5)

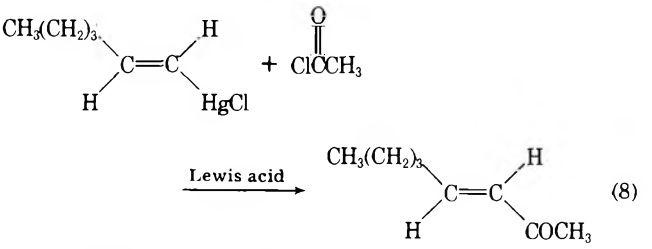
num bromide in dichloromethane at room temperature, gave no enone whatsoever. Therefore, a large number of other reaction conditions were examined. The best results were obtained using 4 equiv of aluminum powder in dichloromethane (48% yield). This reaction presumably proceeds via transmetallation to a more reactive vinylalane (eq 6 and 7).

Treatment of distyrylmercury with acetyl chloride and aluminum chloride in methylene chloride gave a much better reaction and a 53% yield of enone. Distyrylmercury is significantly more soluble in dichloromethane than is styrylmercuric chloride. As a result, the success of this reaction may be due to a combination of increased reactivity and increased solubility of the distyrylmercury. Both the aluminum powder and distyrylmercury reactions result in utilization of roughly



half of the styryl groups available and therefore appear to be equally useful synthetically.

Reaction of trans-1-Hexenylmercuric Chloride with Acetyl Chloride. A new model system was then investigated to determine if the difficulties encountered in the styryl system were unique to that system or a general characteristic of all vinylmercuric chlorides (eq 8). *trans*-1-Hexenylmercuric



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chloride was treated with acetyl chloride and aluminum bromide in dichloromethane for 1 h at 0 °C. Analysis of the reaction mixture by GLC showed an excellent yield of enone, although a mixture of approximately equal quantities of *cis*- and *trans*-3-octen-2-one was obtained.

In an effort to improve the stereospecificity of the reaction, studies on the effect of the Lewis acid (Table I) and solvent (Table II) were carried out. Titanium tetrachloride, aluminum bromide, and aluminum chloride were found to be the only synthetically useful Lewis acids. Antimony pentachloride, stannic chloride, and boron trichloride showed evidence of undergoing transmetallation reactions with the vinylmercuric chloride, although no ketone products were seen by GLC. A precipitate, presumably mercuric chloride, is observed in the successful reactions, and a similar precipitate was observed in these three nonketone-forming reactions as well. Although it is not known exactly what is happening in these reactions, it is assumed that a transmetallation reaction occurs leading to new vinylmetallics, which do not provide any enone product.

As can be seen in Table II, dichloromethane was a significantly better solvent for the reaction than any other solvent tested. Polar solvents are necessary to dissolve the vinylmercuric chloride, but solvents which are capable of coordinating with the Lewis acid are undesirable since they weaken the ability of the Lewis acid to promote acylation. One difficulty with styrylmercuric chloride was its insolubility in dichloromethane, which probably explains its lack of reaction under conditions where other vinylmercuric chlorides react readily.

The effect of reaction temperature on the stereospecificity of the three Lewis acid systems which were found to be effective in this reaction was studied (Table III). The stereospecificity obtained with aluminum bromide was found to improve on lowering the temperature to −78 °C. However, the

Table I. Effect of Lewis Acids on the Reaction of *trans*-1-Hexenylmercuric Chloride and Acetyl Chloride[a]

Lewis acid	Time, h	% yield of 3-octen-2-one[b] Cis	Trans	Total
$SbCl_5$	0.1	0	0	0[c]
$SbCl_3$	24	0	0	0
$SnCl_4$	1	0	0	0[c]
SbF_3	24	0	0	0
BF_3-Et_2O		6	7	13
$ZnCl_2$	6	7	5	12
BCl_3		0	3	3[c]
$FeCl_3$	0.1	2	23	25
Al powder	24	7	41	48
$TiCl_4$	0.25	23	76	99
$AlBr_3$	0.50	44	49	93
$AlCl_3$	0.25	5	95	100

[a] A 1-mmol amount each of Lewis acid, acetyl chloride, and *trans*-1-hexenylmercuric chloride in 10 mL of CH_2Cl_2 at ~25 °C. [b] GLC yield corrected by the use of an internal standard. [c] Transmetalation reaction possible.

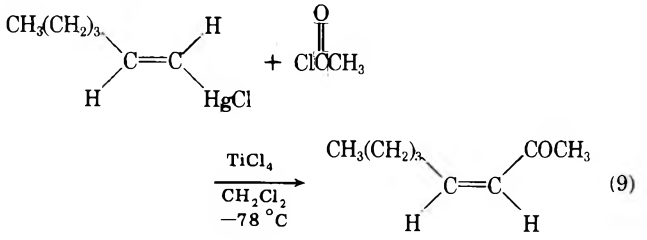
Table II. Effect of Solvents on the Reaction of *trans*-1-Hexenylmercuric Chloride and Acetyl Chloride[a]

Lewis acid	Time, h	Solvent	% yield of 3-octen-2-one[b] Cis	Trans	Total
$AlBr_3$	24	DMF[c]	1	2	3
		HMPA[d]	0	4	4
	0.25	$CHCl_3$	9	6	15
		$C_6H_5NO_2$	13	13	26
		CH_3NO_2	Trace	21	21
		CH_2Cl_2	44	49	93
$AlCl_3$	24	DMF[c]	0	0	0
		Et_2O	0	0	0
		HMPA[d]	0	2	2
	0.25	$CHCl_3$	0	4	4
	18	THF[e]	3	19	22
	0.25	$C_6H_5NO_2$	19	19	38
		CH_3NO_2	14	26	40
		CH_2Cl_2	5	95	100

[a] A 1-mmol amount each of Lewis acid, acetyl chloride, and *trans*-1-hexenylmercuric chloride in 10 mL of solvent at ~25 °C. [b] GLC yield corrected by the use of an internal standard. [c] DMF, *N,N*-dimethylformamide. [d] HMPA, hexamethylphosphoramide. [e] THF, tetrahydrofuran.

improvement never equalled the stereospecificity of the room-temperature reaction of aluminum chloride. The stereospecificity observed with aluminum chloride was relatively insensitive to changes in reaction temperature.

The stereospecificity of the titanium tetrachloride reaction was especially interesting. At −78 °C the major product observed was the cis-enone resulting from inversion of stereochemistry about the carbon-carbon double bond (eq 9). This



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reaction will be discussed in greater detail later.

Studies to determine the optimum reaction time showed that the aluminum chloride reaction was complete in less than 5 min, while aluminum bromide required 30 min to reach completion (Table IV).

The recent report that $Pd(PPh_3)_4$ catalyzes the reaction of

Table III. Effect of Temperature on Stereospecificity in the Reaction of *trans*-1-Hexenylmercuric Chloride and Acetyl Chloride[a]

Lewis acid	Temp, °C	Time, h	% yield of 3-octen-2-one[b] Cis	Trans	Total
$AlBr_3$	25	0.5	44	49	93
	0		35	64	99
	−22		37	61	98
	−78		16	84	100
$AlCl_3$	25	0.25	5	95	100
	0		8	86	94
	−22		8	92	100
	−78		5	88	93
$TiCl_4$	25	0.25	23	76	99
	−78		29	6	35
		3	91	3	94

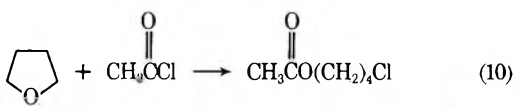
[a] A 1-mmol amount each of *trans*-1-hexenylmercuric chloride, acetyl chloride, and Lewis acid in 10 mL of CH_2Cl_2. [b] GLC yield corrected by the use of an internal standard.

Table IV. Effect of Time on the Reaction of *trans*-1-Hexenylmercuric Chloride and Acetyl Chloride at 25 °C[a]

Lewis acid	Time, min	% yield of 3-octen-2-one[b] Cis	Trans	Total
$AlBr_3$	1	18	41	59
	5	19	41	60
	20	23	42	65
	30	44	49	93
	1440	0	51	51
$AlCl_3$	1	5	86	91
	5	5	95	100
	15	5	95	100
	30	7	93	100
	60	6	94	100
	1440	10	90	100

[a] A 1-mmol amount each of *trans*-1-hexenylmercuric chloride, acetyl chloride, and Lewis acid in 10 mL of CH_2Cl_2. [b] GLC yield corrected by the use of an internal standard.

dialkyl- or diarylmercurials with acid bromides[14] led us also to try various transition-metal catalysts on this system. The results of this study are summarized in Table V. Only two systems proved to be of any utility, $Pd(PPh_3)_4$ in HMPA and $[ClRh(CO)_2]_2$ in dichloromethane. Neither of these systems worked as well as the aluminum chloride promoted reaction. Some interesting observations were made, however. Two reactions were observed when the rhodium catalysts were tried in THF, neither of which was expected. The acetyl chloride reacted with the solvent to give 1-acetoxy-4-chlorobutane (eq 10), while the vinylmercuric chloride reacted with itself to form a symmetrical 1,3-diene (eq 11). In HMPA only the



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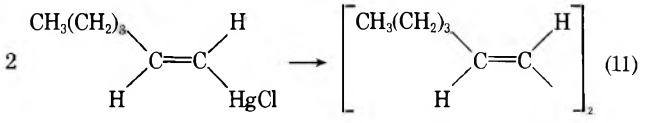


(11)

symmetrical 1,3-diene was observed. This latter reaction provided the basis for our recently reported catalytic procedure for the synthesis of symmetrical 1,3-dienes.[15]

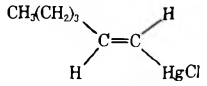
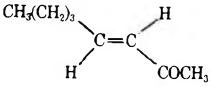
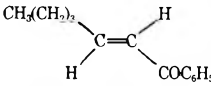
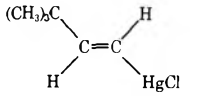
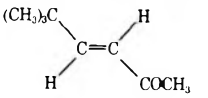
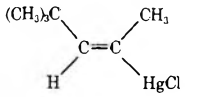
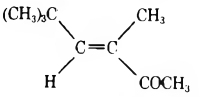
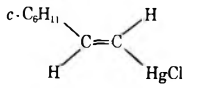
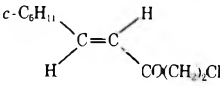
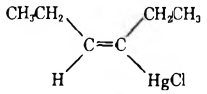
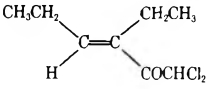
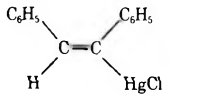
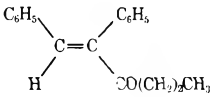
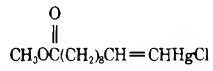
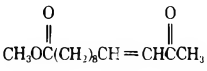
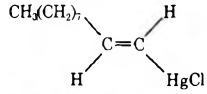
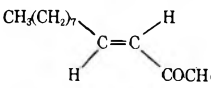
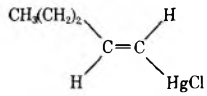
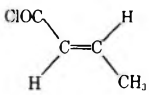
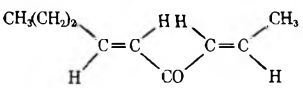
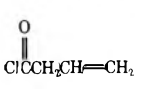
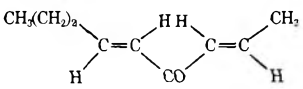
Synthesis of α,β-Unsaturated Ketones. Using our best reaction conditions, aluminum chloride in dichloromethane, we have examined the scope of this new α,β-unsaturated ketone synthesis. All reactions were carried out at room tem-

Table V. Transition Metal Catalyzed Reaction of *trans*-1-Hexenylmercuric Chloride and Acetyl Chloride[a]

Catalyst[b]	Solvent[c]	Time, h	Temp, °C	% yield of 3-octen-2-one[d] Cis	Trans	Total
$[(C_6H_5)_3P]_2Rh(CO)Cl$	CH_2Cl_2	0.5	0	7	7	14
		6	25	4	12	16
	THF	24		0	7	7[e]
$[(C_6H_5)_3P]_3RhCl$	THF	24	25	0	0	0
$Pd[P(C_6H_5)_3]_4$	THF	24	25	0	0	0
	HMPA	6		0	45	45[f]
			60	0	46	46[f]
				0	58	58
			100	0	45	45[f]
$[ClRh(CO)_2]_2$[g]	CH_2Cl_2	1	25	0	24	24[h]
	THF	6		0	0	0[e]
	HMPA	1.5		0	0	0[i]

[a] A 1-mmol amount each of *trans*-1-hexenylmercuric chloride and acetyl chloride. [b] A 10% catalyst based on vinylmercuric chloride. [c] A 10-mL volume. [d] GLC yield corrected by the use of an internal standard. [e] The two major products were 1-acetoxy-4-chlorobutane and *trans,trans*-5,7-dodecadiene. [f] A 1% palladium reagent. [g] A 5% dimeric rhodium catalyst. [h] *trans,trans*-5,7-Dodecadiene is also seen. [i] Only *trans,trans*-5,7-dodecadiene is seen.

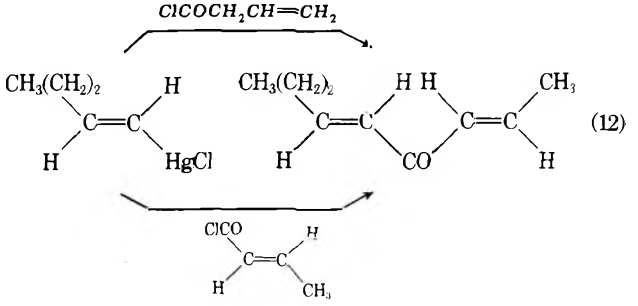
Table VI. Synthesis of α,β-Unsaturated Ketones[a]

Vinylmercurial	Registry no.	Acid chloride	Registry no.	Ketone	Registry no.	Isolated yield %
	50874-36-7	$ClCOCH_3$	75-36-5		18402-82-9	97
		$ClCOC_6H_5$	98-88-4		64235-53-6	64[b]
	36525-02-7	$ClCOCH_3$			20859-11-4	95
	38010-69-4				23732-17-4	99
	36525-01-6	$ClCO(CH_2)_2CH_3$	141-75-3		61759-47-5	96
	36525-04-9	$ClCOCHCl_2$	79-36-7		61759-48-6	89[c]
	16188-35-5	$ClCO(CH_2)_2CH_3$			61798-66-1	72[d]
		$ClCOCH_3$				100[e]
	56453-77-1	$ClCOCH(CH_3)_2$	79-30-1		61759-50-0	97
	36525-00-5		625-35-4		61759-51-1	97
			1470-91-3			91

[a] A 10-mmol amount each of vinylmercurial, acid chloride, and aluminum chloride in 100 mL of CH_2Cl_2 stirred for 5 min at room temperature. [b] GLC yield containing 14% cis ketone. [c] Ketone decomposes readily. [d] Ketone separated from a mixture of *cis*- and *trans*-stilbene by column chromatography. [e] Both the vinylmercuric chloride and ketone are cis, trans mixtures.

perature for 5 min. A series of vinylmercurials and acid chlorides were examined. The results are summarized in Table VI. The isolated yields are generally greater than 95%, with stereochemical purity also greater than 95% in most cases. Alkyl-, aryl-, and functionally substituted vinylmercurials were all found to work well. Aliphatic, unsaturated, and aryl acid

chlorides were also found to work satisfactorily. α,β-Unsaturated acid chlorides reacted cleanly to produce fully conjugated dienones in high yield. β,γ-Unsaturated acid chlorides, on the other hand, react to produce the same dienones as the α,β isomers (eq 12). Esters are tolerated in the mercurial



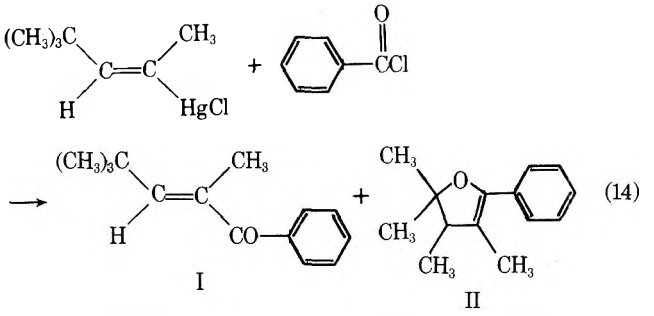
(12)

component, and halides should be tolerated in either component of the reaction.

Six systems were tried unsuccessfully. Pivaloyl chloride decarbonylated under the influence of aluminum chloride before the vinylmercurial could be added to the reaction flask. Neither levulinyl chloride nor methylsuccinyl chloride (prepared from succinic anhydride[16]) reacted as desired. Vinylmercuric chloride reacted with 3,3-dimethylbutyryl chloride to produce 5,5-dimethyl-1-hexen-3-one and 1-chloro-5,5-dimethyl-3-hexanone in approximately equal amounts (eq 13). We were unable readily to eliminate HCl from the β-chloro ketone on treatment with base. (*E*)-3-Acetoxy-2-chloromercuri-2-butene was reacted with isobutyryl chloride, but the product mixture obtained showed an NMR spectrum much too complex to be the desired product.

$$(CH_3)_3CCH_2COCl + CH_2{=}CHHgCl \rightarrow (CH_3)_3CCH_2COCH{=}CH_2 + (CH_3)_3CCH_2COCH_2CH_2Cl \quad (13)$$

Two products, I and II, were obtained when benzoyl chloride was reacted with (*E*)-2-chloromercuri-4,4-dimethyl-2-pentene (eq 14). This reaction takes longer than with aliphatic



(14)

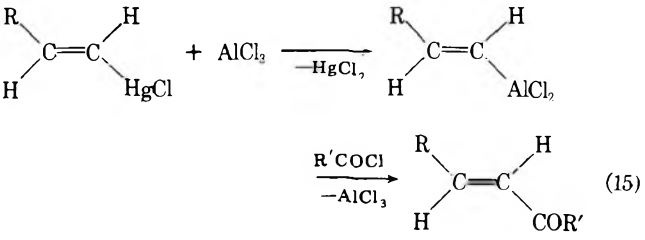
acid chlorides. Initially the two products are obtained in approximately equal amounts, but by the time the reaction is complete the dihydrofuran predominates. Further discussion of this reaction will be put off until the mechanistic discussion.

Reactions with Titanium Tetrachloride. As indicated earlier, unusual stereochemical results were found when examining the reaction of *trans*-1-hexenylmercuric chloride, acetyl chloride, and titanium tetrachloride at −78 °C. When this reaction was scaled up to 10 mmol an isolated yield of 78% *cis*-3-octen-2-one was obtained. A 3-h reaction period was necessary, and less than 3% of the trans isomer was seen by NMR.

A number of other acid chlorides and vinylmercurials were examined in this reaction. Three acid chlorides were tried with *trans*-1-decenylmercuric chloride, but it appears that this mercurial is very unreactive toward acid chlorides and titanium tetrachloride. Both *trans*-cyclohexylethenylmercuric chloride and *trans*-3,3-dimethyl-1-butenylmercuric chloride also failed to react with acetyl chloride at −78 °C after 3 h. Raising the reaction temperature to −45 °C gave only the trans enone.

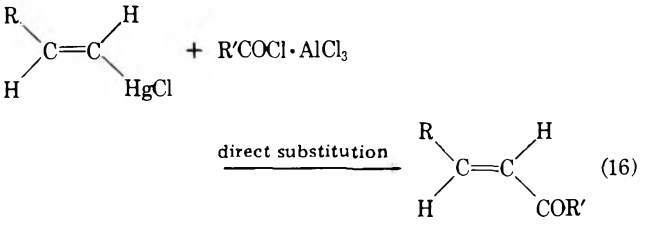
Three other acid chlorides, butyryl chloride, 3-methylbutyryl chloride, and 3,3-dimethylbutyryl chloride, were then tried with *trans*-1-hexenylmercuric chloride, but mixtures of cis and trans enones were always obtained. Finally, the reaction of *trans*-1-hexenylmercuric chloride and butyryl chloride was chosen as a model system for further studies. In studying this reaction the following variables were investigated: reaction time (6 h was usually optimum), reaction temperature (warmer than −78 °C decreased the amount of cis isomer seen), stoichiometry, and the order and mode of addition of the reagents. Only a random array of yields were obtained, and after much frustration it was decided that this reaction was not sufficiently reproducible to make it of value synthetically.

Mechanism. *There are at least three possible mechanisms* that can be written for the aluminum chloride promoted reactions: (1) the formation of a vinylalane by transmetallation with aluminum chloride, followed by acylation (eq 15); (2)



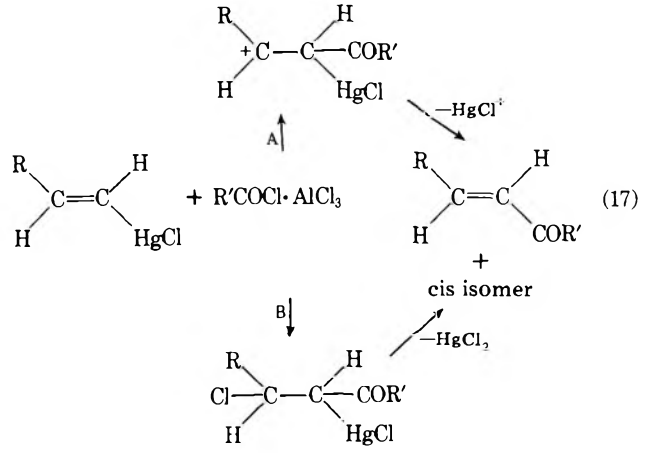
(15)

direct electrophilic substitution at the carbon–mercury bond (eq 16); and (3) addition of the acid chloride–aluminum



(16)

chloride complex to the carbon–carbon double bond, followed by elimination of mercuric chloride to form the α,β-unsaturated ketone (eq 17).



(17)

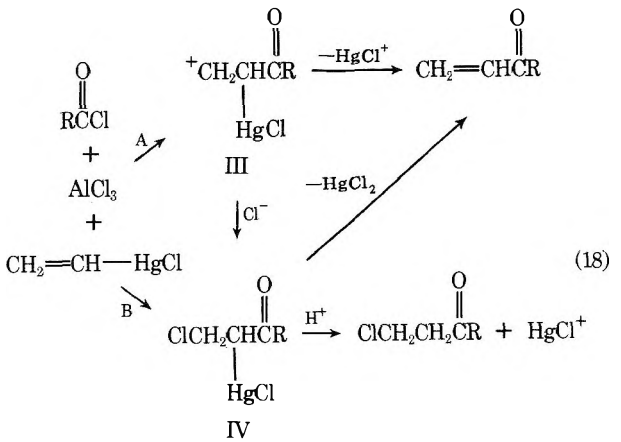
In order to investigate the first possible mechanism, two exchange reactions were investigated. Aluminum chloride was reacted with either *trans*-1-decenylmercuric chloride or stilbenylmercuric chloride in methylene chloride, and the reaction was quenched with 10% sodium hydroxide. If exchange occurred, the vinylalane formed would be expected to react with water to form a hydrocarbon. If no exchange oc-

curred, no hydrocarbon would be observed. A basic quench was used to prevent the generation of acid from hydrolysis of the unreacted aluminum chloride, which could then cleave the carbon–mercury bond. Quenching the stilbenylmercuric chloride–aluminum chloride mixture after 5 min at room temperature led to a 14% yield of *cis*- and *trans*-stilbenes. The reaction of *trans*-1-decenylmercuric chloride and aluminum chloride resulted in a 7% yield of 1-decene when quenched after 5 min. Quenching after 3 h did not increase the yield of hydrocarbon in either reaction. *trans*-1-Decenylmercuric chloride was chosen for the ease of analyzing the resultant hydrocarbon, while stilbenylmercuric chloride was chosen because stilbene was seen in its reaction with butyryl chloride (see Table VI). From these results it appears that stilbene may have arisen from acid cleavage of the starting mercurial. In conclusion, it appears that the first mechanism (vinylmercurial exchange with aluminum chloride) is unlikely since exchange does not occur quickly enough to account for a near-quantitative yield of ketone in less than 5 min. However, one cannot rule out the very rapid acylation of a vinylalane generated in only minor amounts through an unfavorable transmetallation equilibrium.

The second and third mechanisms must both be considered seriously. Direct electrophilic cleavage at the carbon–mercury bond would be expected to result in complete retention of stereochemistry. A large portion of the reaction could be occurring by this route since the reaction is highly stereospecific. However, the presence of small quantities of *cis*-α,β-unsaturated ketone suggests that at least some of the product might arise from an addition–elimination mechanism. Another possibility is that the cis isomer arises from Lewis acid isomerization of the trans enone. Isomerization of the enones in this fashion does not appear to occur, as will be discussed later in this section.

Three reactions tend to support the addition–elimination mechanism: (1) the reaction of 3,3-dimethylbutyryl chloride with vinylmercuric chloride, which gives 5,5-dimethyl-1-hexen-3-one and 1-chloro-5,5-dimethyl-3-hexanone (eq 13); (2) the reaction of benzoyl chloride with (*E*)-4,4-dimethyl-2-chloromercuri-2-pentene, which gives (*E*)-1-phenyl-2,4,4-trimethyl-2-penten-1-one (I) and 4,5-dihydro-2-phenyl-3,4,5,5-tetramethylfuran (II) (eq 14); and (3) the titanium tetrachloride promoted reactions, which result in a high percentage of stereochemically inverted enones. Each of these will be discussed in turn.

In the reaction of vinylmercuric chloride with 3,3-dimethylbutyryl chloride, the formation of the β-chloro ketone could arise from either route shown in eq 18. The β-chloromercurial

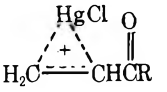


(18)

IV

R = $(CH_3)_3CCH_2$

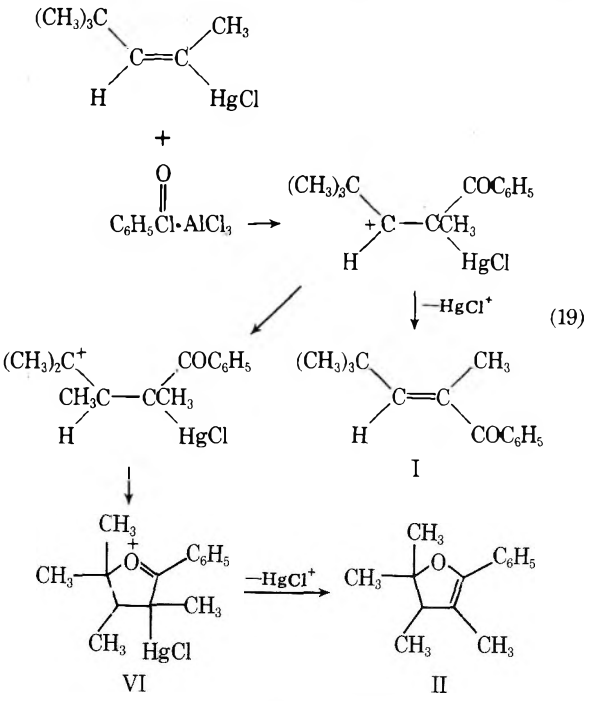
IV is probably an intermediate in the reaction. Carbonium ion III, or a mercurinium ion V, may be an intermediate or merely a transition state on the way to IV. The unsaturated ketone



V

can arise from either III by elimination of a chloromercury ion or IV by elimination of mercuric chloride. The β-chloro ketone probably comes from IV by acid cleavage of the carbon–mercury bond. α-Chloromercuri ketones, such as IV, have previously been reported to be especially vulnerable to acid cleavage.[17] The acid could arise either from an impurity in aluminum chloride or on aqueous workup.

Studies on the reaction of benzoyl chloride and (*E*)-4,4-dimethyl-2-chloromercuri-2-pentene (eq 14) suggest that the dihydrofuran II arises directly from starting materials by rearrangement of an intermediate carbonium ion (eq 19).



(19)

I

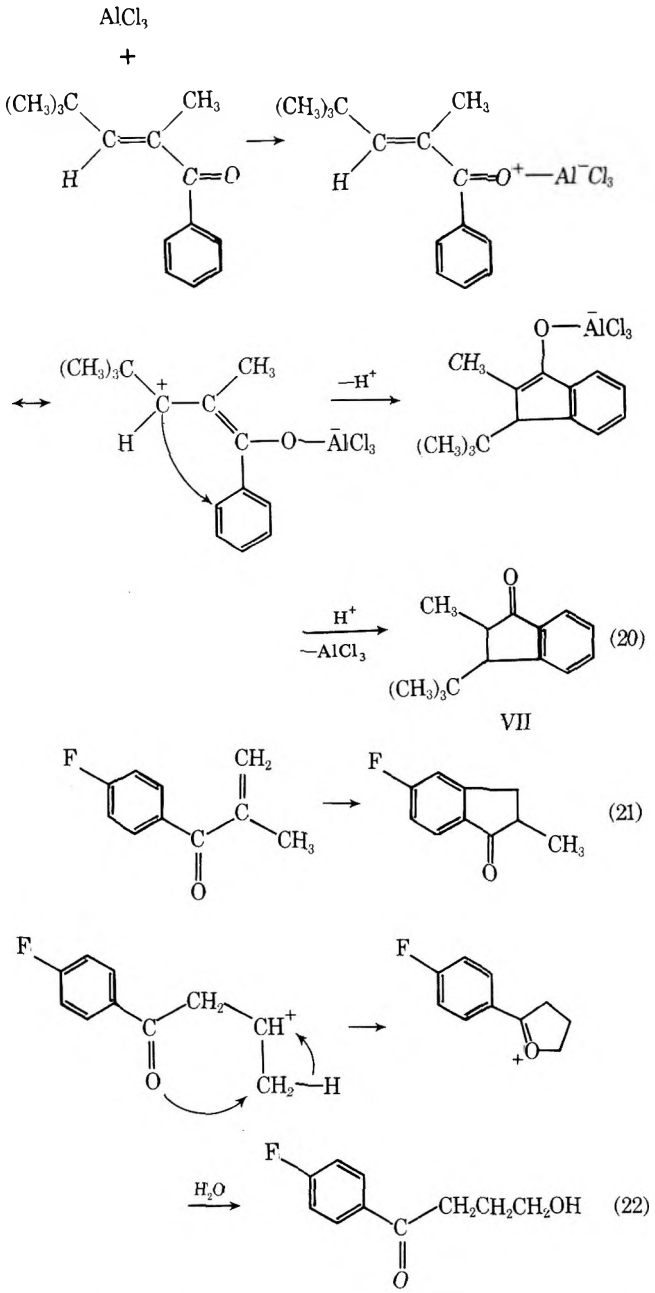
VI

II

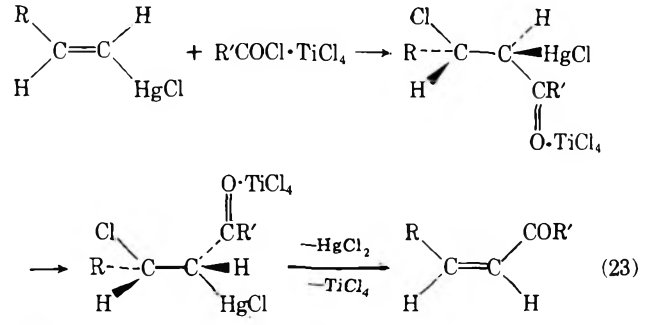
Sampling the reaction after short reaction times showed that both enone I and dihydrofuran II were present in the reaction shortly after mixing, but enone I reached a maximum yield of 31% in 1 h and then decreased to 20%, while the yield of dihydrofuran II continued to rise until reaching 45% after 6 h. Dihydrofuran II is stable under the reaction conditions. Stirring II with aluminum chloride does not result in rearrangement. Stirring enone I with equimolar amounts of aluminum chloride and mercuric chloride did not result in any rearrangement. However, excess aluminum chloride caused complete rearrangement to 2-methyl-3-*tert*-butyl-1-indanone (VII) (eq 20). Small amounts of indanone VII were also observed in the reaction of benzoyl chloride and (*E*)-4,4-dimethyl-2-chloromercuri-2-pentene. The structures of the rearrangement products II and VII were assigned on the basis of spectral data. Since both enone I and dihydrofuran II arise directly as the reaction progresses, it appears that this reaction at least occurs by an addition–elimination mechanism.

Literature precedent exists for much of the chemistry observed in this system. Pines observed that 4′-fluoro-2-methylacrylophenone cyclized to 2-methyl-5-fluoro-1-indanone under the influence of aluminum chloride or sulfuric acid (eq 21).[18] A cyclic oxonium ion was also observed by ^{13}C NMR in their studies (eq 22). This shows the plausibility of intermediate VI (eq 19), which would be expected to lose $HgCl^+$ and form the dihydrofuran II.

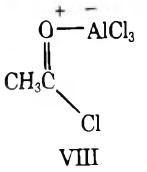
The titanium tetrachloride reaction probably proceeds by an addition–elimination reaction as well. Either a trans-



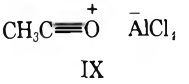
addition, trans-elimination or cis-addition, cis-elimination sequence would be expected to result in stereochemical inversion of the carbon–carbon double bond. Such a trans-addition, trans-elimination sequence has been proposed previously to explain the formation of a *trans*-vinyl bromide from the bromination of a *cis*-alkenylmercuric bromide.[19] A similar scheme may be invoked to explain the inversion of stereochemistry here (eq 23).



The difference between the reaction of aluminum chloride and titanium tetrachloride may be in the nature of the complex formed with the acid chloride or in the formation of different intermediates in the two reactions. In an effort to determine if a difference in the Lewis acid complex was responsible for the difference in the course of these reactions, infrared studies on the $TiCl_4$- and $AlCl_3$–acetyl chloride complexes were carried out. Cook reported that, if acetyl chloride is complexed through the oxygen (VIII), the C=O



VIII



IX

stretch is lowered from 1808 to 1637 cm^{-1}, while formation of an acylium ion (IX) raises the absorption to 2307 and 2203 cm^{-1}.[20] Cook found all three absorptions in a neat mixture of acetyl chloride and aluminum chloride, while in chloroform only the 1637-cm^{-1} absorption was seen. We have found that equal amounts of aluminum chloride and acetyl chloride in dichloromethane at 25 °C gives rise to absorptions at 1805 and 1640 cm^{-1} with little decrease in the strength of the 1805-cm^{-1} band. Likewise, equimolar amounts of $TiCl_4$ and acetyl chloride at 25 °C give rise to both the 1805- and 1630-cm^{-1} bands. The slight difference in frequencies for the complexes may indicate slightly tighter complexing for $TiCl_4$ than for $AlCl_3$. *The intensity of the 1805-cm^{-1} band in the titanium* tetrachloride reaction decreased by ~10% on standing for 2 h, indicating a relatively small degree of complexation. Similar results were seen for aluminum chloride. These results do not appear to account for the differences in the stereochemistry of the two reactions.

The final point of discussion concerns the stability of the products under the reaction conditions. Stirring *trans*-3-octen-2-one with 1 equiv of aluminum chloride at room temperature in dichloromethane, or with equimolar amounts of aluminum chloride and mercuric chloride, showed that 96 and 91%, respectively, of the trans enone was still present in the reaction mixture after 8 h. After 27 h, the yields of ketone were 86 and 87%, respectively. No cis enone was seen in either reaction. Quite clearly the cis product is not arising by isomerization of the trans enone.

The isomerization of cis enones was studied on *cis*-5-decen-4-one. Stirring the cis enone with aluminum chloride at room temperature resulted in a 91:5% cis/trans mixture after 5 min and a 43:22% mixture of enones after 24 h. An equimolar mixture of aluminum chloride and mercuric chloride resulted in a 95:5% cis/trans mixture after 5 min and a 5:35% mixture after 24 h. The titanium tetrachloride isomerization was studied in the same manner. With the cis enone, after 5 min no trans enone was seen and 88% of the cis enone remained. After 24 h, only traces of either enone were observed. After 5 min with equimolar amounts of titanium tetrachloride and mercuric chloride, 3% trans enone was observed while 84% of the cis enone remained. After 24 h, 2% of each enone was observed.

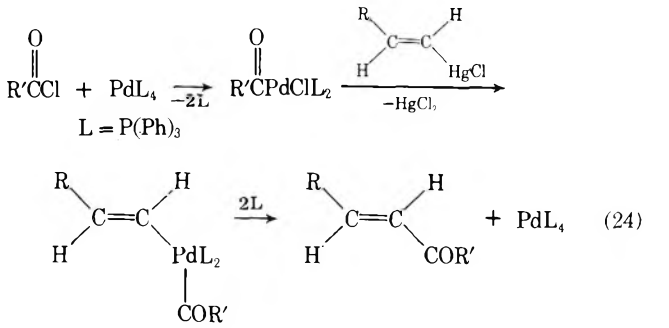
Based on the evidence obtained, it appears that the Lewis acid promoted acylation of vinylmercuric chlorides proceeds by way of an addition–elimination reaction. While the evidence is not conclusive, all of the side reactions discussed, as well as the formation of small amounts of cis enone observed in most reactions, may be explained by this mechanism. However, none of the data available precludes a direct substitution reaction as being the major route with small amounts of addition–elimination, accounting for the small amounts of the less stable cis enones.

The titanium tetrachloride reaction most likely proceeds via trans addition, trans elimination or cis addition, cis elimination, both of which would result in inversion of stereochemistry around the carbon–carbon double bond. However,

experimental evidence which could either prove or disprove this proposal is lacking.

Enone isomerization probably does not account for the small amounts of cis enone observed with aluminum chloride or the substantial yields of cis enone with titanium tetrachloride.

The transition metal catalyzed reaction is envisioned as involving an initial oxidative addition between $Pd(PPh_3)_4$ and the acid chloride. Transfer of the vinyl group from the mercurial to the resulting acylpalladium species and subsequent reductive elimination would then provide the α,β-unsaturated ketone and regenerate the catalyst (eq 24). An identical



(24)

mechanism has been suggested previously for the palladium(0)-catalyzed acylation of dialkyl- and diarylmercurials[14] and is entirely consistent with the known chemistry of palladium.

Conclusion

α,β-Unsaturated ketones can be readily prepared from vinylmercurials and acid chlorides. Best yields and stereochemical purity are obtained when one employs 1 equiv of aluminum trichloride in methylene chloride and the reaction is run 5 min at room temperature. Substitution of titanium tetrachloride for aluminum chloride at −78 °C gives enones of inverted stereochemistry, but the results are not reproducible. Catalytic amounts of $Pd(PPh_3)_4$ in HMPA will also promote acylation of the vinylmercurials, but the yields are lower than the aluminum trichloride reactions. Rhodium(I) catalysts give still lower yields. Mechanistically, the formation of the major side products and stereochemically inverted enones seems best explained by a mechanism involving the addition of a Lewis acid–acid chloride complex to the carbon–carbon double bond of the vinylmercurial and subsequent mercuric chloride elimination. It is not possible at present to decide whether the major products are produced by the same mechanism or by direct electrophilic acylation of the carbon–mercury bond.

Experimental Section

Reagents. All chemicals were used directly as obtained commercially unless otherwise noted. HMPA was distilled from lithium aluminum hydride under vacuum. Dichloromethane was shaken with concentrated sulfuric acid, washed with water and saturated sodium chloride, dried over calcium chloride, and distilled. Ether and THF were distilled from $LiAlH_4$.

The vinylmercuric chlorides used were prepared according to literature procedures and have all been described previously.[9,10,15]

$(Ph_3P)_2Rh(CO)Cl$ (Alfa Inorganics–Ventron), $[ClRh(CO)_2]_2$ (PCR), aluminum chloride (Fisher Scientific), and aluminum bromide (Fisher Scientific) were all used directly as obtained commercially. Wilkinson's catalyst, $(Ph_3P)_3RhCl$, was prepared according to published procedures.[21]

All GLC yields are corrected by the use of appropriate hydrocarbon internal standards and calculated correction factors.

Reaction of Styrylmercuric Chloride with Acetyl Chloride. The following procedure for the reaction of styrylmercuric chloride and acetyl chloride is representative. Styrylmercuric chloride (1.0mmol), acetyl chloride (1.0 mmol), and an internal hydrocarbon standard were dissolved in *N,N*-dimethylformamide (DMF) (10 mL) under nitrogen. Aluminum bromide (1.0 mmol) was then added, and the reaction was stirred for 24 h at 25 °C. A solid formed in the reaction, and the liquid was decanted into 3 M sodium thiosulfate and ether was added. The ether was then analyzed by GLC (10′ DC-550 at 200 °C).

Distyrylmercury (0.5 mmol) was used in some reactions in the place of styrylmercuric chloride (1.0 mmol). When water-immiscible solvents were used for the reaction, samples were taken and quenched with water before GLC analysis.

The GLC correction factor was calculated using a commercial sample of *trans*-4-phenyl-3-buten-2-one. The product was verified by comparison with the commercial authentic sample.

Reaction of trans-1-Hexenylmercuric Chloride and Acetyl Chloride. An authentic sample of *trans*-3-octen-2-one was prepared according to the literature procedure.[22] 1-Hexene (12.5 mL, 100 mmol) was dissolved in a mixture of acetic acid (5.6 mL) and trifluoroacetic anhydride (14.0 mL) and stirred at room temperature for 20 min, then 40 °C for 1.5 h, and finally at room temperature overnight. The product was distilled under aspirator vacuum and then GLC prepped: ^1H NMR (CCl_4) δ 0.92 (3 H, not resolved, CH_3), 1.40 (4 H, m, $-CH_2CH_2-$), 2.18 (3 H, s, $COCH_3$), 2.2 (2 H, m, $CH_2CH=$), 5.95 (1 H, d, J = 17 Hz, COCH=), 6.80 (1 H, d t, J = 17, 7 Hz, COCH=CH); IR (max) (thin film) 2970, 2950, 2860, 1675, 1630, 1460, 1430, 1360, 1255, 1180, 980, 930, 735 cm^{-1}; MS m/e 126.1042 ± 0.0006 (calcd for $C_8H_{14}O$, 126.1045). Further samples of *trans*-3-octen-2-one were prepared by the procedure developed in this work.

The following procedure is representative of that used in the model studies in this section. Tetradecane, *trans*-1-hexenylmercuric chloride (1.0 mmol), and acetyl chloride (1.0 mmol) were dissolved in dichloromethane (10 mL). Aluminum bromide (1.0 mmol) was added and the reaction stirred at room temperature under nitrogen. Samples (0.5 mL) were taken, added to water, and then analyzed by GLC.

When temperatures other than room temperature were desired, the vinylmercurial and acid chloride were added and cooled down to the desired temperature in the appropriate temperature bath before the Lewis acid was added. Samples were taken as above. Addition of the vinylmercurial to a solution of Lewis acid and acid chloride also results in a satisfactory reaction.

In studying the effect of various Lewis acids (Table I), all variables were kept constant except reaction time and the Lewis acid. The solvents were investigated at room temperature for the time periods listed in Table II. Likewise, the effects of temperature, Table III, and reaction time, Table IV, were studied holding all other variables constant.

The transition metal catalyzed reactions were studied as with the Lewis-acid reactions. The transition-metal complex (0.1 mmol) was added to a solution of the vinylmercuric chloride and acid chloride in the appropriate solvent and analyzed by GLC after the appropriate workup. The ether and dichloromethane reactions were quenched with water. The THF reactions were quenched with saturated ammonium chloride, and the HMPA reactions were quenched by adding water and ether and then analyzing the ether layer, or by analyzing without quenching.

The side products in the transition-metal reactions were identified as follows. In THF, the product from the reaction of acetyl chloride and THF, 1-acetoxy-4-chlorobutane, had a GLC retention time (10% DC-550, 10 ft, 150 °C) very similar to that for *trans*-3-octen-2-one and was determined to be different by coinjecting ketone and the reaction mixture and observing two peaks. The side product was confirmed to have come from THF by stirring the rhodium catalyst, THF, and acetyl chloride in the absence of vinylmercurial and observing a product of identical retention time by coinjection with the above reaction mixture. 1-Acetoxy-4-chlorobutane (prepped by GLC): ^1H NMR (CCl_4) δ 1.8 (4 H, m, $-CH_2CH_2-$), 2.02 (3 H, s, $COCH_3$), 3.6 (2 H, m, CH_2Cl), 4.1 (2 H, m, CH_2OCOCH_3); IR (max) (thin film) 2960, 1740, 1450, 1240, 1045, 950, 880, 750, 720 cm^{-1}.

The structure of the symmetrical 1,3-diene from the reaction of *trans*-1-hexenylmercuric chloride and the rhodium catalyst in the presence of acetyl chloride (eq 11) was confirmed by spectral data and GLC comparison with an authentic sample of diene prepared by our own published procedure.[15]

Synthesis of α,β-Unsaturated Ketones. The following synthesis of *trans*-3-octen-2-one is representative. To a thoroughly dried round-bottom flask equipped with a septum inlet and flushed with nitrogen was added dichloromethane (100 mL), aluminum chloride (1.33 g, 10 mmol), and acetyl chloride (0.80 mL, 10 mmol). After stirring briefly *trans*-1-hexenylmercuric chloride (3.1 g, 10 mmol) was added while backflushing with nitrogen, and the reaction was stirred for 5 min. A white solid (presumably mercuric chloride) precipitated almost immediately. The reaction mixture was then poured into

water, and the layers were separated. The aqueous layer was extracted with dichloromethane. The organic layer was then washed with 5% sodium bicarbonate, 3 M sodium thiosulfate, and water. The combined aqueous washes were reextracted with dichloromethane, and the combined organic layers were dried over anhydrous sodium sulfate. Removal of solvent yielded 1.22 g (97%) of essentially pure *trans*-3-octen-2-one as a colorless oil. GLC analysis showed 5% or less of the undesired cis isomer. Spectral properties were identical with those of an authentic sample prepared earlier by an alternate method.

The following compounds were prepared in like manner.

***trans*-5,5-Dimethyl-3-hexen-2-one:** ^{1}H NMR (CCl_4) δ 1.10 (9 H, s, $C(CH_3)_3$), 2.15 (3 H, s, $COCH_3$), 5.90 (1 H, d, J = 16 Hz, COCH=), 6.70 (1 H, d, J = 16 Hz, COCH=CH); IR (max) (thin film) 3030, 2950, 2860, 1680, 1620, 1365, 1290, 1250, 980 cm^{-1}; MS *m/e* 126.1044 ± 0.0006 (calcd for $C_8H_{14}O$, 126.1045).

(*E*)-3,5,5-Trimethyl-3-hexen-2-one: ^{1}H NMR (CCl_4) δ 1.20 (9 H, s, $C(CH_3)_3$), 1.83 (3 H, d, J = 1.5 Hz, $=CCH_3$), 2.20 (3 H, s, $COCH_3$), 6.50 (1 H, q, J = 1.5 Hz, CH=); IR (max) (thin film) 2960, 2860, 1680, 1640, 1470, 1370, 1250, 1200, 1030 cm^{-1}; MS *m/e* 140.1201 ± 0.0007 (calcd for $C_9H_{16}O$, 140.1201).

***trans*-1-Cyclohexyl-1-hexen-3-one:** ^{1}H NMR (CCl_4) δ 0.9 (3 H, t, J = 6 Hz, CH_2CH_3), 1–2 (13 H, m, c-C_6H_{11} and CH_2CH_3), 2.3 (2 H, t, J = 7 Hz, $COCH_2$), 5.90 (1 H, d, J = 16 Hz, COCH=CH), 6.65 (1 H, d d, J = 16, 6 Hz, COCH=CH); IR (max) (thin film) 2920, 2840, 1670, 1620, 1448, 1365, 1190, 978 cm^{-1}; MS *m/e* 180.1512 ± 0.0009 (calcd for $C_{12}H_{20}O$, 180.1514).

(*E*)-1,1-Dichloro-3-ethyl-3-hexen-2-one: ^{1}H NMR (CCl_4) δ 1.1 (6 H, overlapping triplets, J = 7 Hz, CH_3's), 2–2.6 (4 H, m, J = 7 Hz, CH_2's), 5.5 (1 H, t, J = 7 Hz, CH=C), 6.0 (1 H, s, $COCHCl_2$); IR (max) (thin film) 2950, 2920, 2860, 1660–1640, 1460, 1375, 1310, 1250, 1210, 1140, 1080, 990, 790, 760, 735 cm^{-1}; sample decomposed before mass spectra could be obtained.

(*E*)-1,2-Diphenyl-1-hexen-3-one: ^{1}H NMR (CCl_4) δ 0.90 (3 H, t, J = 7 Hz, CH_3), 1.65 (2 H, sextet, J = 7 Hz, CH_2CH_2CO), 2.50 (2 H, t, J = 7 Hz, CH_2CO), 7–7.7 (11 H, m, $C_6H_5CH=CC_6H_5$); IR (max) (thin film) 3060, 3030, 1685, 1615, 1595, 1495, 1450, 1200, 1135, 1070, 765, 700 cm^{-1}; MS *m/e* 250.1359 ± 0.0013 (calcd for $C_{18}H_{18}O$, 250.1358).

12-Carbomethoxy-3-dodecen-2-one: ^{1}H NMR δ 1.3 (12 H, br s, CH_2's), 2.1 (3 H, s, $COCH_3$), 2.2 (4 H, m, $=CHCH_2$ and CH_2COOCH_3), 3.55 (3 H, s, $COOCH_3$), 5.95 (1 H, d, J = 16 Hz, COCH=), 6.7 (1 H, d t, J = 16, 7 Hz, COCH=CH) (there is evidence in the NMR of the cis isomer being present as well, but the peaks are poorly resolved); IR (max) (KBr) 2980, 2920, 2850, 1745, 1680, 1600, 1470, 1440, 1385, 1340, 1320, 1280, 1245, 1205, 1175, 1000, 980, 880, 720, 690 cm^{-1}; MS *m/e* 240.1721 ± 0.0008 (calcd for $C_{14}H_{24}O_3$, 240.1726).

***trans*-2-Methyl-4-tridecen-3-one:** ^{1}H NMR (CCl_4) δ 1.00 (3 H, t, J = 7 Hz, CH_2CH_3), 1.05 (6 H, d, J = 7 Hz, $CH(CH_3)_2$), 1.3 (12 H, br s, CH_2), 2.2 (2 H, m, $CH_2CH=$), 2.7 (1 H, septet, J = 7 Hz, $CH(CH_3)_2$), 6.0 (1 H, d, J = 16 Hz, COCH=), 6.75 (1 H, dt, J = 16, 7 Hz, COCH=CH); MS *m/e* 210.1989 ± 2.7 (calcd for $C_{14}H_{26}O$, 210.1984).

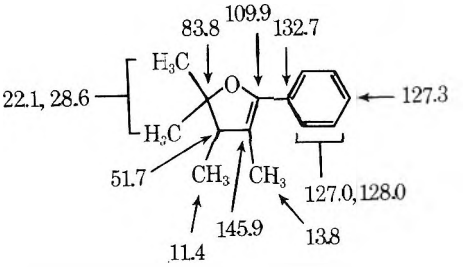
***trans, trans*-2,5-Nonadien-4-one:** ^{1}H NMR (CCl_4) δ 1.00 (3 H, t, J = 7 Hz, CH_2CH_3), 1.5 (2 H, sextet, J = 7 Hz, CH_2CH_3), 1.94 (3 H, d, J = 7 Hz, $=CHCH_3$), 2.20 (2 H, t, J = 7 Hz, $=CHCH_2$), 6.15 (2 H, d, J = 16 Hz, COCH='s), 6.80 (2 H, d t, J = 16, 7 Hz, COCH=CH's); IR (max) (thin film) 3040, 3020, 2950, 2940, 2860, 1665, 1640–1620, 1440, 1380, 1335, 1300, 1200, 1150, 1080, 1040, 980 cm^{-1}; MS *m/e* 138.1040 ± 3.6 (calcd for $C_9H_{14}O$, 138.1045).

***trans*-1-Phenyl-2-hepten-1-one:** ^{1}H NMR (CCl_4) δ 1.00 (3 H, t, J = 7 Hz, CH_3), 1.5 (4 H, m, CH_2CH_2), 2.3 (2 H, m, $=CHCH_2$), 6.85 (2 H, m, vinyl), 7.4 (3 H, m, H_{3-5} of COPh), 7.85, (2 H, m, $H_{2,6}$ of COPh); IR (max) (thin film) 3060, 2960, 2930, 2870, 1670, 1620, 1600, 1580, 1450, 1390, 1280, 1220, 1180, 1000, 980, 920, 880, 860, 790 cm^{-1}; sample identical with a sample prepared from condensing the lithium enolate of acetophenone (lithium diisopropylamide, THF, −78 °C) with valeraldehyde followed by dehydration.[23]

In most reactions the stereochemically inverted enone was evident to the extent of 2–5% by close examination of the vinyl region of the NMR spectrum (chemical shift and coupling constants). These compounds were not, however, characterized further, and it is not clear whether this is a valid representation of the stereochemistry of the reaction or simply an indication of the stereochemical purity of the vinylmercurial starting material.

Reactions with Titanium Tetrachloride. These reactions were investigated in the same manner as were the Lewis-acid reactions previously discussed. Two cis enones were isolated and characterized, *cis*-3-octen-2-one and *cis*-5-decen-4-one. The correction factor used for *cis*-3-dodecene-2-one was measured from a sample of the trans isomer. *cis*- and *trans*-3-octen-2-one agree within ±2% for their correction factors, so that errors introduced by the use of the trans isomer are minimal.

Chart I



Spectral data on the compounds not previously given follow.

***cis*-3-Octen-2-one:** ^{1}H NMR (CCl_4) δ 0.9 (3 H, t, J = 7 Hz, CH_2CH_3), 1.4 (2 H, sextet, J = 8 Hz, CH_2CH_3), 2.1 (5 H, m with s superimposed, $COCH_3$ and $=CHCH_2CH_2$), 3.0 (2 H, t, J = 4 Hz, $=CHCH_2$), 5.5 (2 H, m, CH=CH); IR (max) (thin film) 2940, 2910, 2860, 1715, 1680, 1365, 1160, 965 cm^{-1}; MS *m/e* 126.1047 ± 0.0006 (calcd for $C_8H_{14}O$, 126.1045).

***cis*-5-Decen-4-one:** ^{1}H NMR (CCl_4) δ 0.90 (6 H, t, J = 7 Hz, CH_3's), 1.2–2.1 (6 H, m, 3 CH_2), 2.35 (2 H, t, J = 7 Hz, $COCH_2$), 3.0 (2 H, m, $CH_2CH=$), 5.5 (2 H, m, CH=CH); MS *m/e* 154.1354 ± 2.7 (calcd for $C_{10}H_{18}O$, 154.1358).

***trans*-5-Decen-4-one:** ^{1}H NMR (CCl_4) δ 0.90 (6 H, t, J = 7 Hz, CH_3's), 1.4 (6 H, m, 3 CH_2), 2.3 (2 H, m, $=CHCH_2$), 2.4 (2 H, t, J = 7 Hz, $COCH_2$), 6.1 (1 H, d, J = 16 Hz, COCH=), 6.8 (1 H, d t, J = 16, 7 Hz, COCH=CH); MS *m/e* 154.1357 ± 0.6 (calcd for $C_{10}H_{18}O$, 154.1358).

Mechanism. The exchange reactions of stilbenylmercuric chloride and *trans*-1-decenylmercuric chloride with aluminum chloride were studied as follows. The mercurial (1.0 mmol) and an appropriate internal hydrocarbon standard were dissolved in dichloromethane (10 mL). Aluminum chloride (1.0 mmol) was added, and the reaction mixture was stirred at room temperature. A sample was taken after 5 min and quenched by pouring into 10% sodium hydroxide. Samples were analyzed by GLC. Correction factors were calculated from authentic samples of 1-decene and stilbene.

The isomerization of *trans*-3-octen-2-one by aluminum chloride was studied as follows. *trans*-3-Octen-2-one (0.216 mmol) and an internal standard were dissolved in dichloromethane (2.3 mL). Aluminum chloride (0.271 mmol) was added, and the mixture was stirred at room temperature. Samples were taken at 0.5, 1, 4, 8, and 27 h and quenched with water before GLC analysis. Other isomerizations were studied in like manner. When mercuric chloride was used, it was added in approximately equimolar amounts.

Studies on the reaction of (*E*)-4,4-dimethyl-2-chloromercuri-2-pentene and benzoyl chloride were carried out in the same manner as the reactions of *trans*-1-hexenylmercuric chloride with acetyl chloride.

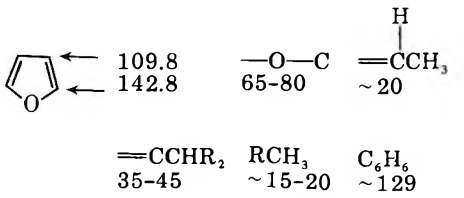
(*E*)-1-Phenyl-2,4,4-trimethyl-2-penten-1-one: ^{1}H NMR (CCl_4) δ 1.3 (9 H, s, $C(CH_3)_3$), 2.1 (3 H, d, J = 1 Hz, $=CCH_3$), 6.15 (1 H, q, J = 1 Hz, COC=CH), 7.5 (5 H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) 13.4 ppm ($=CCH_3$), 30.1 ($C(CH_3)_3$), 33.7 ($C(CH_3)_3$), 127.9 and 129.4 ($C_{2,3}$ of Ph), 131.3 (C_4 of Ph), 134.8 (COC=C), 138.6 C_1 of Ph), 154.6 (COC=C), 200.1 (CO); IR (max) (thin film) 3060, 3030, 2960, 2870, 1650, 1600, 1580, 1470, 1450, 1370, 1315, 1300, 1290, 1210, 1040, 965, 875, 710 cm^{-1}.

4,5-Dihydro-2-phenyl-3,4,5,5-tetramethylfuran: ^{1}H NMR (CCl_4) δ 1.05 (3 H, d, J = 6 Hz, $CHCH_3$), 1.28 and 1.38 (3 H, s, $(CH_3)_2C$), 1.85 (3 H, s, $=CCH_3$), 2.57 (1 H, q, J = 6 Hz, $CHCH_3$), 7.2–7.5 (5 H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) 11.4 ppm ($CHCH_3$), 13.8 ($=CCH_3$), 22.1 and 28.6 ($(CH_3)_2C$), 51.7 ($CHCH_3$), 83.8 ($(CH_3)_2C$), 109.9 (=CPh), 127.0 and 128.0 ($C_{2,3}$ of Ph), 127.3 (C_4 of Ph), 132.7 (C_1 of Ph), 145.9 (C=CCH$_3$); IR (max) (thin film) 3080, 3060, 3020, 2985, 2920, 2860, 1670, 1600, 1500, 1450, 1380, 1365, 1260, 1100, 1070, 990, 860, 770, 690 cm^{-1}; MS *m/e* 202 (parent, 51), 200 (19), 187 (66), 185 (16), 129 (22), 121 (17), 105 (base peak, 100), 97 (19), 77 (36).

2-Methyl-3-*tert*-butyl-1-indanone: ^{1}H NMR (CCl_4) δ 1.00 (9 H, s, $C(CH_3)_3$), 1.23 (3 H, d, J = 7 Hz, $CHCH_3$), 2.50 (1 H, d q, J = 2, 7 Hz, $CHCH_3$), 2.72 (1 H, d, J = 2 Hz, CHC), 7.2–7.8 (4 H, m, C_6H_4); IR (thin film) (max) 3070, 2960, 2870, 1725, 1610, 1460, 1395, 1365, 1325, 1290, 1270, 1230, 1210, 1150, 1085, 960, 930, 920, 790, 745 cm^{-1}; MS *m/e* 202 (parent, 2), 187 (3), 174 (2), 158 (3), 145 (100, parent − *t*-Bu), 131 (27), 116 (15) 104 (6), 57 (17, *t*-Bu).

The ^{13}C NMR assignments (in ppm) for dihydrofuran II are shown in Chart I. The bases for these assignments (in ppm) were taken from

Chart II



"The Chemist's Companion" and are listed in Chart II.[24] Isomerization studies in this system were carried out in the same manner as the isomerization of enones already discussed.

In the reaction of 3,3-dimethylbutyryl chloride with vinylmercuric chloride, **5,5-dimethyl-1-hexen-3-one** was identified by its ^{1}H NMR spectrum: δ 1.0 (9 H, s, $C(CH_3)_3$), 2.4 (2 H, s, CH_2CO), 5.65 (1 H, d d, J = 4, 8 Hz, COCH=), 6.15 (2 H, m, COCH=C**H**$_2$). Further characterization was not carried out.

1-Chloro-5,5-dimethyl-3-hexanone was characterized fully: ^{1}H NMR (CCl_4) δ 1.0 (9 H, s, $C(CH_3)_3$), 2.25 (2 H, s, CCH_2CO), 2.75 (2 H, t, J = 7 Hz, $COCH_2CH_2Cl$), 3.6 (2 H, t, J = 7 Hz, CH_2Cl); IR (max) (thin film) 2940, 1710, 1360, 1180, 830 cm^{-1}; MS m/e 162.0812 ± 0.0008 (calcd for $C_8H_{15}OCl$, 162.0812).

Acknowledgment. We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Research Corporation for financial support (R.C.L.) and the National Science Foundation for an NSF Traineeship (J.C.B.).

Registry No.—1-Acetoxy-4-chlorobutane, 6962-92-1; *trans*-11-chloromercuriundec-10-enoic acid, 56453-79-3; *cis*-11-chloromercuriundec-10-enoic acid, 56453-80-6; *trans*-12-carbomethoxy-3-dodecen-2-one, 61759-52-2; *cis*-12-carbomethoxy-3-dodecen-2-one, 61759-49-7; *cis*-3-octen-2-one, 51193-77-2; *cis*-5-decen-4-one, 64235-54-7; *trans*-5-decen-4-one, 64235-55-8; (*E*)-1-phenyl-2,4,4-trimethyl-2-penten-1-one, 64235-56-9; 4,5-dihydro-2-phenyl-3,4,5,5-tetramethylfuran, 64235-57-0; 2-methyl-3-*tert*-butyl-1-indanone, 64235-58-1; 3,3-dimethylbutyryl chloride, 7065-46-5; 5,5-dimethyl-1-hepten-3-one, 2177-33-5; 1-chloro-5,5-dimethyl-3-hexanone, 64235-59-2.

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Intramolecular Phenoxymercuration of 2-Allylphenols. Regioselectivity and Stereochemistry

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Intramolecular phenoxymercuration of 2-(2-cyclohexenyl)-4-methoxyphenol (1) using $Hg(OAc)_2$ gave 1,2,3,4,4a,9b-hexahydro-4-acetoxymercuri-8-methoxydibenzofuran (**2a**, 59%) as the sole product. The use of $HgCl_2$ in this reaction afforded only 2,4-propano-3-chloromercuri-6-methoxychroman (**3b**, 53%), indicating a change in the regioselectivity of the reaction. The stereochemistry of these mercurials was established by x-ray analyses which showed a trans arrangement of the Hg and the oxygen atom in both cases. That is, the reaction proceeds by an antarafacial addition to the C=C double bond of **1**. The use of mercuric chloroacetates in this reaction, e.g., $Hg(OCOCH_2Cl)_2$, gave both types of products, **2** and **3**, and the formation of the chroman compound **3** increased with increasing the electron-withdrawing property of the acetoxy ligands in $Hg(OCOCX_3)_2$: $OCOCH_3$ < $OCOCH_2Cl$ < $OCOCHCl_2$ < $OCOCCl_3$. This suggests that the difference in regioselectivity observed with $Hg(OAc)_2$ and $HgCl_2$ depends on the electronic effect of the ligands on HgX_2. The use of HgX_2 having ligands more electronegative than acetate, such as X = NO_3 and ClO_4, led to the chroman compound **3**.

The reaction of 2-allylphenols with palladium(II) salts, which we have recently studied,[1,2] generally gives 2-substituted benzo- and/or dihydrobenzofurans. These products are considered to arise from an intramolecular phenoxypalladation process, but the palladation adduct is not isolated in this reaction. A way to produce this adduct may be by a metal-exchange reaction between the corresponding organomercury and palladium salts. Since palladium exchange with orga-

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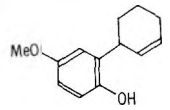
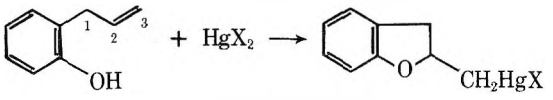
nomercurials has been shown to occur with retention of configuration at carbon,[3,4] the use of an organomercurial of known configuration may shed further light on the stereochemistry of the palladium adduct formed. From such a viewpoint, we planned to prepare the mercurated dihydrobenzofuran derived from 2-(2-cyclohexenyl)-4-methoxyphenol (1) and to define its stereochemistry.



1

The reaction of 2-allylphenol with mercuric(II) salts was first reported by Adams in 1922 to give 2-mercurated methyl-2,3-dihydrobenzofurans.[5] Recently it has been shown that the reaction proceeds through electrophilic attack of Hg(II) on the double bond to produce a positively charged species which is trapped by the nucleophilic neighboring group.[6] In all such intramolecular phenoxymercurations of 2-allylphenols so far reported,[7-11] the internal nucleophilic attack usually occurs at the C-2 carbon of the allylic side chain rather than at the C-3 carbon, thus giving rise to mercurated



dihydrobenzofurans. However, when 1 was allowed to react with mercuric salts, the regioselectivity was found to be markedly affected by the anionic ligand of HgX_2. In order to understand this new observation, it was also required to clarify the stereochemistry of the mercurials obtained. Thus, in the present paper, our attention has been directed to the regioselectivity and stereochemistry of the intramolecular phenoxymercuration of **1**.

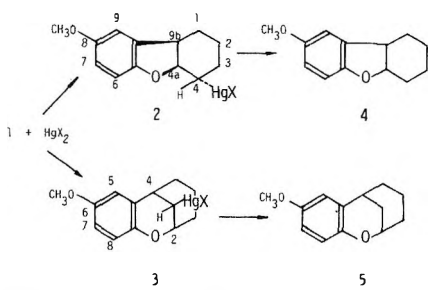
Results and Discussion

Cyclization of 1 with HgX_2. The reaction of **1** with $Hg(OAc)_2$ in water at room temperature for 24 h resulted in the formation of the mercurated dihydrobenzofuran **2a** in 59% yield (see Scheme I). By contrast, the use of $HgCl_2$ in this reaction gave a 53% yield of the mercurated chroman **3b**, indicating a change in the regioselectivity of the reaction. In neither reaction could any other product be detected, and unreacted starting material was recovered unchanged. Sodium borohydride reduction of **2a** and **3b** gave **4** and **5**, respectively (Experimental Section).

The use of $Hg(NO_3)_2$ also gave the chroman **3c** (53%) as the sole product. Similarly, the reaction of **1** with $Hg(ClO_4)_2$ followed by $NaBH_4$ reduction gave the chroman **5**. Again, no dihydrobenzofuran was detected in these reactions. These results indicate that the degree of dissociation of the Hg-X bond ($ClO_4 > NO_3 > OAc > Cl$) does not correlate with the difference in regioselectivity observed with $Hg(OAc)_2$ and $HgCl_2$.

When mercuric monochloroacetate was used in this reaction, both types of the products **2e** and **3e** were formed in a ratio of 56:44. The use of mercuric dichloroacetate changed the product ratio of **2/3**, the chroman **3f** being predominantly formed over the dihydrobenzofuran **2f** (Table I). Mercuric trichloroacetate or mercuric trifluoroacetate gave only the chroman **3g** or **3h**. These data indicate that the regioselectivity of this reaction depends on the electron-withdrawing property of the acetoxy ligands in $Hg(OCOCX_3)_2$. This parallels our previous observation that the regioselectivity in the Pd(II)-induced intramolecular cyclization of 2-(3-methyl-2-butenyl)phenol changes with the carboxylate ligands on Pd(II) salts.[2]

Scheme I



a, X = OAc; b, X = Cl; c, X = NO_3; d, X = ClO_4; e, X = $OCOCH_2Cl$; f, X = $OCOCHCl_2$; g, X = $OCOCCl_3$; h, X = $OCOCF_3$

Structures of the Mercurials 2 and 3. The NMR spectrum of **2a** shows that the H_{4a} proton is coupled to the H_{9b} and H_4 protons with equal coupling constants of 7 Hz. However, our observation that $J(H_{9b}-H_{4a}) = J(H_{9b}-H_{1,cis}) = J(H_{9b}-H_{1,trans}) = 7$ Hz indicates that no stereochemical information may be deduced from the coupling constants. The H_{4a} proton has the vicinal $^1H-^{199}Hg$ coupling constant of 144 Hz, which appears to suggest that H_{4a} and the Hg atom are cis since the value is close to the cis-vicinal coupling constant of $J(Hg-H)_{vic}$ = 99 Hz reported for *trans*-1-chloromercuri-2-methoxycyclohexane. However, it has been shown that values of $J(Hg-H)_{vic}$ are generally around 100 Hz, except that it rises to around 600 Hz when the dihedral angle defined by the C,C,H plane and the C,C,Hg plane is close to 180°.[12] Thus, a configurational assignment based on the vicinal coupling constant of 144 Hz is not conclusive. Accordingly, we have carried out single crystal x-ray analyses of these mercurials to define the stereochemistry of structures **2** and **3**.

Unfortunately, no crystal of **2a** (X = OAc) suitable for analysis could be obtained, and hence the acetate **2a** was converted into the chloride **2b** (X = Cl) by treatment with NaCl. Since the acetate **2a** was regenerated from the chloride **2b** by treatment with AgOAc and the NMR spectra of **2a** and **2b** were similar, it can be concluded that no stereochemical change of the furan moiety occurred during this transformation. The crystallographic studies were therefore carried out using the chlorides **2b** and **3b**.

The final positional and thermal parameters for the nonhydrogen atoms of the mercurials **2b** and **3b** are listed in Tables II and III, respectively. Interatomic distances and bond angles are collected in Tables IV and V. These tables are available as supplementary material.

Figures 1 and 2 show a perspective view of the molecules **2b** and **3b**, respectively. As seen in Figure 1, the cyclohexane ring of **2b** is in the chair form where the Hg and oxygen atoms are both equatorial, i.e., in a trans configuration. The C_{9a} atom occupies an axial position, and thus C_{9a} and the oxygen atom are in a cis configuration about the $C_{9b}-C_{4a}$ bond of the fused furan ring, which exists in the half-chair form. It is to be noted that the dihedral angle between the C_{4a},C_4,Hg plane and the C_{4a},C_4,H plane can be estimated to be 54° by assuming a normal position for the hydrogen atom.

The bond distances of Hg–Cl (2.33 Å) and Hg–C (2.11 Å) agree with the values of 2.53 and 2.34 Å reported for *trans*-1-chloromercuri-2-methoxycyclohexane,[13] and also the C–Hg–Cl bond angle of 174.8° is close to the reported value of 178°.[13]

Figure 2 shows that the cyclohexane ring of **3b** is also constructed with the chair form where both the Hg and the oxygen atom occupy the axial position. That is, the configuration of these atoms is trans.

These results indicate that the present reaction proceeds by antarafacial addition to the C=C double bond of **1**, regardless of the anionic ligands of HgX_2. Thus, it may be safely concluded that the difference in regioselectivity observed with $Hg(OAc)_2$ and $HgCl_2$ is not related to the stereochemistry of the addition step.

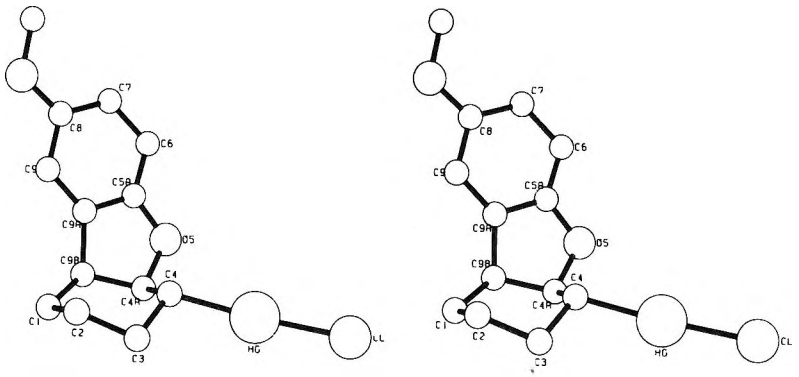


Figure 1. A stereoscopic view of the molecular structure of 1,2,3,4,4a,9b-hexahydro-4-chloromercuri-8-methoxydibenzofuran (**2b**).

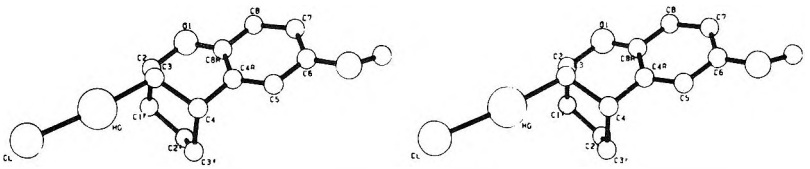


Figure 2. A stereoscopic view of the molecular structure of 2,4-propano-3-chloromercuri-6-methoxychroman (**3b**).

Table I. Cyclization of 1 with Mercuric Haloacetates
$1 + HgX_2 \rightarrow 2 + 3$

Mercuric salts (HgX_2) X⁻	Cyclized products Yield,[a] %	2:3
$OCOCH_3$	59	100:
$OCOCH_2Cl$	79	56:44[b]
$OCOCHCl_2$	50	24:76[b]
$OCOCCl_3$[c]	40	:100
$OCOCF_3$	43	:100

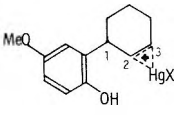
[a] Yields are of isolated products. [b] The ratio was determined from the NMR spectrum (100 MHz) of the crude reaction mixture by integrating the methoxy signals of **2** and **3**. These peaks appeared around δ 3.75 with a slightly different chemical shift (0.01 ppm). [c] The reagent was prepared in situ from mercuric oxide and trichloroacetic acid in water.

The trans-addition product is usually observed not only in solvomercuration of simple olefins[14-16] but also in the intramolecular carboxy- and hydroxymercuration of norbornenyl compounds.[17-20] However, the result described here is the first report as to the stereochemistry of intramolecular phenoxymercuration of 2-allylphenols.

Regioselectivity of the Reaction. Since the reversible nature of oxymercuration is well-known,[16,21,22] one could postulate that the formation of **2a** arises from a reversible deoxymercuration of the chroman **3a** (X = OAc) formed first during the reaction or that **3b** arises, similarly, from the dihydrobenzofuran **2b** (X = Cl). However, the following results indicate that no transformation of **3a** → **2a** occurs under the reaction conditions. (1) The acetate **3a** (X = OAc) prepared from **3b** (X = Cl) by treatment with AgOAc was stable in water in the presence of 1 equiv of HOAc. (2) The mercurial **3a** could be recovered unchanged after being added to a solution of **1** and $Hg(OAc)_2$ in water. Similarly, the dihydrobenzofuran **2b** (X = Cl) was not transformed into the chroman **3b** under the reaction conditions. Therefore, the mercurials **2a** (X = OAc) and **3b** (X = Cl) obtained are not interconvertible under the reaction conditions used.

In view of the results so far described, we propose that the difference of regioselectivity observed here may be ascribed to the electronic effect of the anionic ligands of HgX_2. A similar interpretation has been given for the stereospecificity of oxymercuration of allenes[23] and the stereoselectivity of the cyclopropane ring-opening reaction using mercuric salts.[24]

On the basis of mercurinium ion intermediate **6**, resulting



6

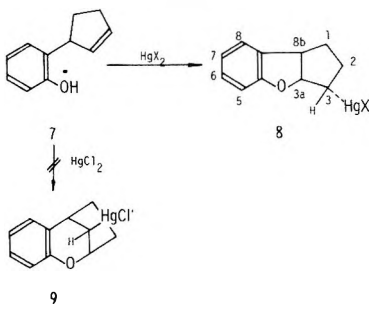
from the electrophilic attack of Hg(II) at the double bond of **1**,[6,16] the present result would be rationalized as follows. When a more electronegative ligand, e.g., X = Cl, is attached to the Hg atom, carbenium ion character will increase at the C-3 carbon of the intermediate **6** because the development of a positive charge at the C-2 carbon is probably unfavored by the electron-withdrawing inductive effect of the neighboring phenoxy group. Therefore, the nucleophilic attack occurs predominantly at the C-3 carbon, leading to the chroman **3b**. A similar inductive effect which has been noted to affect the regioselectivity of nucleophilic scission of 3-methoxycyclohexene oxide[25] may support this explanation.

On the other hand, when the ligand is the less electronegative acetate (X = OAc), the positive charge on **6** will not be localized at a carbon atom, and the internal nucleophile will prefer to attack at the more sterically accessible C-2 position, forming the dihydrobenzofuran **2a**. The attack at this position could be conceivably facilitated by an interaction between the phenolic oxygen atom and the Hg atom as a specific directing effect[26-30] or by formation of an aryloxy–mercuric acetate species (ArO–HgOAc), as has been proposed in the cyclization of 2′-hydroxychalcones using $Hg(OAc)_2$.[31] However, such processes do not appear to be compatible with the trans stereochemistry of the addition product **2a**.

The dependence of regioselectivity on the electron-withdrawing property of the acetoxy ligands on Hg(II) as shown in Table I can be thus regarded as reflecting the extent of a localization of the positive charge on the carbon atoms.

The results obtained from the mercuration of 2-(2-cyclopentenyl)phenol (**7**) are also relevant to a discussion of regioselectivity. Thus, the reaction of **7** with $Hg(OAc)_2$ gave the acetoxymercuric dihydrobenzofuran **8a** (X = OAc, 60%) as expected, but the use of $HgCl_2$ also led to a dihydrobenzofuran **8b** (X = Cl, 65%), and no chroman **9** was formed (see Scheme II). Models indicate **9** to be a highly strained structure, and therefore a process leading to **9** is energetically unfavorable. The stereochemistry of the addition step in these reactions is also antarafacial since the observed $J(Hg-H)_{vic}$ of 144 Hz for H_{3a} in the NMR spectra of **8a** and **8b** is the same as that of the mercurated dihydrobenzofurans **2a** and **2b**. Further,

Scheme II



a, X = OAc; b, X = Cl

the acetate **8a** can be converted into the same chloride **8b** by treatment with NaCl. A cis configuration between the H_{3a} and the H_{8b} proton is indicated by the value of $J(H_{3a}-H_{8b})$ = 7 Hz.[32]

In brief, the regioselectivity of intramolecular phenoxymercuration of 2-allylphenols is largely dependent on the structure of the substrates. In fact, 2-allylphenol itself always gives 2-mercurated methyl-2,3-dihydrobenzofurans, regardless of the nature of the ligands of HgX_2,[5] whereas only 3-mercurated 2,2-dimethylchroman is formed from 2-(3-methyl-2-butenyl)phenol, even with $Hg(OAc)_2$.[2] In the latter reaction, a positive charge developing at the C-3 carbon of the allylic side chain is highly stabilized by the two methyl substituents at this position, while the former reaction will produce the secondary carbenium ion at the C-2 carbon since it is obviously more stable than the primary one at the C-3 carbon. Thus, either the chroman or the dihydrobenzofuran compound is formed in these reactions.

Conclusions

(1) The Hg(II)-mediated cyclization of 2-allylphenols proceeds by an antarafacial addition, as is usually observed in oxymercuration of alkenes. (2) The difference in regioselectivity observed here is ascribed to the electronic effect of the anionic ligands on HgX_2. This result appears to give a rationale to our previous interpretation[2] on the regioselectivity in the Pd(II)-induced cyclization of 2-(3-methyl-2-butenyl)-phenol.

Experimental Section

NMR spectra were recorded on a 100-MHz Model JNM-4H-100 (JEOL) spectrometer or on a 60-MHz Model JNM-MH-60 (JEOL) spectrometer; chemical shifts (δ) are expressed in parts per million relative to Me_4Si. IR spectra were recorded on a Hitachi 215 spectrophotometer. Elemental analyses were performed by Y. Harada at the Department of Chemistry, Faculty of Engineering Science, Osaka University. All temperatures were uncorrected.

Materials. 2-(2-Cyclohexenyl)-4-methoxyphenol (**1**) was prepared from 3-bromocyclohexene and *p*-methoxyphenol by the reported procedures.[33] 2-(2-Cyclopentenyl)phenol (**7**) was similarly prepared from 3-chlorocyclopentene and phenol. Mercuric monochloro- and dichloroacetate were prepared from mercuric oxide (yellow) and the corresponding acetic acids by the known procedures.[34] Preparation of mercuric trichloroacetate was carried out by the same procedures as above, but isolation of this compound was as unsuccessful as that reported in the literature.[34] Accordingly, this reagent was used in situ by preparing it from mercuric oxide and trichloroacetic acid in water. Mercuric trifluoroacetate was obtained by treatment of mercuric oxide with trifluoroacetic acid in the presence of trifluoroacetic anhydride.[35] The other mercuric salts used were commercial products.

Reaction of 1 with HgX_2. 2-(2-Cyclohexenyl)-4-methoxyphenol (**1**, 3 mmol) was added to a solution of mercuric salt (3 mmol) in water (9 mL). The resulting heterogeneous mixture was stirred at 25 °C for 24 h, during which time a heavy, grayish oil setted out. After the aqueous solution was poured off by decantation, a small amount of methanol was added to the residue, and the resulting white precipitate was filtered and dried. The crude reaction product was purified by recrystallization from methanol. From the filtrate only unreacted **1** was recovered.

2a (X = OAc). Into a stirring solution of $Hg(OAc)_2$ (0.960 g, 3 mmol) in water (9 mL) was added **1** (0.612 g, 3 mmol). The resulting precipitate of **2a** (0.828 g, 59%) was recrystallized from methanol: mp 127–128 °C; IR (Nujol) 1590, 1475, 1375, 1307, 1275, 1240, 1220, 1197, 1177, 1150, 1141, 1130, 1090, 1025, 935, 911, 890, 868, 847, 808, 770, 748, 725, 673 cm^{-1}; NMR (100 MHz) δ ($CDCl_3$) 1.44–2.42 (m, 6 H), 2.03 (s, 3 H, $OCOCH_3$), 3.09 (ddd, 1 H, J = 7, 8.5, 3.5 Hz, H_4), 3.40 (q, 1 H, J = 7 Hz, H_{9b}), 3.76 (s, 3 H, OCH_3), 4.95 (t, 1 H, J = 7 Hz and $J(^1H-^{199}Hg)$ = 144 Hz, H_{4a}). The assignment of these protons was supported by a double-irradiation experiment. Double irradiation of H_4 (δ 3.09) simplified the signal of H_{4a} (δ 4.95) to show a doublet (J = 7 Hz). The signal of H_{4a} was also transformed into a doublet (J = 7 Hz) by irradiating the C_{9b} proton (δ 3.40). Double irradiation of H_{4a} simplified both the signals of H_4 and H_{9b} to show a double doublet (J = 3.5, 8.4 Hz) and a triplet (J = 7 Hz), respectively.

Anal. Calcd for $C_{15}H_{18}O_4Hg$: C, 38.89; H, 3.89. Found: C, 38.50; H, 3.85.

3b (X = Cl). Into a stirring solution of $HgCl_2$ (1.310 g, 5 mmol) in water (15 mL) was added **1** (1.620 g, 5 mmol). The reaction gave a 53% yield of **3b.** Recrystallization from methanol afforded an analytically pure sample of **3b:** mp 201–202 °C; IR (Nujol) 1490, 1425, 1365, 1353, 1335, 1320, 1307, 1263, 1240, 1210, 1183, 1145, 1102, 1080, 1043, 1020, 995, 950, 935, 895, 882, 830, 802, 750, 720, 700 cm^{-1}; NMR (60 MHz) δ ($CDCl_3$) 1.4–2.3 (m, 6 H), 3.26 (m, 2 H), 3.73 (s, 3 H, OCH_3), 4.77 (m, 1 H), 6.50 (m, 1 H, phenyl), 6.71 (m, 2 H, phenyl).

Anal. Calcd for $C_{13}H_{15}HgClO_2$: C, 35.52; H, 3.42. Found: C, 35.64; H, 3.45.

3c ($X = NO_3$). Into a stirring solution of $Hg(NO_3)_2 \cdot H_2O$ (1.000 g, 3 mmol) in water (9 mL) was added **1** (0.612 g, 3 mmol). The resulting precipitate of **3c** (0.730, 53%) was recrystallized from methanol: mp 145 °C dec; IR (Nujol) 1520, 1490, 1443, 1427, 1320, 1303, 1270, 1238, 1205, 1140, 1102, 1080, 1040, 1022, 950, 953, 925, 898, 883, 807, 798, 737, 700 cm^{-1}; NMR (60 MHz) δ ($CDCl_3$) 1.5–2.2 (m, 6 H), 3.28 (m, 1 H), 3.43 (m, 1 H), 3.75 (s, 3 H, OCH_3), 4.78 (m, 1 H), 6.51 (m, 1 H, phenyl), 6.73 (m, 2 H, phenyl).

Anal. Calcd for $C_{13}H_{15}O_5NHg$: C, 33.51; H, 3.25. Found: C, 33.32; H, 3.24.

3d ($X = ClO_4$). Into a stirring solution of $Hg(ClO_4)_2$ (1.360 g, 3 mmol) in water (9 mL) was added **1** (0.612 g, 3 mmol). No solid product was obtained from this reaction. The resulting oily substance was indicated by NMR to contain only the mercurial **3d** and unreacted starting material **1**. The NMR spectrum (60 MHz) of **3d** as a 1:1 mixture of **3d** and **1** in $CDCl_3$ showed the following resonances: δ 1.4–2.3 (m, 6 H), 3.11 (m, 1 H), 3.30 (m, 1 H), 3.71 (s, 3 H, OCH_3), 4.75 (m, 1 H), 6.45 (m, 1 H, phenyl), 6.67 (m, 2 H, phenyl). Deoxymercuration of this mixture by a manner described below gave the chroman **5**, and no dihydrobenzofuran **4** was obtained.

2e and 3e ($X = OCOCH_2Cl$). Into a stirring solution of $Hg(OCOCH_2Cl)_2$ (1.164 g, 3 mmol) in water (9 mL) was added **1** (0.612 g, 3 mmol). The resulting colorless solid (1.220 g, 79%) was shown by NMR to contain the mercurials **2e** and **3e** in a ratio of 56:44. The mercurated chroman **3e** could be readily separated by recrystallization from methanol. **3e:** mp 141–142 °C; IR (Nujol) 1660, 1600, 1500, 1433, 1400, 1348, 1307, 1262, 1237, 1207, 1145, 1100, 1080, 1040, 995, 948, 932, 890, 882, 833, 805, 778, 700, 685 cm^{-1}; NMR (100 MHz) δ ($CDCl_3$) 1.4–2.3 (m, 6 H), 3.24 (m, 2 H), 3.74 (s, 3 H, OCH_3), 4.11 (s, 2 H, $OCOCH_2Cl$), 4.72 (m, 1 H), 6.47 (m, 1 H, phenyl), 6.68 (m, 2 H, phenyl).

Anal. Calcd for $C_{15}H_{17}O_4HgCl \cdot 0.5H_2O$:[36] C, 35.61; H, 3.49. Found: C, 35.56; H, 3.37.

Isolation of **2e** in a pure form was unsuccessful. Repeated recrystallization of the reaction products afforded a 70% purity of **2e.** The following data were deduced from a 3:7 mixture of **2e** and **3e. 2e:** NMR (100 MHz) δ ($CDCl_3$) 1.4–2.3 (m, 6 H), 2.96–3.54 (m, 2 H), 3.76 (s, 3 H, OCH_3), 4.11 (s, 2 H, $OCOCH_2Cl$), 4.92 (t, 1 H, J = 7 Hz), 6.68 (m, 3 H, phenyl).

Anal. Calcd for $C_{15}H_{17}O_4HgCl \cdot 0.5H_2O$: C, 35.61; H, 3.49. Found: C, 35.55; H, 3.41.

2f and 3f ($X = OCOCHCl_2$). Into a stirring solution of $Hg(OCOCHCl_2)_2$ (1.370 g, 3 mmol) was added **1** (0.612 g, 3 mmol). The resulting colorless solid (0.790 g, 50%) was shown by NMR to contain the mercurials **2f** and **3f** in a ratio of 24:76. The mercurated chroman **3f** could be readily separated by recrystallization from methanol. This compound showed no clear decomposition point, although it started to decompose at 139 °C. **3f:** IR (Nujol) 1675, 1495, 1450, 1335, 1350, 1262, 1240, 1220, 1205, 1145, 1100, 1077, 1035, 993, 945, 885, 868, 835, 805, 782, 756, 700 cm^{-1}; NMR (100 MHz) δ ($CDCl_3$) 1.2–2.4 (m, 6 H), 3.24 (m, 2 H), 3.75 (s, 3 H, OCH_3), 4.73 (m, 1 H), 6.00 (s, 1 H, $OCOCHCl_2$), 6.46 (m, 1 H, phenyl), 6.70 (m, 2 H, phenyl).

Anal. Calcd for $C_{15}H_{16}O_4Cl_2Hg$: C, 33.87; H, 3.03. Found: C, 33.84; H, 2.99.

Isolation of **2f** in a pure form was also unsuccessful. The NMR (100 MHz) spectrum of the reaction products showed the following resonances, except for those due to **3f**: ($CDCl_3$) δ 1.2–2.4 (m, 6 H), 3.28–3.60 (m, 2 H), 3.76 (s, 3 H, OCH_3), 4.92 (t, 1 H, J = 8 Hz), 6.00 (s, 1 H, $OCOCHCl_2$), 6.68 (m, 3 H, phenyl).

An elemental analysis showed the mixture to have a formula of $C_{15}H_{16}O_4Cl_2Hg$. Anal. Calcd: C, 33.87; H, 3.03. Found: C, 33.32; H, 2.98.

The formation of **2f** was further confirmed by converting it to the chloride **2b** (X = Cl). Thus, a mixture of the reaction products **2f** and **3f** was treated with NaCl in water, and the resulting crystals were recrystallized from chloroform. The mercurial **3b** was readily crystallized from the solution. Crystals obtained from the mother liquid were found by NMR to contain a 1:1 mixture of **2b** and **3b**.

3g (X = $OCOCCl_3$). A solution of HgO (0.620 g, 3 mmol) and CCl_3COOH (0.980 g, 3 mmol) in water (9 mL) was stirred for 15 min, and then 1 (0.612 g, 3 mmol) was added to this solution. After 24 h, the aqueous solution was decanted, and the residue was dissolved in chloroform. The chloroform solution was filtered and concentrated, leaving an oily substance which was crystallized by adding a small amount of ether. The resulting crystals of **3g** (0.680 g, 40%) were recrystallized from methanol. This compound showed no clear decomposition point, although it started to decompose at 135 °C. **3g:** IR (Nujol) 1670, 1437, 1423, 1360, 1310, 1260, 1235, 1200, 1168, 1140, 1097, 1077, 1045, 993, 945, 878, 865, 830, 815, 760, 695, 680 cm^{-1}; NMR (60 MHz) δ ($CDCl_3$) 1.4–2.3 (m, 6 H), 3.30 (m, 2 H), 3.72 (s, 3 H, OCH_3), 4.73 (m, 1 H), 6.49 (m, 1 H, phenyl), 6.72 (m, 2 H, phenyl).

Anal. Calcd for $C_{15}H_{15}O_4Cl_3Hg$: C, 31.82; H, 2.67. Found: C, 32.76; H, 2.94.

3h (X = $OCOCF_3$). Into a stirring solution of $Hg(OCOCF_3)_2$ (1.280 g, 3 mmol) in water (9 mL) was added 1 (0.612 g, 3 mmol). The resulting amorphous solid was filtered to give a 43% yield of **3h** (0.685 g): mp 124–128 °C; IR (Nujol) 1690, 1585, 1500, 1415, 1380, 1310, 1240, 1190, 1140, 1110, 1080, 1037, 997, 950, 885, 853, 835, 810, 790, 733, 700 cm^{-1}; NMR (60 MHz) δ ($CDCl_3$) 1.4–2.3 (m, 6 H), 3.28 (m, 1 H), 3.75 (s, 3 H, OCH_3), 4.72 (m, 1 H), 6.50 (m, 1 H, phenyl), 6.73 (m, 2 H, phenyl). Owing to the difficulty of purification by recrystallization, no satisfactory analytical data were obtained for this compound.

Sodium Borohydride Reduction of 2a and 3b. Sodium borohydride reduction of **2a** was performed by the procedure of Bordwell and Douglass.[37] A solution of sodium borohydride (0.019 g, 0.5 mmol) in 2.5 M sodium hydroxide was added to a stirring solution of **2a** (0.231 g, 0.5 mmol) in 2 mL of water–ethanol (80:20). The reaction mixture was stirred at room temperature for 20 min and filtered. The aqueous solution was extracted with carbon tetrachloride. The extract was found to contain the dihydrobenzofuran **4** (22%) and the original olefin **1** (57%) by GLC analysis. The two compounds could be separated by means of alumina column chromatography. An analytically pure sample of **4** was obtained by preparative GLC. The spectral data of **4** were identical with those of an authentic sample prepared by the procedure of Fráter and Schmid.[33] **4** (colorless liquid): IR (neat) 2925, 2850, 1600, 1480, 1433, 1430, 1265, 1255, 1215, 1187, 1175, 1130, 1027, 945, 902, 880, 847, 803, 793, 738 cm^{-1}; NMR (100 MHz) δ (CCl_4) 1.12–2.12 (m, 8 H), 3.04 (q, 1 H, J = 7 Hz, H_{9b}), 3.67 (s, 3 H, OCH_3), 4.50 (dt, 1 H, J = 7, 4.5 Hz, H_{4a}), 6.55 (m, 3 H, phenyl). The signal at a lower field (δ 4.50) can be assigned to the tertiary proton (H_{4a}) on the C_{4a} carbon adjacent to the oxygen atom. Thus, the quartet at δ 3.04 is assigned to the benzylic proton of H_{9b}. Double irradiation of cyclohexene protons at δ 1.60 simplified the quartet to a doublet (J = 7 Hz).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 75.76; H, 8.00.

Deoxymercuration of **3b** was carried out in an identical manner with that described above. In this case, a large amount of **3b** remained unreacted. The GLC analysis of the extract showed that the chroman **5** and the original olefin **1** were formed in 19% and 17% yield, respectively, based on the starting material charged. **5** (colorless liquid): IR (neat) 2930, 2850, 1493, 1463, 1463, 1450, 1430, 1302, 1255, 1200, 1153, 1083, 1055, 1040, 962, 927, 825, 807, 740, 695 cm^{-1}; NMR (100 MHz) δ (CCl_4) 1.12–2.00 (m, 8 H), 2.88 (m, 1 H), 3.64 (s, 3 H, OCH_3), 4.46 (m, 1 H), 6.46 (m, 1 H, phenyl), 6.64 (2 H, phenyl).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.38; H, 7.96.

Preparation of Authentic Samples 4 and 5. A solution of **1** (5 mmol) in benzene (300 mL) was irradiated at 10–15 °C for 48 h by means of a 500-W high-pressure mercury lamp. After the solvent was removed, the residue was distilled under reduced pressure to afford a mixture of **4**, **5**, and unreacted **1**. The phenol **1** was removed by washing the mixture with Claisen's alkali. After this treatment, a 45:55 mixture of **4** and **5** was obtained in 19% yield.

Table VI. Summary of X-Ray Diffraction Experiments

	2b	3b
Formula	$C_{13}H_{15}O_2HgCl$	$C_{13}H_{15}O_2HgCl$
Formula weight, g	439.3	439.3
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
Z	8	4
Unit-cell parameters		
a, Å	8.219 (5)	9.075 (3)
b, Å	11.952 (2)	6.726 (3)
c, Å	26.855 (3)	21.144 (4)
β, deg	95.68 (5)	98.59 (5)
V_c, Å^3	2625.1	1276.1
Density (calcd), g/cm^3	2.222	2.286
Crystal dimensions, mm	0.05 × 0.03 × 0.2	0.2 × 0.15 × 0.3
μ, cm^{-1}	243.2	124.7
Radiation	Cu Kα (β filter)	Mo Kα (β filter)
2θ range	$3° < 2\theta < 113°$	$3° < 2\theta < 52.5°$
Scan mode	ω scan	$\omega-2\theta$ scan
Scan range, °ω	2.4 + 0.15 tan θ	1.5 + 0.35 tan θ
Reflections measured	4010	2804
Radiation damage	10% in F(obsd)	8% in F(obsd)

Transformation of 2a (X = OAc) into 2b (X = Cl). Into a solution of **2a** (0.46 g, 1 mmol) in methanol (5 mL) was added sodium chloride (0.059 g, 1 mmol) dissolved in a small amount of water. The solution precipitated a white solid which was filtered off after 15 min. An analytically pure sample was crystallized from methanol. **2b:** mp 154–155 °C; IR (Nujol) 1480, 1380, 1330, 1267, 1215, 1195, 1175, 1115, 1082, 1030, 980, 950, 925, 860, 805, 800, 770, 760, 721, 700 cm^{-1}; NMR (100 MHz) δ ($CDCl_3$) 2.3–2.2 (m, 6 H), 2.96 (ddd, 1 H, J = 8.5, 7, 4 Hz, H_4), 3.40 (q, 1 H, J = 6.5, 7 Hz, H_{9b}). 3.76 (s, 3 H, OCH_3), 4.91 (t, 1 H, J = 7 Hz and $J(^1H-^{199}Hg)$ = 144 Hz, H_{4a}), 6.68 (m, 3 H, phenyl).

Anal. Calcd for $C_{13}H_{15}HgClO_2$: C, 35.52; H, 3.42. Found: C, 35.35; H, 3.33.

Transformation of 3b (X = Cl) into 3a (X = OAc). To a solution of **3b** (0.439 g, 1 mmol) in acetone (15 mL) was added silver acetate (0.167 g, 1 mmol) dissolved in water, After the solution was stirred for 30 min in the dark, the resulting precipitate (AgCl) was filtered off, and the solvent was removed to leave an amorphous material which could not be crystallized by adding methanol or other solvents. The NMR spectrum of this material showed only the presence of **3a:** IR ($CHCl_3$) 2920, 2830, 1623, 1600, 1363, 1305, 1142, 1076, 947 cm^{-1}; NMR (100 MHz) δ ($CDCl_3$) 1.40–2.28 (m, 6 H), 2.04 (s, 3 H, $OCOCH_3$), 3.11 (m, 2 H), 3.72 (s, 3 H, OCH_3), 4.69 (m, 1 H), 6.48 (m, 1 H, phenyl), 6.70 (m, 2 H, phenyl).

Crystallographic Procedures. Crystals **2b** and **3b** were grown from methanol solutions as transparent thin needles and prisms, respectively, which were both slightly light-sensitive. Preliminary oscillation and Weissenberg photographs of both crystals indicated them to be monoclinic. The systematic absences, $0k0$ for $k = 2n + 1$ and $h0l$ for $l = 2n + 1$, uniquely showed the space group to be $P2_1/c$ for both crystals. Accurate cell dimensions were obtained through least-squares refinements of the setting angle of high-angle reflections measured on a four-circle Rigaku automatic diffractometer. Since the crystals of **2b** were very thin needles, the intensity data for this compound were collected using Cu Kα radiation generated from a rotating anode in order to get sufficient diffracted intensities. The intensities for **3b** were obtained with Mo Kα radiation from a sealed tube, and only those reflections whose peak intensities were greater than 10 Hz at the calculated setting positions were collected in order to minimize the radiation damage of this compound. During the course of collection of each data set, the intensities of three monitoring reflections were measured on every 50 reflections. Since the intensities were gradually decreased for both crystals, all the data were corrected using the decay curve obtained from the monitoring reflections. The reflections were also corrected for Lorentz–polarization factors, but not absorption effects. The experimental details are given in Table VI.

The structure of **2b** was solved by a Patterson function and subsequent Fourier synthesis. The positional and anisotropic thermal factors of all nonhydrogen atoms were refined by block-diagonal least squares with unit weights using the 3071 nonzero reflections. The final reliability index, R (defined as $\sum||F_o| - |F_c||/|F_o|$), was 0.073.

The structure of **3b** was solved by means of the automatic crystal structure analysis processing program, developed by Tanaka et al.[38] in 1975, based on the heavy-atom method. Refinements of the atomic

parameters for the nonhydrogen atoms using block-diagonal least squares with unit weights led to an R of 0.094 for the 1567 nonzero reflections observed.

Reaction of 7 with $Hg(OAc)_2$ or $HgCl_2$. The reaction was carried out in a manner identical with that described in the reaction of 1 with HgX_2. The mercurials **8a** (**a**, X = OAc) and **8b** (**b**, X = Cl) were readily crystallized from methanol. **8a:** 60% yield; mp 116–117 °C; IR (Nujol) 1610, 1480, 1420, 1370, 1295, 1260, 1230, 1200, 1183, 1165, 1155, 1100, 1047, 1015, 1003, 940, 920, 867, 827, 807, 740. 725, 680 cm^{-1}; NMR (100 MHz) δ ($CDCl_3$) 1.75–2.32 (m, 4 H), 2.02 (s, 3 H, $OCOCH_3$), 3.16 (m, 1 H, H_3), 3.96 (nearly triplet, 1 H, J = 7.5, H_{8b}), 5.55 (dd, 1 H, J = 7.5, 2 Hz and $J(^1H-^{199}Hg)$ = 144 Hz, H_{3a}), 6.6–7.2 (m, 4 H, phenyl).

Anal. Calcd for $C_{13}H_{14}HgO_3$: C, 37.27; H, 3.38. Found: C, 37.19; H, 3.37.

8b: 65% yield; mp 164–165 °C; IR (Nujol) 1610, 1480, 1420, 1370, 1295, 1260, 1230, 1200, 1183, 1165, 1155, 1100, 1047, 1015, 1003, 940, 920, 867, 827, 807, 740, 725, 680 cm^{-1}; NMR (100 MHz) δ ($CDCl_3$) 1.5–2.4 (m, 4 H), 3.14 (m, 1 H), 3.96 (nearly triplet, 1 H, J = 7.5 Hz, H_{8b}), 5.54 (dd, 1 H, J = 7, 2.5 Hz and $J(^1H-^{199}Hg)$ = 144 Hz, H_{3a}), 6.6–7.2 (m, 4 H, phenyl).

Anal. Calcd for $C_{11}H_{11}OHgCl$: C, 33.42; H, 2.81. Found: C, 33.38; H, 2.85.

Acknowledgment. We wish to thank Mr. Y. Terawaki for measuring the NMR spectra. This work was supported financially by grants from the Ministry of Education, Japan (No. 185192 and No. 110305).

Supplementary Material Available: Tables II and III, listing the final positional and thermal parameters for the nonhydrogen atoms, and Tables IV and V, listing the bond distances and bond angles (5 pages). Ordering information is given on any current masthead page.

Registry No.—**1,** 64252-19-3; **2a,** 64252-20-6; **2b,** 64252-21-7; **2e,** 64252-22-8; **2f,** 64252-23-9; **3a,** 64252-24-0; **3b,** 64252-25-1; **3c,** 64252-26-2; **3d,** 64252-27-3; **3e,** 64252-28-4; **3f,** 64252-29-5; **3g,** 64252-30-8; **3h,** 64252-31-9; **4,** 27124-68-1; **5,** 64252-32-0; **7,** 6627-83-4; **8a,** 64252-33-1; **8b,** 64252-34-2; 3-chlorocyclopentene, 96-40-2; phenol, 108-95-2; $Hg(OAc)_2$, 1600-27-7; $HgCl_2$, 7487-94-7; $Hg(NO_3)_2$, 10045-94-0; $Hg(ClO_4)_2$, 7616-83-3; $Hg(OCOCH_2Cl)_2$, 26719-07-3; $Hg(OCOCHCl_2)_2$, 26788-74-9; HgO, 21908-53-2; CCl_3COOH, 76-03-9; $Hg(OCOCF_3)_2$, 13257-51-7; AgOAc, 563-63-3.

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Addition Reaction of Benzene to α-Substituted Chalcone Derivatives by Means of Palladium(II) Acetate

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The reaction of several α-substituted chalcone derivatives with benzene and acetic acid in the presence of palladium(II) acetate was investigated. When the α substituents are bulky and powerfully electron withdrawing, such as benzoyl, nitro, ethoxycarbonyl, and carboxyl groups, the addition of benzene to their carbon–carbon double bond occurs. The formation of the benzene adducts proceeded catalytically with respect to palladium(II) acetate. A mechanism involving the carbanion derived from heterolytic fission of the initially formed intermediate σ-palladium complex is suggested.

The aromatic substitution reaction of olefins by use of palladium(II) salts has received wide attention since Moritani and Fujiwara et al.[1] and Heck et al.[2] independently reported their pioneering work. In the previous work on the Moritani–Fujiwara arylation, the authors reported that electron-withdrawing groups such as a nitro on the olefinic carbon atom affect the arylation very strongly[3] and that β-substituted β-methylstyrenes did not give the usual phenylation compounds, but exclusively the corresponding β-diphenylmethylstyrenes because of a steric effect.[4] In the present paper is described a novel catalytic addition reaction of benzene to the carbon–carbon double bond of some α-substituted chalcones in the

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Table I. Reaction of α-Substituted Chalcones with Benzene and Acetic Acid in the Presence of Palladium Acetate

Registry no.	α-Substituted chalcones		Reaction products, Yields, %[a] Benzene adducts		Substituted compounds	
94-41-7	PhCH=CHCOPh	Ia			Ph_2C=CHCOPh	IIIa (74.8)
4023-77-2	PhCH=C(Ph)COPh	Ib			Ph_2C=C(Ph)COPh	IIIb (46.0)[b]
4258-37-1	PhCH=C(Me)COPh	Ic			PhCH=C($CHPh_2$)COPh	IIIc (66.2)
6935-75-7	PhCH=C(Br)COPh	Id			Ph_2C=CHCOPh	IIIa (42.6)[c]
5398-64-1	PhCH=C$(COPh)_2$	Ie	$Ph_2CHCH(COPh)_2$	IIe (52.5)	Ph_2C=C$(COPh)_2$	IIIe (8.0)
60999-92-0	PhCH=C(NO_2)COPh	If	$Ph_2CHCH(NO_2)$COPh	IIf (20.2)	Ph_2C=C(NO_2)COPh	IIIf (5.1)
17451-18-2	PhCH=C(CO_2Et)COPh	Ig	$Ph_2CHCH(CO_2Et)$COPh	IIg (12.2)	Ph_2C=C(CO_2Et)COPh	IIIg (56.5)
64235-44-5	PhCH=C(CO_2H)COPh	Ih	Ph_2CHCH_2COPh	IIh (36.3)	Ph_2C=CHCOPh	IIIa (7.2)

[a] Yields are of isolated and purified products. [b] A 1.5-fold excess of palladium acetate per mole of Ib was used because palladium acetate was consumed in the cis–trans isomerization of Ib. [c] A small amount of IIIb also was isolated.

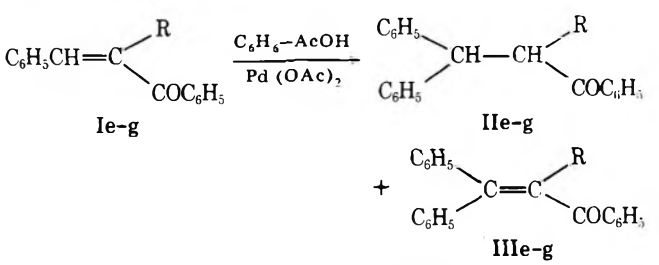
presence of palladium(II) acetate. In spite of the extensive studies of arylation by palladium(II) salts, no report dealing with such an addition reaction has appeared.

Results and Discussion

The reactions were carried out with a mixture of the α-substituted chalcone derivatives and an equimolar amount of palladium acetate in the presence of a large excess of benzene and acetic acid. The reaction mixture was refluxed with stirring until precipitation of black metallic palladium ceased. The results obtained are shown in Table I.

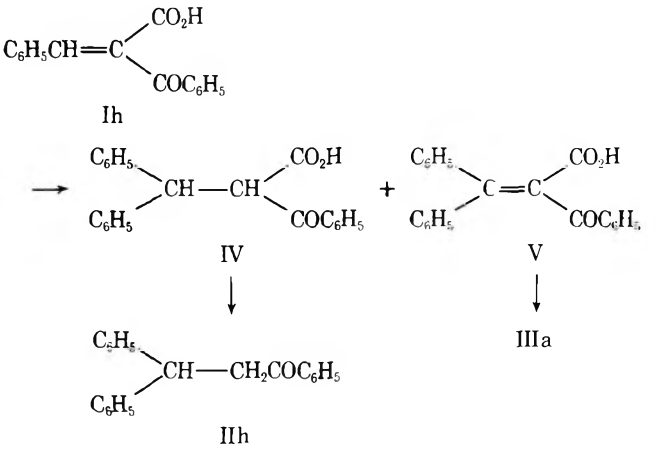
Chalcone (Ia) itself and α-phenylchalcone (Ib) gave the usual phenylated products, 1,1-diphenyl-2-benzoylethylene (IIIa) and 1,1,2-triphenyl-2-benzoylethylene (IIIb), respectively. α-Methylchalcone (Ic), as had been reported previously, gave (*E*)- and (*Z*)-α-diphenylmethylchalcone (IIIc) exclusively and the formation of these products can be illustrated by the repetition of the normal phenyl substitution.[4] With α-bromochalcone (Id), IIIa was obtained as the main product, together with trace of IIIb. This result can be explained by application of the mechanism for phenylation of β-bromo-β-nitrostyrene,[3] which included the usual phenyl-substitution step, followed by internal rearrangement via a π complex and subsequent elimination of *bromidopalladium acetate*.[5] All of these above four examples can be virtually regarded as phenyl-substitution reactions.

In contrast to these examples, α-benzoylchalcone (Ie) gave a colorless compound, $C_{28}H_{22}O_2$ (IIe), as a major product, accompanied by a small amount of phenyl-substituted product (IIIe). The structure of IIe was determined to be 1,1-diphenyl-2,2-dibenzoylethane by its NMR, IR, UV, and mass spectra and elemental analyses. IIe is regarded as the benzene adduct of Ie. As far as we know, this is the first example of addition of benzene to a carbon–carbon double bond being brought about by palladium salts. Likewise, α-nitrochalcone (If) and α-ethoxycarbonylchalcone(ethyl α-benzoylcinnamate) (Ig) give the corresponding benzene adducts (IIf and IIg), along with the usual phenyl-substituted products (IIIf and IIIg).

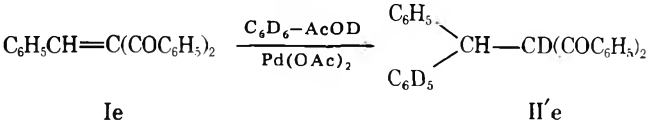


R = COC_6H_5, NO_2, $COOC_2H_5$

With α-carboxylchalcone(α-benzoylcinnamic acid) (Ih), the decarboxylated benzene adduct and phenyl-substituted compound, 1,1-diphenyl-2-benzoylethane (IIh) and IIIa, were obtained. These products might be produced by decarboxylation of an initially formed benzene adduct (IV) and phenyl-substituted compound (V), since V, obtained by hydrolysis of IIIg, gave IIIa under the reaction conditions.[6]



Similar decarboxylation with palladium salts was reported by Sakakibara et al. in the phenylation of cinnamic acid.[7] IIe–h could be regarded both as the benzene adducts of Ie–h and the reduction products of the corresponding usual phenyl-substituted compounds (IIIe–g and IIIa). However, reduction of the carbon–carbon double bond of IIIe–g and IIIa under the reaction conditions used seems unlikely, since IIIe was recovered unchanged when treated to the reaction conditions. Moreover, when Ie was treated with C_6D_6 and CH_3CO_2D under similar conditions, the hexadeuterio compound (II'e) was obtained instead of IIe.[8] The formation of



II'e indicated that fission of the olefinic hydrogen–carbon bond of Ie does not occur during the reaction. These findings suggest that the benzene adducts (IIe–h) were not derived from the usual phenyl-substituted compounds (IIIe–g and IIIa) but were formed by another type of reaction.

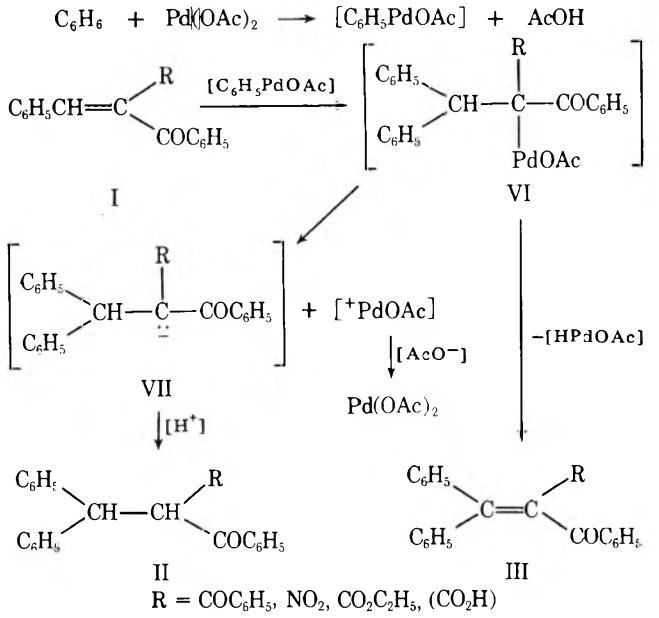
Heck has proposed a mechanism for arylation using palladium acetate and arylmercury compounds, in which the first step is cis addition of *arylpalladium acetate* to the olefinic double bond, this being followed by cis elimination of *hydridopalladium acetate*.[9] When this reaction mechanism is applied to the benzene addition reactions, the following reaction pathway can be proposed.

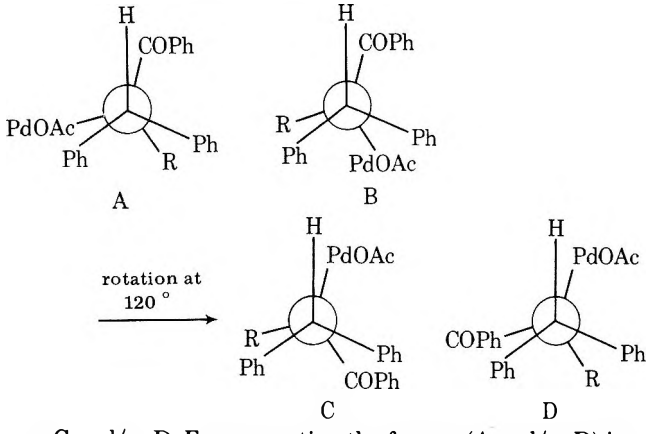
The initially formed intermediate σ complex (VI) derived from cis addition of *phenylpalladium acetate* to I is shown as A and/or B (for (*E*)-isomer of I). For cis elimination of *hydridopalladium acetate*, the favorable conformations of VI

Table II. The Catalytic Benzene Addition to Ie

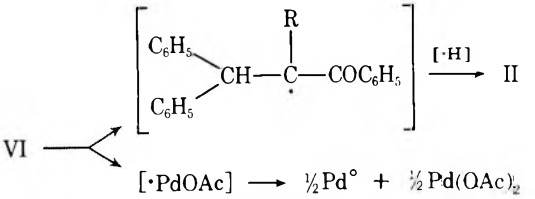
Ie, mol	$Pd(OAc)_2$, mol	Yields of IIe, %
0.01	0.01	52.5 (52.5)[a]
0.01	0.005 (1/2)	53.5 (107)
0.01	0.0025 (1/4)	54.4 (216)
0.01	0.00125 (1/8)	41.3 (330)
0.01	0.00063 (1/16)	33.4 (534)

[a] Based upon palladium acetate.





are C and/or D. For converting the former (A and/or B) into the latter (C and/or D) the rotation about the carbon–carbon bond of 120° is required. This rotation appears to be somewhat sterically restricted. Furthermore, it can be seen that the conformations shown in C and D are unstable because of severe steric hindrance. These steric factors would make the cis elimination of *hydridopalladium acetate* from VI to III difficult. Consequently, the heterolytic fission of the carbon–palladium σ bond to give a carbanion (VII)[10] and palladium acetate cation occurs in competition with cis elimination of *hydridopalladium acetate*. Attack of the solvent cation, H^+, on the carbanion (VII) gives the benzene adduct (II), while the attack of the solvent anion, OAc^-, on the palladium acetate cation results in regeneration of palladium acetate. If this mechanism is correct, palladium acetate should act catalytically in the formation of the benzene adduct (II), although palladium acetate must be consumed stoichiometrically for the generation of III and biphenyl,[11] forming metallic palladium. To confirm this possibility, Ie was treated with varying amounts of palladium acetate under similar conditions and the yields of IIe are shown in Table II. These experimental results indicate that about 1/4 mol equiv of palladium acetate relative to Ie is sufficient to allow this reaction to reach completion. A further consideration may be the possibility of homolytic fission of the carbon–palladium σ bond[12] of VI and attack of the produced radical on solvent to give II. However,



the fact that the yield of IIe based upon palladium acetate is over 200% is not explained by this mechanism.[13] Although the reduction of VI by *hydridopalladium acetate*, generated in the formation of III, is considered,[14] this mechanism can also be ruled out by the fact of the overwhelming formation of IIe compared with IIIe from Ie.[13]

Inoue et al. reported that when some benzocycloalkenes were treated with *phenylpalladium chloride* in protic solvent the phenyl group and an anion part of the solvent added to the olefins simultaneously, because of steric inhibition for cis elimination of *hydridopalladium chloride* (oxyphenylation).[15] In contrast with the oxyphenylation found by Inoue et al., the benzene addition reaction can be attributed to both steric and electronic factors.

It may be concluded that two bulky, electron-withdrawing groups (benzoyl and other groups) on the same carbon atom make the benzene addition reaction possible and that the reaction may proceed through the carbanion derived from an initially formed σ-palladium complex.

Experimental Section

All the melting points are uncorrected. IR spectra were recorded on a Nihonbunko DS-701G spectrometer, and NMR spectra were determined with a Hitachi R-24A spectrometer in $CDCl_3$ using Me_4Si as an internal reference.

Materials. Palladium acetate was prepared according to the method of Stephenson et al.[16] Chalcone (Ia) was commercially available. α-Phenylchalcone (Ib),[17] α-methylchalcone (Ic),[18] α-bromochalcone (Id),[19] α-benzoylchalcone (Ie),[20] α-nitrochalcone (If),[21] and α-ethoxycarbonylchalcone (Ig)[22] were prepared as described in the literature. α-Carboxylchalcone (Ih) and β,β-diphenyl-α-benzoylacrylic acid (V) were obtained by hydrolysis of Ig and IIIg, respectively; Ih: mp 158 °C; V: mp 144 °C.

General Procedure for the Reaction of α-Substituted Chalcone with Benzene and Acetic Acid in the Presence of Palladium Acetate. A mixture of the α-substituted chalcone (0.01 mol) and palladium acetate (0.01 mol) in 150 mL of benzene and 40 mL of acetic acid was refluxed with stirring until the precipitation of metallic palladium ceased. After filtration of the palladium metal, the mixture was washed with water and the solvent was evaporated in vacuo. The residue was chromatographed on silica gel. Elution with hexane gave a small amount of biphenyl; subsequent elution with hexane–benzene (1:1) gave the phenylated compounds. The structures of IIIa and IIIb were confirmed by comparison with authentic samples. The physical data for IIIc have been reported in a previous paper.[4] The physical properties of IIe, IIf, IIh, IIIe, IIIf, and IIIg are given below.

IIe: mp 227 °C; IR (KBr) 1693, 1662, 1599, 1449, 1265, 749, 700 cm^{-1}; NMR ($CDCl_3$) δ 8.05–7.00 (m, 20 H, phenyl), 6.34 (d, 1 H, methine, J = 12 Hz), 5.33 (d, 1 H, methine). Found: C, 86.21; H, 5.60.

IIf: mp 145 °C; IR (KBr) 1680, 1553, 1453, 1358, 1297, 767, 701 cm^{-1}; NMR ($CDCl_3$) δ 8.00–7.00 (m, 15 H, phenyl), 7.04 (d, 1 H, methine, J = 12 Hz), 5.30 (d, 1 H, methine). Found: C, 76.13; H, 5.14; N, 4.26.

IIg: mp 139 °C; IR (KBr) 1739, 1675, 1445, 1212, 1150, 737, 701 cm^{-1}; NMR ($CDCl_3$) δ 8.05–7.00 (m, 15 H, phenyl), 5.42 (d, 1 H, methine, J = 12 Hz), 5.06 (d, 1 H, methine), 3.90 (q, 2 H, methylene, J = 6 Hz), 0.91 (t, 3 H, methyl). Found: C, 80.22; H, 6.24.

IIh: mp 95 °C; IR (KBr) 1672, 1593, 1492, 1447, 1375, 748, 701 cm^{-1}; NMR ($CDCl_3$) δ 8.00–7.14 (m, 15 H, phenyl), 4.80 (t, 1 H, methine, J = 7.0 Hz), 3.69 (d, 2 H, methylene). Found: C, 88.18; H, 6.30.

IIIe: mp 158 °C; IR (KBr) 1663, 1633, 1597, 1445, 1253, 900, 695 cm^{-1}; NMR ($CDCl_3$) δ 8.00–7.16 (m, 20 H, phenyl). Found: C, 86.40; H, 5.30.

IIIf: mp 122 °C; IR (KBr) 1643, 1595, 1522, 1445, 1344, 780, 690 cm^{-1}; NMR ($CDCl_3$) δ 7.90–7.08 (m, 15 H, phenyl). Found: C, 76.70; H, 4.58; N, 4.20.

IIIg: mp 116 °C; IR (KBr) 1731, 1645, 1449, 1233, 1107, 778, 700 cm^{-1}; NMR ($CDCl_3$) δ 7.95–7.10 (m, 15 H, phenyl), 4.03 (q, 2 H, methylene, J = 7 Hz), 0.93 (t, 3 H, methyl). Found: C, 80.95; H, 5.60.

Registry No.—IIe, 60999-93-1; IIf, 60999-95-3; IIg, 60999-96-4; IIh, 606-86-0; IIIe, 60999-94-2; IIIf, 60999-97-5; IIIg, 61024-39-3; V, 64235-45-6; benzene, 71-43-2; $Pd(OAc)_2$, 3375-31-3.

References and Notes

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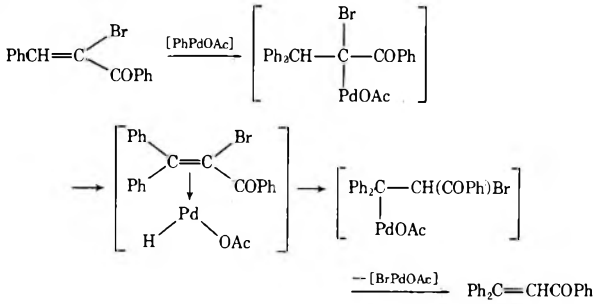

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$$RCH_2CH_2M \rightarrow RCH{=}CH_2 + [M\text{-}H]$$

$$RCH_2CH_2M + [M\text{-}H] \rightarrow RCH_2CH_3 + 2M$$

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A Synthesis of *trans*-15-*n*-Butyl-16-methyldihydropyrene. Synthetic Access to 1,2,3-Trisubstituted Benzene Derivatives via Direct Alkylation of 1,3-Bis(4',4'-dimethyl-2'-oxazolinyl)benzene

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A convenient general synthesis of 15,16-dihydropyrenes requires easy access to 1,2,3-trisubstituted benzene derivatives having appropriate functionality. It is now shown that isophthalic acid on conversion to 1,3-bis(4',4'-dimethyl-2'-oxazolinyl)benzene (**1**), followed by alkylation of the corresponding anion, gives the 2-alkyl derivatives **3** and **4** in high yield. Similarly, alkylation of the anion of 2,6-bis(4',4'-dimethyl-2'-oxazolinyl)toluene (**3**) occurs smoothly to give 2-substituted 1,3-bis(4',4'-dimethyl-2'-oxazolinyl)benzene derivatives (**8** or **9**). The hydrolysis of 2-*n*-butyl-1,3-bis(4',4'-dimethyl-2'-oxazolinyl)benzene (**8**) to 2-*n*-butylisophthalic acid and its subsequent conversion to dithiacyclophane **13** followed by a Wittig rearrangement and a Hofmann elimination to give *trans*-15-*n*-butyl-16-methyldihydropyrene (**15**) are described.

The route involving synthesis of dithiacyclophanes,[1-4] followed by elimination of sulfur to give cyclophanes,[5-9] cyclophanedienes,[10-12] and dihydropyrenes,[1] has proved to be an extremely useful method. The general application of this method, though, requires the availability of 1,2,3-trisubstituted benzene derivatives with appropriate functionality as starting materials. For the important case requiring 2,6-bis(bromomethyl)toluene, this starting compound can be made in a reasonable fashion from commercial chemicals. However, for other examples, where the internal substituents of the target dihydropyrenes are varied, the synthesis of the requisite starting materials is a tedious chore.[13] We now describe a method of alkylating aromatic rings which provides 1,2,3-trisubstituted benzene derivatives conveniently and in high yield.

Metalation of anisoles followed by reaction with an electrophile has been a useful synthetic procedure and recent developments of this method have been summarized in a series of papers by Slocum.[14] The extensive studies of Meyers on aryloxazolines led to the discovery that the reaction of *o*-methoxyaryloxazolines with Grignaid reagents and organolithium compounds results in the displacement of the methoxyl by alkyl or aryl substituents.[15] Gschwend and Hamdan showed that the reaction of simple aryloxazolines with alkyllithium reagents followed by treatment with an electrophile leads to introduction of the electrophilic substituent ortho to the oxazoline group.[16] Furthermore, *o*-methylaryloxazolines on reaction with *n*-butyllithium followed by reaction with an electrophile generates a product in which the electrophilic substituent is attached to the methyl group. Subsequently, Gschwend et al. extended this method to show that *N,N*-dimethylbenzamides can be readily converted to ortho-substituted aryl ketones.[17]

It appeared to us that the oxazoline ring served two func-

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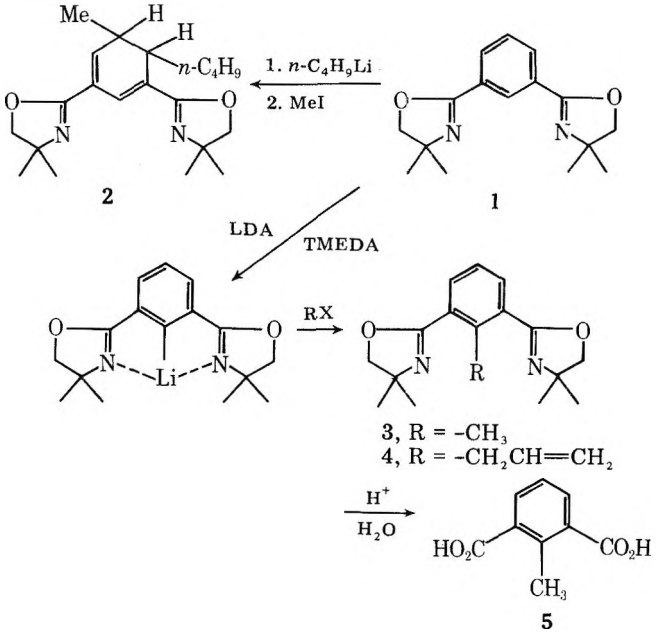
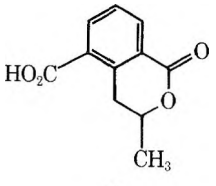
tions: (1) it increased the acidity of the aromatic protons; and (2) by providing the imino nitrogen for coordination with the lithium it directed substitution ortho to the oxazoline ring. Thus, it seemed likely that 1,3-bis(4′,4′-dimethyl-2′-oxazolinyl)benzene (1), which is readily prepared from commercial isophthalic acid, would undergo reaction with *n*-butyllithium to yield the 2-lithio derivative. However, when **1** was treated with *n*-butyllithium followed by addition of methyl iodide, the product isolated was a mixture of isomers having the spectral properties and composition for the various dihydrobenzenes such as **2** to be expected from addition of *n*-butyllithium to the aromatic ring followed by methylation. Apparently, with two oxazoline substituents addition of *n*-butyllithium to the aromatic ring becomes favored over the simple acid–base reaction. Substitution of *sec*-butyllithium or phenyllithium for *n*-butyllithium did not change the course of the reaction.

However, when a benzene solution of **1** was treated with 3 equiv of lithium diisopropylamide (LDA) and 3 equiv of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), a deep purple solution of the anion resulted which, on reaction with methyl iodide, gave 2,6-bis(4′,4′-dimethyl-2′-oxazolinyl)toluene (**3**) in 98% yield. Hydrolysis of **3** by heating in aqueous 3 N hydrochloric acid for 20 h gave a crystalline dicarboxylic acid, identical in all respects with the known 2-methylisophthalic acid (**5**).[1]



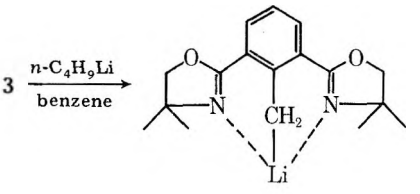
2 **1** **5**

Similarly, treatment of the lithio derivative of **1** with allyl bromide gave the allyl derivative **4**. Hydrolysis of **4** with aqueous hydrochloric acid was accompanied by lactonization to give compound **6**.



6

Analogous to Gschwend's observation, the methyl derivative **3** was easily converted to the corresponding lithio derivative **7**, which readily underwent alkylation to give compounds **8** and **9**. It is noteworthy that reaction of **3** with *n*-butyllithium in benzene proceeded smoothly to give the corresponding lithio derivative **7** in quantitative yield without any evidence of nucleophilic addition to the ring as had occurred with **1**.



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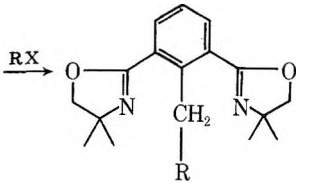


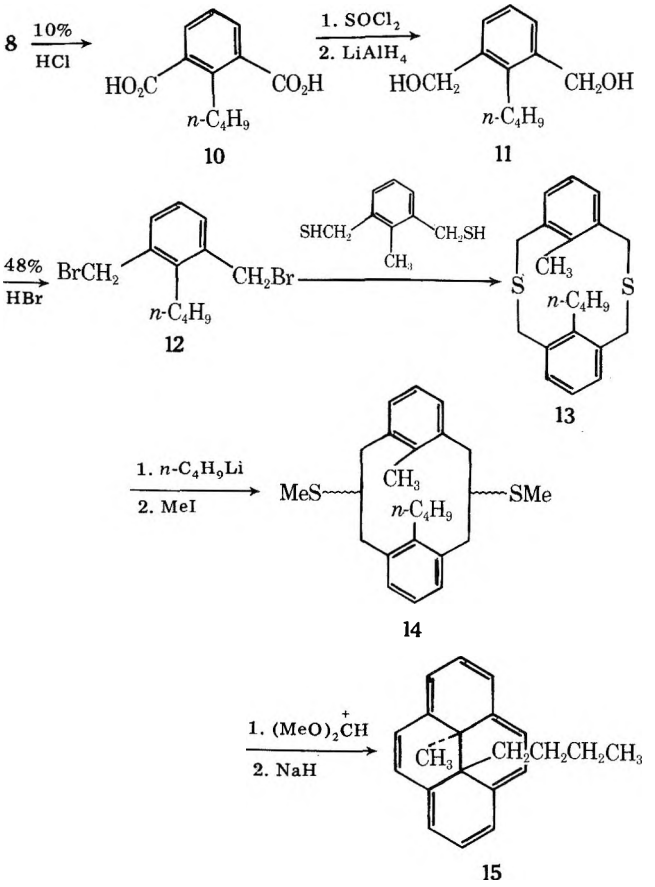
8, R = $-CH_2CH_2CH_3$
9, R = $-CH_2C{\equiv}CH$

Apparently, the benzylic protons of **3** are sufficiently acidic that the acid–basic exchange completely dominates.

Alkylation of **7** using *n*-propyl bromide gave the corresponding *n*-butyl derivative **8** in 84% yield. Similarly, alkylation of **7** with propargyl bromide occurred smoothly to give **9**.

To examine the usefulness of this synthetic method the *n*-butyl derivative **8** was carried through to give *trans*-15-*n*-butyl-16-methyldihydropyrene (**15**), as shown in Scheme I. Hydrolysis of **8** with 10% hydrochloric acid gave 2-*n*-butylisophthalic acid (**10**) in 91% yield. Conversion of **10** to the corresponding acid chloride followed by reduction with lithium aluminum hydride produced the 2,6-bis(hydroxymethyl)-*n*-butylbenzene (**11**) in 84% yield. Heating a solution of **11** in aqueous 48% hydrobromic acid led in 96% yield to 2,6-bis(bromomethyl)-*n*-butylbenzene (**12**). A coupling reaction of **12** with 2,6-bis(mercaptomethyl)toluene, under the usual conditions,[10] gave the *anti*-9-*n*-butyl-18-methyl-

Scheme I



10 **11** **12** **13** **14** **15**

2,11-dithia[3.3]metacyclophane (**13**) in 80% yield with no evidence for the syn isomer. A Wittig rearrangement of the dithiacyclophane **13** followed by reaction with methyl iodide gave the ring contracted product **14** as a mixture of isomers in 80% yield. This was subjected to the Hofmann elimination procedure[1] and gave *trans*-15-*n*-butyl-16-methyldihydropyrene (**15**) in 68% yield.

trans-15-*n*-Butyl-16-methyldihydropyrene is the first dihydropyrene to be synthesized having different internal substituents at the 15 and 16 positions. It forms deep green crystals, mp 54.0–54.5 °C. Although the ultraviolet–visible spectrum of *trans*-15-*n*-butyl-16-methyldihydropyrene (**15**) is quite similar to that of the parent compound, *trans*-15,16-dimethyldihydropyrene,[18] **15** shows considerably more fine structure and its extinction coefficients in the region of 580–650 nm are in the range of 950–2100, whereas the extinction coefficients for *trans*-15,16-dimethyldihydropyrene in this region are only in the range of 110–330. The ^{1}H NMR spectrum of **15** is pretty much as expected, but provides an extended mapping of the magnetic field due to ring current. Thus, the protons of the internal methyl group appear at τ 14.30, and the butyl group shows four multiplets: the α-methylene protons at τ 13.90–14.14, the β-methylene at τ 11.51–11.91, the γ-methylene at τ 10.20–10.62, and the methyl protons as a triplet at τ 10.10.

The mass spectra of the dihydropyrenes are characterized by a small signal for the parent molecular ion, a somewhat larger signal for the fragment corresponding to loss of one internal alkyl group, and then a large signal for the pyrene molecular ion, corresponding to loss of both internal alkyl groups. In the case of **15**, in which the internal alkyl groups differ, it was of interest to see which would be more readily ejected. On a scale where the pyrene molecular ion is 100, the signal for the parent molecular ion was 2; that of the fragment for loss of the methyl group (M − 15) was 0.5; and that of the fragment for loss of the butyl group (M − 57) was 29. Thus, **15** on electron impact leads predominantly to ejection of the larger *n*-butyl group rather than the methyl group.

Experimental Section[19]

1,3-Bis(4′,4′-dimethyl-2′-oxazolinyl)benzene (1). This was prepared following the general procedure of Meyers et al.[20] To a solution of 35.60 g (0.4 mol) of 2-amino-2,2-dimethylethanol in 500 mL of anhydrous chloroform cooled to 0 °C there was added dropwise with stirring over a 3-h period a solution of 20.30 g (0.1 mol) of isophthaloyl chloride in 100 mL of anhydrous chloroform. The mixture was then allowed to warm to room temperature and was stirred an additional 24 h. The resulting mixture was washed with two 150-mL portions of water and the aqueous washings were extracted with chloroform. The combined chloroform solutions were dried and concentrated to give the expected bis(hydroxyamide) as a viscous oil. This was suspended in 250 mL of chloroform and 39 mL of thionyl chloride was added dropwise with stirring at a rate to maintain gentle boiling under reflux. After the addition was complete, the mixture was stirred at room temperature for an additional 3 h. Addition of 750 mL of ether then caused the separation of a white crystalline solid. This solid, the hydrochloride salt of **1**, was collected by filtration, washed with ether, and dried. A solution of this hydrochloride salt in 150 mL of water was brought to a pH of 10 by addition of a 10% aqueous solution of sodium hydroxide and the resulting oily suspension was extracted with chloroform. After the chloroform extract had been washed with water, it was dried and concentrated to give 23.2 g (85%) of faintly yellow crystals: mp 78–80 °C; NMR ($CDCl_3$) τ 1.53 (s, 1 H, ArH), 1.98 (d, 2 H, J = 7 Hz, ArH), 2.60 (t, 1 H, J = 7 Hz, ArH), 5.93 (s, 4 H, $-OCH_2-$), 8.67 (s, 12 H, $-CH_3$); IR ($CHCl_3$) 1650 cm^{-1} (–C=N–).

Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.60; H, 7.35; N, 10.05.

Alkylation of 1. General Method. To a solution of 2.72 g (0.01 mol) of 1,3-bis(4′,4′-dimethyl-2′-oxazolinyl)benzene (**1**) and 4.50 mL (0.03 mol) of TMEDA in 30 mL of benzene was added a benzene solution containing 0.03 mol of lithium diisopropylamide. The resulting deep purple solution was stirred at room temperature for 7 h and then was quenched by addition of 6.2 mL of methyl iodide. After the mixture had been diluted by addition of 75 mL of ethyl acetate, it was washed with water, dried, and concentrated to give a brown oil. This was taken up in ether and passed over a short silica gel column. Concentration of the eluate followed by recrystallization of the solid residue from hexane gave 2.80 g (98%) of **3** as white crystals: mp 80–82 °C; NMR ($CDCl_3$) τ 2.38 (d, 2 H, J = 7 Hz, ArH), 2.88 (t, 1 H, J = 7 Hz, ArH), 6.02 (s, 4 H, $-OCH_2-$), 7.46 (s, 3 H, $-CH_3$), 8.74 (s, 12 H, $-CH_3$); IR (KBr) 1645 cm^{-1} (–C=N–).

Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.27; H, 7.67; N, 9.46.

2-Methylisophthalic Acid. As proof of structure, a 2.80-g sample of **3** in 100 mL of 3 N hydrochloric acid was hydrolyzed by boiling under reflux for 20 h. The crystalline mass which separated was collected by filtration, washed with water, and dried to give 1.39 g (77%) of crystals, mp 232–235 °C (lit.[1] gives 228–229 °C), identical in all respects with an authentic sample of 2-methylisophthalic acid.

Lactone 6. When the experiment described above for the preparation of **3** was repeated, but substituting allyl bromide for methyl iodide, the corresponding allyl derivative **4** was isolated as a viscous oil in 41% yield. This was subjected directly to hydrolysis using 3 N hydrochloric acid as described for the preparation of **5**. In this case the product isolated had the composition and spectral properties to be expected for lactone **6** rather than the simple dicarboxylic acid. Lactone **6** was isolated, after recrystallization from benzene, as faintly yellow crystals: mp 165–168 °C; NMR ($CDCl_3$) a singlet at τ 0.60 (s, 1 H, ArH), 1.64 (d, 2 H, J = 3.5 Hz, ArH), 5.12–5.53, 6.20, and 6.49 (m, 3 H, ABC), 8.45 (d, 3 H, J = 3 Hz, CH_3–); IR (KBr) 1724 (–OC–), 1695 (>C=O).

Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.87; H, 4.78.

Alkylation of 3. General Method. To a solution of 5.38 g (0.18 mol) of 2,6-bis(4′,4′-dimethyl-2′-oxazolinyl)toluene (**3**) in 300 mL of benzene was added a solution of 0.0226 mol of *n*-butyllithium in hexane with vigorous stirring under a nitrogen atmosphere. After the resulting dark purple solution had been stirred at room temperature for an additional 30 min, 9 g of *n*-propyl bromide was added and the orange mixture was stirred for 24 h. Addition of 100 mL of water was followed by vigorous stirring and then 200 mL of diethyl ether. The organic layer was separated, washed twice with water, dried, and concentrated to give 6.21 g of **8** as a thick oil. This was taken up in ether and chromatographed over silica gel. Concentration of the main eluate fraction gave 5.20 g (84%) of white crystals: mp 67–68 °C; NMR ($CDCl_3$) τ 2.52 (d, 2 H, J = 7 Hz, ArH), 2.80 (t, 1 H, J = 7 Hz, ArH), 5.95 (s, 4 H, $-CH_2O-$), 6.85 (t, 2 H, J = 7 Hz, $ArCH_2-$), 8.2–8.8 (m, 4 H, $-CH_2-$) with a coincidental singlet at 8.63 (12 H, $-CH_3$), 9.11 (t, 3 H, J = 7 Hz, $-CH_3$); IR ($CHCl_3$) 1650 cm^{-1} (–N=C–); mass spectrum (70 eV) *m/e* (rel intensity) 328 (72), 313 (21), 299 (49), 285 (8), 273 (23), 256 (60), 243 (100), 230 (26), 214 (19), 202 (45); UV (cyclohexane) 275 nm (ϵ 1300).

Anal. Calcd for $C_{20}H_{28}N_2O_2$: c, 73.14; H, 8.59; N, 8.53. Found: C, 72.99; H, 8.76; N, 8.32.

2-(3-Butyn-1-yl)-1,3-bis(4′,4′-dimethyl-2′-oxazolinyl)benzene (9). When the experiment described above for the preparation of **8** was repeated, but substituting propargyl bromide for *n*-propyl bromide, the corresponding propargyl derivative **9** was formed. The viscous oil first isolated was chromatographed over silica gel using a 1:3 ether–chloroform solution for elution. The main eluate fraction gave in 26% yield a pale yellow oil: NMR ($CDCl_3$) a doublet at τ 2.29 (d, 2 H, J = 7 Hz, ArH), 2.75 (t, 1 H, J = 7 Hz, ArH), 5.95 (s, 4 H, $-OCH_2-$), 6.55 (t, 2 H, J = 8 Hz, $-CH_2-$), 7.50 (m, 2 H, A_2M_2X, J_{AM} = 8 Hz, J_{MX} = 2 Hz), 8.05 (t, 1 H, J = 2 Hz, –C≡CH), 8.63 (s, 12 H, CH_3–); IR (KBr) 3300 (≡CH) and 1650 cm^{-1} (–N=C–).

Anal. Mol wt calcd for $C_{20}H_{24}N_2O_2$: 324.184. Found (high-resolution mass spectrum): 324.183.

2-*n*-Butylisophthalic Acid (10). A solution of 1.3 g of 2-*n*-butyl-1,3-(4′,4′-dimethyl-2′-oxazolinyl)benzene (**8**) in 150 mL of a 10% aqueous solution of hydrochloric acid was boiled under reflux for 18 h. It was then allowed to stand in the refrigerator for 24 h and the crystalline precipitate which formed was collected by filtration. The aqueous filtrate was extracted with ethyl acetate and concentration of the ethyl acetate gave an additional amount of crystals. The combined solids were recrystallized from a water–methanol mixture to give 847 mg (91%) of colorless crystals: mp 208–209 °C; NMR ($CDCl_3$) τ 2.72 (d, 2 H, J = 7 Hz, ArH), 3.29 (t, 1 H, J = 7 Hz, ArH), 7.41 (t, 2 H, J = 8 Hz, $ArCH_2-$), 8.61 (m, 2 H, $-CO_2H$), 8.9–9.5 (m, 4 H, $-CH_2-$), 9.81 (t, 3 H, J = 6 Hz, $-CH_3$); mass spectrum (70 eV) (rel intensity) 222 (38), 205 (7), 193 (5), 189 (4), 180 (72), 175 (43), 161 (26), 147 (5), 134 (100); UV (EtOH) 281 nm (ϵ 1300).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.79; H, 6.37.

2,6-Bis(hydroxymethyl)-*n*-butylbenzene (11). A solution of 1.62 g of 2-*n*-butylisophthalic acid (**10**) in 15 mL of thionyl chloride containing 2 drops of dimethylformamide was boiled under reflux for 30 min. The solution was then concentrated under vacuum and the residue was taken up in 25 mL of dry tetrahydrofuran. This was added dropwise to a stirred suspension of 1.19 g of lithium aluminum hydride in 75 mL of dry tetrahydrofuran. When the addition was complete, the mixture was boiled under reflux for 6 h and decomposed by the addition of 10 mL of a saturated sodium sulfate solution followed by 10 mL of aqueous 3 N hydrochloric acid. The mixture was then partitioned between 200 mL each of water and ether. The ether extract was separated, dried, and concentrated to give 1.41 g (100%) of a colorless solid. This was recrystallized from benzene to yield 1.19 g (84%) of colorless fibers: mp 63–64 °C; NMR ($CDCl_3$) τ 2.5–2.8 (m, 3 H, ArH), 5.26 (s, 4 H, $-CH_2O-$), 7.26 (t, 2 H, J = 8 Hz, $ArCH_2-$), 8.36 (s, 2 H, –OH), 8.2–8.7 (m, 4 H, $-CH_2-$), 9.03 (t, 3 H, J = 7 Hz, $-CH_3$); IR ($CHCl_3$) 3595 cm^{-1} (–OH); UV (EtOH) 213 (ϵ 11 000), 238 (70), 243 (100), 247 (160), 253 (230), 259 (270), 263 (270), 278 nm (190); mass spectrum (70 eV) (rel intensity) 194 (64), 178 (15), 161 (14), 158 (74), 151 (10), 147 (19), 137 (15), 133 (17), 129 (100).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.79; H, 9.15.

2,6-Bis(bromomethyl)-*n*-butylbenzene (12). A solution of 933 mg of 2,6-bis(hydroxymethyl)-*n*-butylbenzene (**11**) in 40 mL of a 48% aqueous solution of hydrobromic acid was stirred at 50 °C for 30 min. When the solution was allowed to stand overnight in the refrigerator, a crystalline mass separated. This was collected, washed successively with aqueous sodium bicarbonate and water, and dried to give 1.57 g of white crystals. These, on recrystallization from petroleum ether (30–60 °C), gave 1.36 g (90%) of colorless needles: mp 57–58 °C; NMR ($CDCl_3$) τ 2.62–3.00 (m, 3 H, ArH), 5.48 (s, 4 H, $-CH_2Br$), 7.09 (t, 2 H, J = 8 Hz, $ArCH_2-$), 8.2–8.6 (m, 4 H, $-CH_2-$), 9.00 (t, 3 H, J = 6 Hz, $-CH_3$); IR ($CHCl_3$) 550 cm^{-1} (–CBr); mass spectrum (70 eV) (rel intensity) 320 (36), 277 (46), 239 (19), 199 (62), 197 (63), 159 (100).

Anal. Calcd for $C_{12}H_{16}Br_2$: C, 45.03; H, 5.04. Found: C, 45.19; H, 5.13.

9-*n*-Butyl-18-methyl-2,11-dithia[3.3]metacyclophane (13). A solution of 539 mg of 2,6-bis(bromomethyl)-*n*-butylbenzene (**12**) and 384 mg of 2,6-bis(mercaptomethyl)toluene in 300 mL of benzene was added dropwise from a Hershberg funnel to a stirred solution of 200 mg of sodium hydroxide in 800 mL of 95% ethanol under nitrogen. The addition was complete in 24 h; the mixture was stirred an additional 24 h and then concentrated. The residue was dissolved in chloroform, washed with aqueous brine, dried, and concentrated. The resulting solid was taken up in benzene and chromatographed over silica gel. The crystalline solid from the main fraction of eluate was recrystallized from a benzene–petroleum ether (30–60 °C) mixture to give 464 mg (80%) of colorless needles: mp 98–100 °C; NMR ($CDCl_3$) τ 2.64–3.06 (m, 6 H, ArH), 6.28–6.38 (m, 8 H, $ArCH_2S-$), 8.36 (t, 2 H, J = 7 Hz, $ArCH_2-$), 8.70 (s, 3 H, $ArCH_3$), 8.9–9.2 (m, 4 H, $-CH_2-$), 9.22 (m, 3 H, J = 6 Hz, $-CH_3$); UV (EtOH) 285 nm (ϵ 360); mass spectrum (70 eV) (rel intensity) 342 (100), 308 (3), 299 (11), 265 (16), 191 (71), 159 (29), 149 (81).

Anal. Calcd for $C_{21}H_{26}S_2$: C, 73.63; H, 7.62. Found: C, 73.73; H, 7.71.

Wittig Rearrangement of 13 to Give 14. To a solution of 1.01 g of 9-*n*-butyl-18-methyl-2,11-dithia[3.3]metacyclophane (**13**) in 25 mL of dry tetrahydrofuran there was added a solution of 7.36 mmol of *n*-butyllithium in hexane at 0 °C. After the mixture had been stirred for 4 min, it was quenched by addition of 3 mL of methyl iodide and stirred a further 10 min. The mixture was then taken up in dichloromethane, washed with water, dried, and concentrated. The residue was chromatographed over silica gel using a 1:1 mixture of ether–benzene for elution. From the main fraction of eluate there was obtained 875 mg (80%) of a colorless oil: NMR ($CDCl_3$) τ 2.23–3.3 (m, 6 H, ArH), 5.94 (dd, 2 H, $-CH(SMe)CH_2-$), 6.80 (m, 4 H), 7.32 (m, 2 H), 7.89 (s, 6 H, $-SCH_3$), 8.4–9.6 (m, 4 H, $-CH_2-$), 9.39 (t, 3 H, J = 4 Hz, $-CH_3$); mass spectrum (70 eV) (rel intensity) 370 (59), 355 (19), 323 (16), 308 (34), 217 (31), 202 (80), 149 (91), 147 (100).

Anal. Calcd for $C_{23}H_{30}S_2$: C, 74.54; H, 8.16. Found: C, 74.54; H, 8.82.

***trans*-15-*n*-Butyl-16-methyldihydropyrene (15).** A solution of 470 mg of the Wittig product **14** in 15 mL of dichloromethane was added dropwise with stirring to a suspension of 601 mg of dimethoxycarbonium fluoroborate in 5 mL of dichloromethane held at −30 °C under nitrogen. The mixture was then allowed to warm to room temperature and was stirred for 6 h. After addition of 20 mL of ethyl acetate, the mixture was stirred and the liquid decanted. The solid residue of the bis(dimethylsulfonium) salt was washed again with ethyl acetate, decanted, and used directly without further purification. To a stirred solution of the bis(dimethylsulfonium) salt in 20 mL of dry tetrahydrofuran under nitrogen there was added a suspension of 1.10 g of sodium hydride in 30 mL of dry tetrahydrofuran. The resulting mixture was boiled under reflux for 7.5 h, cooled, and decomposed by successive additions of 10 mL of benzene, 10 mL of water, and 10 mL of aqueous 3 N hydrochloric acid. The organic layer was separated, washed with water, dried, and concentrated to give a dark green oil. Chromatography of this oil over silica gel using hexane for elution gave 236 mg (68%) of deep green crystals: mp 54.0–54.5 °C; NMR ($CDCl_3$) τ 1.45 (m, 8 H, ArH), 1.89–2.22 (m, 2 H, ArH), 10.10 (t, 3 H, J = 7 Hz, $-CH_2CH_2CH_2CH_3$), 10.20–10.62 (m, 2 H, $-CH_2CH_2CH_2CH_3$), 11.51–11.91 (m, 2 H, $-CH_2CH_2CH_2CH_3$), 13.90–14.14 (m, 2 H, $-CH_2CH_2CH_2CH_3$), 14.30 (s, 3 H, $-CH_3$); UV (cyclohexane) 238 (ϵ 6300), 273 (780), 324 (34 000), 340 (100 000), 343 (110 000), 358 (25 000), 379 (43 000), 383 (52 000), 420 (3100), 441 (4300), 463 (6200), 478 (6500), 485 (6300), 533 (640), 542 (590), 575 (430), 581 (570), 592 (950), 605 (1400), 618 (1800), 634 (1900), 647 (2100), 652 nm (2100); mass spectrum (70 eV) *m/e* (rel intensity) 274 (2), 269 (0.5), 217 (29), 215 (7), 202 (100), 189 (4).

Anal. Calcd for $C_{21}H_{22}$: C, 91.92; H, 8.08. Found: C, 91.81; H, 8.00.

Acknowledgment. We thank the National Science Foundation for their support of this work. T. D. Harris thanks the National Institute of Health for a postdoctoral fellowship award, 1732GM05326.

Registry No.—**1**, 64682-37-7; **1** HCl, 64682-38-8; **3**, 64682-39-9; **4**, 64682-40-2; **6**, 64682-41-3; **8**, 64682-42-4; **9**, 64682-43-5; **10**, 5293-56-1; **11**, 64682-44-6; **12**, 64682-45-7; **13**, 64682-46-8; **14**, 64682-34-4; **14** bis(dimethylsulfonium)tetrafluoroborate salt, 64682-36-6; **15**, 64682-47-9; 2-amino-2,2-dimethylethanol, 124-68-5; isophthaloyl chloride, 99-63-8; allyl bromide, 106-95-6; propyl bromide, 106-94-5; propargyl bromide, 106-96-7; 2,6-bis(mercaptomethyl)toluene, 41563-67-1.

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α Addition and Ortho Metalation of Phenyl Isocyanide[1]

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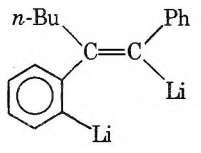
The reaction of *tert*-butyllithium with phenyl isocyanide in the presence of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) resulted in a product of α addition plus ortho lithiation. The ortho-lithiated lithium aldimine (**2**) formed in this manner was reacted with methyl iodide, methylene halides, carbon dioxide, phosgene, oxygen, and cuprous chloride. In addition, several novel heterocyclic compounds, 3-metalloindolines (metal = S, P, Si, Ge, and Sn), were synthesized by reacting **2** with the corresponding metallo dihalides. The new heterocyclic compounds were characterized using ^1H and ^{13}C NMR techniques.

The α addition of organolithium reagents and Grignard reagents to isocyanides has recently been reported.[2,3] The resulting metalloaldimines, which can be viewed as masked acyl carbanions, were used for the syntheses of a variety of functional groups including aldehydes-*1-d*, ketones, α-keto acids and β-hydroxy ketones.

It was observed by Mulvaney and co-workers[4] that diphenylacetylene reacted with 2 equiv of *n*-butyllithium to give as a major product **1**, which results from the trans addition to



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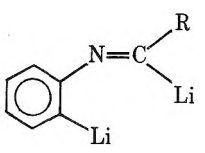

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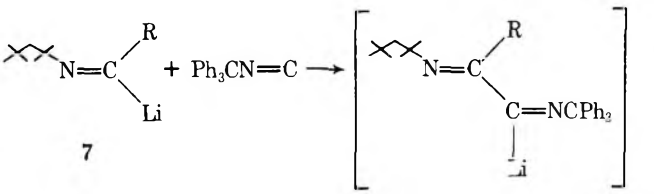
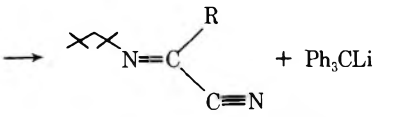
the triple bond as well as ortho lithiation. It was also shown that the ortho lithiation step could be catalyzed by the use of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA).[5,6] By analogy with this reaction, it was suggested[7] that an alkyllithium reagent and phenyl isocyanide, in the presence of TMEDA, should react to yield a product of α addition and ortho lithiation **2**.

n-Butyllithium and phenyllithium reacted with phenyl isocyanide to give products other than simple addition products.[8] *sec*-Butyllithium gave low yields (~10%) of the dilithiated aldimine **2**. It was only when *tert*-butyllithium was used that a high yield of **2** was obtained and then only if the reaction was run at −78 °C and the phenyl isocyanide was added to 2 equiv of *tert*-butyllithium. Low yields resulted if both these requirements were not met.

A reasonable explanation for the requirement of low temperature and the need for excess *tert*-butyllithium in solution is that the lithium aldimine **3** can further react with any excess phenyl isocyanide in solution to form a dimer[8] **4** which may then react, in a number of ways, as shown in Scheme I. This reaction scheme accounts for the formation of the secondary amine **5**, observed in the reaction of *n*-butyllithium with phenyl isocyanide.[8] An intermediate similar to **6** has also been proposed.[8] A bulky *tert*-butyl group should shift the equilibrium toward the monomeric aldimine **3** and thereby prevent unwanted side reactions. Additional support for this interpretation is provided by some recent results in our laboratory.[9] When R is *n*-butyl, the isocyanide–metal exchange reaction[10] proceeds to give a 25% yield of α-iminocyanide **9**. The lithium *tert*-butylaldimine **7** gives only trace amounts of **9** because the steric bulk of the *tert*-butyl group prevents formation of the intermediate dimer **8**.



7 **8**



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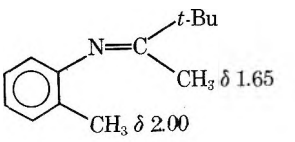
TMEDA is necessary for the ring-metalation step in the formation of the dilithium aldimine **2**; without it no detectable ring metalation took place after stirring for 4 h at room temperature. When the reaction mixture of lithium *tert*-butylaldimine (**3**), *tert*-butyllithium, and TMEDA was alkylated, after stirring for 1 h at room temperature with methyl iodide, a comparison (^1H NMR) of the integrated benzylic and methyl ketimine protons (**10**) showed that 65% ring metalation



10

had taken place. A 4-h time period assured >90% ring metalation. That ring metalation was, in fact, taking place at the ortho position was demonstrated by hydrolysis of **10** to yield

Scheme I. Formation and Reactions of Lithium Aldimine Dimer[8]

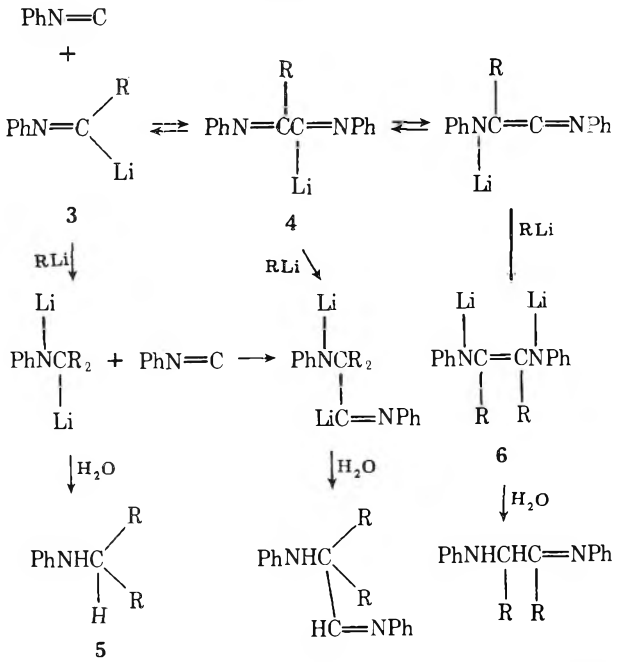


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Table I. C-13 Chemical Shifts[a] and ^1H NMR of the *tert*-Butyl Group for Heterocyclic Compounds

M	Registry no.	C-1	C-2	C-3	*t*-Bu
Acyclic (13)	13114-20-0	152.2	176.9	40.2	1.20
S	17626-88-9	153.4	181.5	38.3	1.49
PhP	64414-15-9	158.5	198.8	40.0	1.22
Ph_2Si	64414-14-8	161.0	200.6	40.2	1.16
Me_2Si	64414-18-2	159.6	201.7	39.7	1.24
Me_2Ge	64414-17-1	161.5	201.3	40.5	1.23
Me_2Sn	64414-16-0	159.6	*b*	4.17	1.18

[a] Ppm from Me_4Si. [b] Decomposed before least intense peak (C-2) could be recorded.

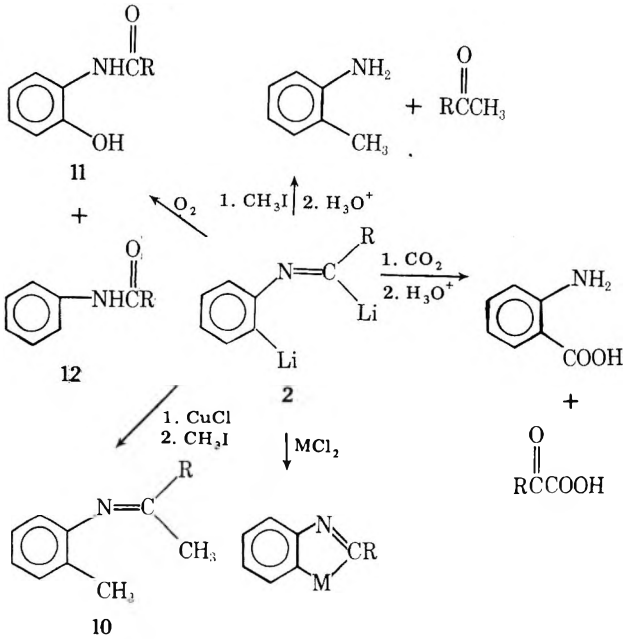
o-toluidine and methyl *tert*-butyl ketone as the sole products.[11] Moreover, treatment of the dilithium aldimine **2** (R = *t*-Bu) with carbon dioxide followed by hydrolysis yielded anthranilic acid and 2-oxo-3,3-dimethylbutanoic acid.

Attempts to synthesize 3-oxoindolines by reaction of **2** with phosgene or ethyl chloroformates or to prepare 3*H*-indoles using methylene halides proved unsuccessful. Molecular oxygen reacted with **2** to yield a mixture consisting of the *tert*-butylcarboxamides of *o*-hydroxyaniline **11** and aniline **12**, respectively. The latter amide **12** did not arise from incomplete reaction of **2**, since workup of the reaction mixture with deuterium oxide showed no deuterium incorporation. Organolithium reagents are known to react with oxidizing reagents to form radical intermediates which can then abstract hydrogen atoms from the solvent.[12]

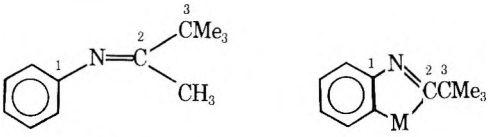
The dilithiated aldimine **2** was reacted with 1 equiv of cuprous chloride to form a lithium cuprate which when treated with methylene iodide did not yield the expected 3*H*-indole or indole itself. Reaction with methyl iodide produced the dimethylated product **10** in 65–75% yield.

The preparation of five-membered unsaturated organometallic heterocyclic and spirocyclic compounds by means of reaction between a 1,4-dilithium derivative and a metallic dihalide has been described previously. A host of metallocyclopentadienes have been synthesized starting with 1,4-dilithio-1,2,3,4-tetraphenylbutadiene.[13] Several metalloindenyl compounds of iron,[14] aluminum,[15] and selenium[16] have been prepared as well as compounds of phosphorous, silicon, germanium and tin.[6] These same workers[6] prepared spirocyclic compounds containing tin, germanium, and silicon.

Scheme II. Reactions of Dilithium Aldimine 2 (R = *t*-Bu)



Dilithium aldimine **2** was reacted with a variety of metallodihalides to generate novel heterocyclic systems (Scheme II). The new compounds were characterized using IR, ^1H NMR, UV, ^{13}C NMR and high-resolution mass spectrometry (see Experimental Section). Table I shows the ^{13}C NMR chemical shifts for the three carbon atoms in these ring systems whose chemical-shift values should be most sensitive to the effects of aromaticity. For comparative purposes, the model acyclic compound **13** is also included.



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It should be noted that all of the heterocyclic compounds with the exception of the benzothiazole (M = S) have similar chemical shifts at carbons 1, 2, and 3. This difference between the sulfur compound and the other heterocyclic systems could be explained in terms of the heteroaromaticity of the benzothiazole and nonaromaticity of the other compounds. This argument is weakened somewhat by the observation that the chemical shifts for the acyclic model **13** more closely parallel those of the benzothiazole than they do the others. Table I shows the ^1H NMR chemical-shift values for the *tert*-butyl group. These data are more directly related to the question of aromaticity of the heterocyclic systems. It is noted that all of the compounds with the exception of benzothiazole have *tert*-butyl groups with δ values of ~1.20 ppm. The downfield chemical shift of the *tert*-butyl group of the benzothiazole relative to the other heterocyclic compounds can best be explained if the benzothiazole is the only compound which is aromatic and therefore possesses a ring current which causes deshielding (anisotropic) of the *tert*-butyl group. Therefore, of these heterocyclic 3-metalloindolines, only the benzothiazole appears to be aromatic.[14]

From a synthetic point of view it should be pointed out that the isonitrile moiety provides a means of protecting an aromatic primary amino group in order to obtain ortho metalation.

Experimental Section

Melting points were measured with a Mel-Temp apparatus. No corrections were made for either melting or boiling points. Proton nuclear magnetic resonance spectra were recorded on a Varian A-60 or Brucker 90-MHz spectrometer; chemical shifts were reported in parts per million downfield from tetramethylsilane and coupling constants are in hertz. C-13 nuclear magnetic resonance spectra were obtained using either the Brucker 90- or 270-MHz spectrometer. The chemical shifts were reported in parts per million downfield from tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. UV spectra were obtained with a Cary 14 spectrophotometer using 1-cm cells and concentrations of 1×10^{-4} M. Low-resolution mass spectra were recorded either on a Nuclide electron-impact mass spectrometer or a AEI-MS902 chemical-ionization mass spectrometer using isobutane as the carrier gas. High-resolution mass spectra were done on the AEI-MS902 electron-impact instrument.

Reagents. Organolithium reagents were purchased from Foote Mineral Co. and were titrated prior to use employing the method of Epplex and Dixon.[15] Mallinckrodt anhydrous ethyl ether was used directly in the preparation of phenyl isocyanide. For reactions involving organolithium reagents, the ethyl ether was distilled over lithium aluminum hydride and stored over sodium hydride prior to use. Phenyl isocyanide was distilled and stored in the freezer before using. Generally, it would last about 4 days at −40 °C before deteriorating to an unacceptable level. If there was doubt as to the quality of the phenyl isocyanide, a control reaction was run simultaneously by quenching the dilithium aldimine (**2**) with methyl iodide (see Determination of Ortho Substitution in the Experimental Section).

All other reagents were distilled or recrystallized whenever their purity was in question.

Phenyl Isocyanide. To a stirred solution of 60 g (.496 mol) of formanilide in 400 mL of dry ether with 125 g (1.24 mol) of dry triethylamine under a nitrogen atmosphere was added 71 g (0.597 mol) of thionyl chloride dropwise at such a rate that the temperature did not exceed −55 °C. After the addition was completed, the temperature was allowed to rise to −25 °C and 250 mL of saturated sodium carbonate solution was added quickly with continued stirring. The two-phase system was transferred to a separatory funnel, and the organic phase was separated, dried over anhydrous sodium carbonate, and evaporated. The residue remaining was distilled under reduced pressure to yield 23.5 g (0.228 mol, 46%) of a light yellow oil: bp 53 °C (12 mm) (lit.[15] 55 °C (15 mm)); IR (CCl_4) 2130 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (s).

***N*-(1-Lithium-2,2-dimethylpropylidene)-2-lithiobenzenamine (2).** To 21.6 mmol of *tert*-butyllithium in 50 mL of anhydrous ether at −78 °C and under a nitrogen atmosphere was added dropwise over 10 min a solution of 1.0 g (9.7 mmol) of phenyl isocyanide in 15 mL of anhydrous ether. The solution was allowed to warm to room temperature, 2.5 g (22 mmol) of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) was quickly added, and the solution was stirred for 4 to 12 h at ambient temperature.

***N*-(1,2,2-Trimethylpropylidene)-2-methylbenzenamine (10).** To 9.7 mmol of the dilithium aldimine (2) prepared as above, in 50 mL of anhydrous ether, cooled to 0 °C, was added 5.7 g (40 mmol) of methyl iodide. The solution was stirred for 30 min at ambient temperature and was then transferred to a separatory funnel, washed three times with water, and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was distilled at reduced pressure to yield 1.68 g (8.9 mmol, 92%) of **10** as a liquid: bp 73–75 °C (1.2 mm); IR (CCl_4) 1655 (s), 1600 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (s, 9 H), 1.65 (s, 3 H), 2.00 (s, 3 H), 6.3–7.3 (m, 4 H); measured mass 189.1507 (rel intensity 12.8%), calcd mass 189.1517 (dev 0.9 mass unit).

Determination of Ortho Substitution. Identification of *o*-Toluidine and Methyl *tert*-Butyl Ketone. *N*-(1,2,2-Trimethylpropylidene)-2-methylbenzenamine (1.7 g, 8.9 mmol) was refluxed for 10 min in 5% aqueous hydrochloric acid and then extracted with ether. The ether solution was dried over anhydrous sodium sulfate and evaporated to yield 0.52 g (5.2 mmol/56%) of a clear liquid which was identified as methyl *tert*-butyl ketone by its IR, ^1H NMR, and the preparation of its oxime: mp 73 °C (lit.[17] 74–75 °C); IR (CCl_4) 1715 (s) cm^{-1}; ^1H NMR (CCl_4) δ 1.12 (s, 9 H), 2.08 (s, 3 H).

The acidic portion was neutralized with 10% sodium hydroxide solution, extracted with ether, dried over anhydrous sodium sulfate, and evaporated to yield 0.54 g (5.1 mmol/57%) of a liquid which was identified as *o*-toluidine by a comparison of its IR, ^1H NMR, and GLC retention times with an authentic sample of o-toluidine. In addition, GLC (10 ft. Carbowax 20 M, 210 °C) showed no meta or para isomers but a small amount of aniline (<5%).

Carbonation of the Dilithium Aldimine (2). Identification of 2-Oxo-3,3-dimethylbutanoic Acid and o-Anthranilic Acid. A solution of 9.7 mmol of dilithium aldimine (2) in 50 mL of ether was cooled to −78 °C and carbon dioxide was bubbled through rapidly. The solution was allowed to warm to ambient temperature with continued passage of carbon dioxide. The solvent was evaporated, 5% aqueous hydrochloric acid was added to the residue, and the mixture was refluxed 10 min, cooled, and extracted with ether. The ethereal solution was dried over anhydrous magnesium sulfate and evaporated to yield 0.917 g of a liquid which was shown to be 90% one component by GLC (6 ft Carbowax 20 M, 140 °C). The minor component was identified as 2,2-dimethylpropanoic acid by comparing retention times with an independently prepared sample from *tert*-butyllithium and carbon dioxide. The residue was recrystallized from ethyl ether–pentane to yield 0.822 g (6.32 mmol, 65%) of a solid, mp 79–81 °C, identified as 2-oxo-3,3-dimethylbutanoic acid (lit.[17b] mp 82 °C): IR (CCl_4) 3380 (m), 2960 (s), 2680 (w), 1770 (m), 1710 (s) cm^{-1}; ^1H NMR δ 1.30 (s, 9 H), 9.15 (s, 1 H).

The remaining aqueous portion was neutralized to pH 5 with 10% sodium hydroxide, extracted with methylene chloride, dried over anhydrous magnesium sulfate, and evaporated to yield a solid which was recrystallized from methylene chloride/pentane to yield 0.718 g (5.25 mmol, 54%) of a solid which did not depress the melting point of an authentic sample of anthranilic acid: IR ($CHCl_3$) 3485 (s), 3365 (s), 3200–2450 (s), 1670 (s), 1615 (s), 1590 (m), 1560 (m) cm^{-1}; ^1H NMR (CH_3CN), δ 6.0 (br, 3 H), 6.5–8.0 (m, 4 H).

Oxygenation of the Dilithium Aldimine. Identification of *N*-Phenyl-2,2-dimethylpropanamide (12) and *N*-(o-Hydroxyphenyl)-2,2-dimethylpropanamide (11). Oxygen was bubbled through a solution of 9.7 mmol of dilithum aldimine (2) in anhydrous ether cooled to −78 °C as the solution was allowed to come to room temperature. The ethereal solution was washed several times with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was taken up in a minimum amount of methylene chloride, placed on a neutral alumina column, and eluted with dry ethyl ether. The first material to be eluted was 0.61 g (3.45 mmol, 36%) of a yellow solid identified as *N*-phenyl-2,2-dimethylpropanamide (12) by its melting point, which was 129–131 °C (lit.[17c] mp 132 °C); IR (CCl_4) 3435 (m), 1690 (s), 1600 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (s, 9 H) 6.8–7.7 (m, 5 H); positive chemical ionization mass spectrum P + 1 = 178.

The second, more polar fraction weighed 0.595 g (2.77 mmol, 29%) and was identified as *N*-(o-hydroxyphenyl)-2,2-dimethylpropanamide (11) by its melting point, which was 132–133 °C (lit.[17d] 133 °C): IR ($CHCl_3$) 3420 (s), 1650 (s), 1600 (m) cm^{-1}; ^1H NMR (acetone-d_6) δ 1.34 (s, 9 H), 3.33 (br, 1 H), 6.7–7.9 (m, 4 H), 8.6 (br, 1 H); positive chemical ionization mass spectrum, P + 1 = 194.

***N*-(1-Copper-2,2-dimethylpropylidene)benzenamine.** To 10.2 mmol of *tert*-butyllithium in 50 mL of anhydrous ether, cooled to −78 °C and under a nitrogen atmosphere, was added 1.0 g (9.7 mmol) of phenyl isocyanide in 15 mL of anhydrous ether over a 10-min period. The solution was allowed to come to room temperature and 0.96 g (9.7 mmol) of anhydrous cuprous chloride was added, causing an instantaneous color change. The solution of *N*-(1-copper-2,2-dimethylpropylidene)benzenamine was stirred for 2 h at room temperature.

Nitrogen was blown through the reaction vessel containing 9.7 mmol of copper aldimine solution from above, evaporating most of the ether, which was replaced with 50 mL of anhydrous THF. This solution was refluxed for 1 h, extracted with dilute ammonium hydroxide followed by saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered through celite, and redried over anhydrous sodium sulfate. The volume of the solution was carefully reduced to 3 mL in a distilling apparatus to avoid loss of any *tert*-butyl cyanide should it be present. GLC on a 3-ft Porapak N column showed no *tert*-butyl cyanide or benzene. Preparative GLC on a 9-ft XE-60 column at 200 °C showed the previously identified *N*-phenyl-2,2-dimethylpropanamide (12) in 34% yield and *N*-(2,2-dimethylpropylidene)benzenamine[17d] in 30% yield: IR (CCl_4) 3050 (w), 2960 (s), 1655 (s), 1600 (m) cm^{-1}; ^1H NMR (CCl_4) δ 1.13 (s, 9 H), 6.7–7.4 (m, 5 H), 7.61 (s, 1 H); positive chemical ionization mass spectra P + 1 = 162.

Lithium Cuprate Aldimine. To 9.7 mmol of the dilithium aldimine (2) in ethereal solution at ambient temperature was added 0.96 g (9.7 mmol) of anydrous cuprous chloride. The dark-green solution was stirred for 1 h at room temperature.

A solution of 9.7 mmol of lithium cuprate aldimine from the above reaction was transferred to a separatory funnel and extracted twice with water and once with dilute ammonium hydroxide. The ethereal solution was filtered through celite, dried over anhydrous potassium carbonate, and evaporated to yield an oil which was crystallized in pentane to yield 9.48 g (2.7 mmol, 28%) of a solid previously identified as *N*-phenyl-2,2-dimethylpropanamide (12) by mp, IR, and ^1H NMR. The mother liquors were evaporated to yield 1.76 g of an oil which was analyzed by GLC (XE-60). The major component (35%) was identified as *N*-(2,2-dimethylpropylidene)benzenamine for an adjusted yield of 26%.

Methylation of the Lithium Cuprate Aldimine. To 9.7 mmol of the lithium cuprate aldimine in ether at ice-bath temperature, under a nitrogen atmosphere, was added an excess of methyl iodide (5.7 g, 40 mmol). The solution was stirred at ambient temperature for 30 min and the usual workup was carried out. ^1H NMR and GLC showed a 65–75% yield of *N*-(1,2,2-trimethylpropylidene)-2-methylbenzenamine (10) which has previously been identified.

***N*-(1,2,2-Trimethylpropylidene)benzenamine (13).** To 20 mmol of *tert*-butyllithium in 50 mL of anhydrous ether, at −78 °C under nitrogen, was added dropwise over a 10-min period a solution of 2.00 g (19.4 mmol) of phenyl isocyanide in 15 mL of anhydrous ether. The solution was allowed to come to 0 °C, 2.84 g (20 mmol) of methyl iodide was added quickly, and the solution was stirred for 30 min at ambient temperature. The reaction mixture was washed with water, dried over sodium sulfate, and evaporated. The residue was distilled to yield 2.95 g (15.9 mmol, 87%) of 13: a liquid; bp 41 °C (0.01 mm); IR (CCl_4) 3050 (w), 2940 (s), 1650 (s), 1590 (m) cm^{-1}; ^1H NMR (CCl_4) δ 1.20 (s, 9 H), 1.71 (s, 3 H), 6.4–7.4 (m, 5 H); UV (CCl_4) 258 (ε 2700), 277 (ε 2700) nm; ^{13}C NMR ($CDCl_3$) δ 15.0, 27.8, 40.2, 118.9, 122.5, 128.8, 152.2, 176.9; measured mass 175.1365 (rel intensity 9.2%), calcd mass 175.1360 (dev 0.4 mmass unit).

General Procedure for the Preparation of the Heterocyclic Compounds. To 19.4 mmol of the dilithium aldimine (2) in 100 mL

of ether, at ice-bath temperature, was quickly added 19.4 mmol of dichloride (2.00 g of SCl_2, 3.47 g of $PhPCl_2$, 4.91 g of $(Ph)_2SiCl_2$, 2.51 g of Me_2SiCl_2, 3.38 g of Me_2GeCl_2, and 4.28 g of Me_2SnCl_2). The reaction mixture was allowed to stir at room temperature from 4 to 12 h before washing three times with water. The ethereal solution was dried over anhydrous sodium sulfate and evaporated, and the residue was distilled at reduced pressure, except in the case of the diphenyl silyl compound which was recrystallized from diethyl ether.

Characterization of 2-*tert*-Butylbenzothiazole.[18] A yellow liquid, 2.40 g (12.6 mmol, 65%), was isolated: bp 59 °C (0.01 mm); IR (CCl_4) 3050 (w), 2960 (s), 1510 (w), 1455 (w), 1440 (m), 1365 (m), 1235 (m) cm^{-1}; ^1H NMR (CCl_4) δ 1.49 (s, 9 H), 7.0–8.0 (m, 4 H); UV (CCl_4) 258 (ϵ 10 000), 284 (ϵ 1700), 295 (ϵ 1700) nm; ^{13}C NMR ($CDCl_3$) δ 30.7, 38.3, 121.3, 122.7, 124.4, 125.7, 135.0, 153.4. 181.5; measured mass 191.9746 (rel. intensity 51.2%), calcd mass 191.9768 (dev 2.3 mmass units).

Characterization of 2-*tert*-Butyl-3-phenylbenzoazaphosphole. A yellow liquid, 2.40 g (12.6 mmol, 52%), was isolated: bp 115–117 °C (0.04 mm); IR (CCl_4) 3050 (w), 2960 (s), 1480 (m), 1445 (s), 860 (s) cm^{-1}; ^1H NMR (CCl_4) δ 1.22 (s, 9 H), 7.0–8.0 (m, 9 H); UV (CCl_4) 258 (ϵ 9000) 305 (ϵ 2400) nm; ^{13}C NMR ($CDCl_3$) 30.4 (d, J = 5.6 Hz), 40.0 (d, J = 18.5 Hz), 123.4, 125.9, 128.3 (d, J = 20.3 Hz), 128.7 (d, J = 9.2 Hz), 129.2, 129.9, 131.5 (d, J = 16.7 Hz), 134.4, 134.7, 137.6 (d, J = 10.3 Hz), 158.5 (d, J = 11.1 Hz), 198.8; measured mass 267.1153 (rel intensity 100.0%), calcd mass 267.1176 (dev 2.3 mmass units).

Characterization of 2-*tert*-Butyl-3,3-diphenylbenzoazasilole. Dry ether was added to the residue and the crystals were filtered, recrystallized from ether/pentane, and placed under high vacuum (0.005 mm) at 80 °C to remove all the ether to yield 2.08 g (6.11 mmol, 63% yield) of a white solid: mp 128–129 °C; IR ($CHCl_3$) 3050 (w), 2950 (s), 1950 (w), 1885 (w), 1815 (2), 1765 (w), 1590 (s), 1115 (s) cm^{-1}; ^1H NMR δ 1.16 (s, 9 H), 7.15–7.75 (m, 14 H); UV (CCl_4) 252 (ϵ 8400), 256 (ϵ 8400), 307 (ϵ 4400) nm; ^{13}C NMR ($CDCl_3$) δ 29.5, 40.2, 124.5, 127.0, 127.6, 128.2, 130.4, 131.7, 132.8, 135.3, 135.6, 161.0, 200.6 ppm; measured mass 341.1611 (rel intensity 86.5%), calcd mass 341.1599 (dev 1.2 mmass units).

Characterization of 2-*tert*-Butyl-3,3-dimethylbenzoazasilole. A colorless liquid, 2.22 g (10.2 mmol, 53%), was obtained: bp 86–88 °C (0.35 mm); IR ($CHCl_3$) 3050 (w), 2940 (s), 1645 (w), 1590, 1565 (w) cm^{-1}; ^1H NMR (CCl_4) δ 0.39 (s, 6 H), 1.24 (s, 9 H), 7.0–7.5 (m, 4 H); UV (CCl_4) 255 (ϵ 3500), 273 (ϵ 3600), 302 (ϵ 3600) nm; ^{13}C NMR −2.9, 28.7, 39.7, 124.1, 126.4, 129.3, 131.1, 131.4, 159.6, 201.7 ppm; measured mass 217.1284 (rel intensity 53.1%), calcd mass 217.1287 (dev. 0.3 mmass unit).

Characterization of 2-*tert*-Butyl-3,3-dimethylbenzoazagermole. A slightly yellow, viscous oil, 3.46 g (13.2 mmol, 68%), was obtained: bp 71–74 °C (0.01 mm); IR (CCl_4) 3050 (m), 2950 (s), 1940 (w), 1905 (w), 1835 (w), 1805 (w), 1600 (m) cm^{-1}; ^1H NMR δ 0.59 (s, 6 H), 1.23 (s, 9 H), 7.0–7.6 (m, 4 H); UV (CCl_4) 253 (ϵ 4600), 265 (ϵ 4600) 293 (ϵ 3400) nm; ^{13}C NMR ($CDCl_3$) δ −1.6, 28.7, 40.5, 118.6, 124.8, 126.6, 128.6, 130.1, 131.4, 161.5, 201.3 ppm; measured mass 263.0714 (rel. intensity 30.3%), calcd mass (based on Ge, 36% abundance) 263.0729 (dev. 1.5 mmass units).

Characterization of 2-*tert*-Butyl-3,3-dimethylbenzoazastannole. A yellow viscous oil, 2.46 g (8.0 mmol, 41%), was obtained: bp 80–82 °C (0.01 mm); IR (CCl_4) 3050 (m), 2950 (s), 1940 (w), 1905 (w), 1840 (w), 1805 (w), 1595 (m) cm^{-1}; ^1H NMR (CCl_4) δ 0.52 (s, 6 H, ^{117}Sn, J = 62 Hz, ^{119}Sn, J = 66 Hz), 1.18 (s, 9 H), 7.0–7.7 (m, 4 H); UV (CCl_4) 252 (ϵ 6100), 256 (ϵ 6100) 294 (ϵ 3800) nm; ^{13}C NMR ($CDCl_3$) δ −7.1, 28.8, 41.7, 119.4, 126.0, 126.6, 127.1, 128.9, 130.1, 135.4, 159.6; measured mass 309.0560 (rel. intensity 25.9%), calcd mass (based on ^{120}Sn, 33% abundance) 309.0537 (dev. 2.3 mmass units).

Registry No.—**2** (R = *t*-Bu), 64414-13-7; **10**, 6441401206; **11**, 64414-11-5; **12**, 6625-74-7; *tert*-butyllithium, 594-19-4; phenyl isocyanide, 931-54-4; methyl iodide, 74-88-4; methyl *tert*-butyl ketone, 75-97-8; methyl *tert*-butyl ketone oxime, 2475-93-6; 2-oxo-3,3-dimethylbutanoic acid, 815-17-8; anthranilic acid, 118-92-3; *N*-(1-copper-2,2-dimethylpropylidene)benzenamine, 64414-10-4; cuprous chloride, 7758-89-6; *N*-(2,2-dimethylpropylidene)benzenamine, 26029-60-7; SCl_2, 10545-99-0; $PhPCl_2$, 644-97-3; $(Ph)_2SiCl_2$, 80-10-4; Me_2SiCl_2, 75-78-5; Me_2GeCl_2, 1529-48-2; Me_2SnCl_2, 753-73-1.

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Notes

Isocyanide–Metal Exchange.[1] The Synthesis of Masked Acyl Cyanides

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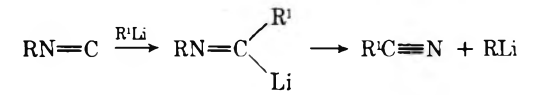
During the investigation of the synthetic utility of lithium aldimines (1), formed by the addition of alkyllithium reagents to isocyanides,[2] it was discovered that a number of them dissociated to produce cyanides in very good yields.[3] A detailed study of the isocyanide–metal exchange reaction showed that



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both steric and electronic effects play a role in the dissociation mechanism. Synthetically, this reaction provided a convenient route to the preparation of nitriles from lithium reagents. The use of the isocyanide–metal exchange reaction for the preparation of masked acyl cyanides is the subject of this report.

The reaction of lithium aldimine (2), prepared by lithiation of 1,1,3,3-tetramethylbutyl isocyanide (TMBI) with triphenylmethyl isocyanide, gave the masked acyl cyanide **3**. The

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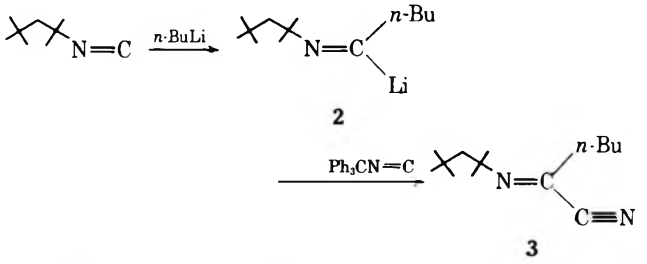
Table I. Reaction of 2-Lithio-2-cyano-1,3-dithiane with RX

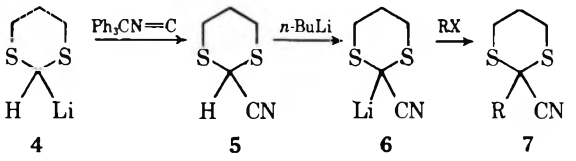
RX	CH_3I	*n*-BuBr	*i*-PrI	$PhCH_2Br$	$PhC(=O)CH_2Br$
Yield, %[a]	81	100	91	94	97

[a] Isolated yield based on **5**



yield of **3** was quite low (26%) and when *tert*-butyllithium was used instead of *n*-butyllithium for metalation only traces of product could be detected. The low yield obtained is probably due to a steric effect in the addition of **2** to triphenylmethyl isocyanide.

An attractive alternative to the masked acyl carbanion **2** was the 2-lithio-1,3-dithiane (**4**) which has been explored by Seebach.[4] Thus, when **4** was reacted with triphenylmethyl isocyanide at low temperature, the isocyanide–metal exchange reaction occurred to yield 2-cyano-1,3-dithiane (**5**) in 83%



yield.[5] The masked acyl cyanide could readily be converted to the anion **6** by reaction with butyllithium. Alkylation of **6** was easily achieved using a series of alkyl halides to yield **7** in excellent yield (Table I).

Experimental Section

Bulk solvents were distilled before use. Industrial grade dimethylformamide (DMF) was purified by distillation from barium oxide at atmospheric pressure, after discarding a forecut, the fraction with bp 150 to 152 °C being collected. Reagent grade diethyl ether and tetrahydrofuran were distilled from lithium aluminum hydride prior to use. All other reagent grade materials were used as received from the commercial suppliers unless further purification was judged necessary.

Infrared spectra were obtained with a Perkin-Elmer Model 257 grating infrared spectrophotometer. Solution spectra were run on 3% solution using either carbon tetrachloride or chloroform as solvent and employing a 0.5-mm sodium chloride cell. Nuclear magnetic resonance spectra were obtained on a Varian Associates A-60 or a Brucker 90-MHZ spectrophotometer using tetramethylsilane as internal standard. Mass spectra were obtained from a AEI Picker high-resolution mass spectrophotometer. Melting points were determined in capillary tubes using a Mel-Temp apparatus and are uncorrected. Elemental analyses were run by J. Beller's Microanalytisches Laboratorium, Gottingen, Germany.

2-Cyano-1,3-dithiane. To a stirred solution of 1.20 g (0.01 mol) of 1,3-dithiane[6] in 15 mL of dry tetrahydrofuran at −30 °C was added 8.0 mL (0.01 mol) of *n*-butyllithium in hexane (1.12 mol) dropwise under a nitrogen atmosphere. The solution was stirred at −30 °C for 1 h and then 2.69 g (0.01 mol) of triphenylmethyl isocyanide[7] in 20 mL of dry tetrahydrofuran was added dropwise. The solution turned red and was then stirred overnight at room temperature. The reaction was worked up by adding 10 mL of H_2O and then extracting with ether. The ether extract was washed with saturated salt solution, dried over anhydrous sodium sulfate, and concentrated, giving a yellow oil which was subjected to column chromatography over alumina with pentane/ether. Initially, a mixture of 10% ether in pentane was used to elute triphenylmethane; then, 20% ether eluted unreacted 1,3-dithiane, and 40% ether eluted unreacted triphenylmethyl isocyanide. Finally, using 100% ether, 2-cyano-1,3-dithiane was eluted (1.2 g, 82.8%) as a colorless solid. Recrystallization from ether–pentane gave colorless crystals; mp 86–88 °C [lit.[5] 90 °C]; IR (CCl_4) 2940 (s), 2908 (s), 2228 (m), 1435 (s). 1429 (s), 1418 (s), 1290 (m), 1280 (m), 1245 (m), 940 (m), 910 (s), 875 (m) cm^{-1}; NMR ($CDCl_3$) δ 2.08 (m, 2 H), 3.37 (m, 4 H), 4.44 (s, 1 H).

Anal. Calcd for $C_5H_7S_2N$: C, 41.36; H, 4.85; N, 9.64; S, 44.17. Found: C, 41.45; H, 4.81; N, 9.72; S, 43.95.

2-Cyano-2-methyl-1,3-dithiane. To a stirred solution of 0.725 g (0.005 mol) of 2-cyano-1,3-dithiane in 25 mL of dry tetrahydrofuran at −40 to −60 °C was added, dropwise, 4.5 mL (0.005 mol) of 1.1 M *n*-butyllithium in hexane under a nitrogen atmosphere. The solution was stirred at −40 °C for 90 min and then 1.0 mL (0.016 mol) of CH_3I was added. The mixture was stirred for an additional 30 min and then overnight at room temperature. The reaction mixture was worked up by adding 10 mL of water and then extracting with ether. The ether extract was washed with saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to give 0.9 g (quantitative) of a yellow oil which was subjected to column chromatography over alumina using binary eluting mixture composed of 1:1 pentane–ether. A total of 0.65 g (81.2%) of colorless solid was collected. Recrystallization from ether–hexane gave colorless crystals: mp 51–53 °C; IR (CCl_4) 2935 (m), 2910 (s), 2830 (w), 2225 (m), 1452 (s), 1438 (s), 1430 (s), 1380 (m), 1285 (s), 1140 (s), 908 (s), 870 (m) cm^{-1}; NMR (CCl_4) δ 1.81 (s, 3 H), 1.98 (m, 2 H), 3.11 (m, 4 H).

Anal. Calcd for $C_6H_9S_2N$: C, 45.24; H, 5.74; N, 8.79; S, 40.26. Found: C, 45.38; H, 5.67; N, 8.80; S, 40.31.

2-Cyano-2-isopropyl-1,3-dithiane. The procedure described for the methylation of 4 was used. The reaction mixture was poured onto ice water and extracted with ether several times. The ether extract was washed with saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to give a yellow liquid which was subjected to column chromatography over alumina, using 10% of ether in pentane as eluent. An oil, 91% yield, was collected: IR (CCl_4) 2990 (s), 2950 (s), 2925 (s), 2238 (w), 1475 (s), 1448 (m), 1438 (s), 1405 (s), 1388 (s), 915 (m), 885 (m) cm^{-1}; NMR (CCl_4) δ 1.26 (d, 6 H, J = 7 Hz), 2.18 (m, 3 H), 3.1 (m, 4 H).

Anal. Calcd for $C_8H_{13}S_2N$: C, 51.29; H, 6.99; N, 7.48; S, 34.23. Found: C, 51.33; H, 7.02; N, 7.45; S, 34.16.

2-Cyano-2-*n*-butyl-1,3-dithiane. The procedure for methylation of 4 was used. The reaction mixture was worked up by adding 10 mL of water and extracting with ether several times. The ether extract was washed with saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to give a quantitative yield of yellow solid. The solid was taken into ether and decolorized with Norit. Evaporation of ether gave a colorless solid. Recrystallization from ether–hexane gave colorless crystals: mp 53–54 °C; IR (CCl_4) 2970 (s), 2920 (s), 2880 (s), 2240 (w), 1478 (m), 1445 (s), 1435 (s), 1423 (s), 1395 (w), 1292 (s), 1254 (w) and 915 (m) cm^{-1}.

Anal. Calcd for $C_9H_{15}S_2N$: C, 53.69; H, 7.51; N, 6.96; S, 31.84. Found: C, 53.80; H, 7.51; N, 6.95; S, 31.92.

2-Cyano-2-benzyl-1,3-dithiane. The procedure for methylation of 4 was used. The reaction mixture was worked up by adding 10 mL of water and extracting with ether several times. The ether extract was washed with saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to give a 94% yield of yellow solid. Recrystallization with ether–hexane gave colorless crystals: mp 108–110 °C; IR (CCl_4) 3078 (m), 2925 (s), 2240 (m), 1617 (w), 1510 (m), 1458 (s), 1445 (s), 1435 (s), 1428 (s), 1293 (s), 928 (m), 915 (s), and 703 (s) cm^{-1}; NMR ($CDCl_3$) δ 2.08 (m, 2 H), 2.96 (m, 4 H), 3.30 (s, 2 H), 7.38 (s, 5 H).

Anal. Calcd for $C_{12}H_{13}S_2N$: C, 61.24; H, 5.57; N, 5.95; S, 27.24. Found: C, 61.37; H, 5.52; N, 5.96; S, 27.18.

2-Cyano-2-phenacyl-1,3-dithiane. The procedure for methylation of 4 was used. The reaction mixture was worked up by adding 10 mL of water and extracting with ether several times. The ether extract was washed with saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to give a 97% yield of an orange solid which was dissolved in chloroform and decolorized twice with charcoal. Recrystallization using chloroform–hexane gave colorless crystals: mp 144–145 °C; IR ($CHCl_3$) 2920 (m), 2242 (m), 1705 (s), 1610 (s), 1592 (m), 1462 (m), 1350 (s), and 1295 (m) cm^{-1}; NMR ($CDCl_3$) δ 2.02 (m, 2 H), 3.20 (m, 4 H), 3.62 (s, 2 H), and 7.73 (m, 5 H).

Anal. Calcd for $C_{13}H_{13}S_2NO$: C, 59.28; H, 4.98; N, 5.32; S, 24.34; O, 6.08. Found: C, 59.40; H, 5.02; N, 5.45; S, 24.26; O, 6.21.

Registry No.—2-Cyano-1,3-dithiane, 33927-42-8; 1,3-dithiane, 505-23-7; triphenylmethyl isocyanide, 1600-49-3; 2-cyano-2-methyl-1,3-dithiane, 64414-35-3; methyl iodide, 74-88-4; 2-cyano-

2-isopropyl-1,3-dithiane, 64414-34-2; isopropyl iodide, 75-30-9; 2-cyano-2-*n*-butyl-1,3-dithiane, 64414-33-1; *n*-butyl bromide, 109-65-9; 2-cyano-2-benzyl-1,3-dithiane, 64414-32-0; benzyl bromide, 100-39-0; 2-cyano-2-phenyl-1,3-dithiane, 64414-31-9; phenyl bromide, 70-11-1.

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Pteridines. 44. A Convenient Synthesis of 6-Formylpterin[1,2]

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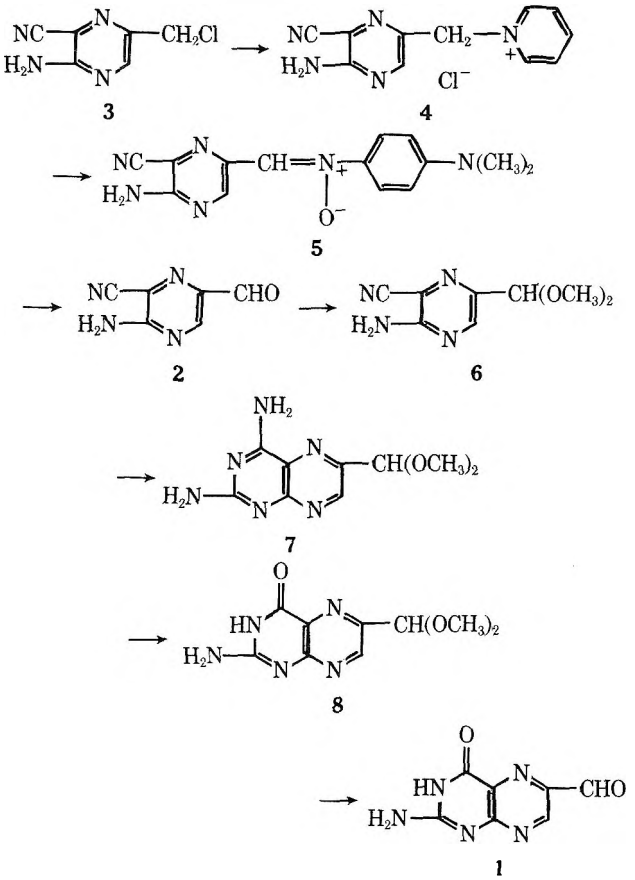
6-Formylpterin (1) is a key intermediate for the preparation of pteroic acid,[4,5] folic acid,[5-7] and various derivatives and analogues of the latter.[5,8-11] In addition, the formation of 6-formylpterin appears to be a characteristic of cancer cells, and its presence in urine has been reported to be diagnostic of malignancy.[12] As a consequence, a convenient synthetic route to this compound would be most desirable. Two methods recently revived from the early literature are the periodate cleavage of 6-polyhydroxyalkylpteridines[8] and the bromine–HBr cleavage of folic acid.[13] These procedures jointly suffer the obvious disadvantage of requiring complex and expensive precursors for the oxidative cleavage reactions, and the latter is clearly unacceptable for the preparation of 1 as an intermediate for the synthesis of folic acid. Alternative procedures have involved dibromination of the 6-methyl group of 6-methylpterin followed by aqueous hydrolysis,[14] and the condensation of α-bromo-β,β-diethoxypropanal with 2,4,5-triamino-6(1*H*)-pyrimidone followed by oxidation of the resulting 5,6-dihydropterin and hydrolysis of the acetal.[6] One must bear in mind, however, that all of the above procedures must of necessity give final products of dubious isomeric integrity if the inherently ambiguous condensation of a diaminopyrimidine with an unsymmetrical dicarbonyl compound (or an α-halo or hydroxy ketone) was employed at any stage of the synthesis.

Recent papers from this laboratory have described an unequivocal approach to pteridine synthesis which involves guanidine cyclization of suitably substituted pyrazine intermediates, which are prepared by unambiguous procedures.[15] Following this strategy, a 5-formylpyrazine, or a protected derivative thereof, has been sought as an intermediate for the synthesis of 6-formylpterin. One such synthon, 2-amino-3-cyano-5-oximinomethylpyrazine 1-oxide, has already been developed and utilized.[16] We now report a high-yield synthesis of 2-amino-3-cyano-5-formylpyrazine (2) and its conversion to 2,4-diamino-6-formylpteridine and 6-formylpterin dimethyl acetals (7 and 8 respectively); acid hydrolysis of the latter gives 1.

The Krőhnke method[17,18] was utilized to convert 2-amino-3-cyano-5-chloromethylpyrazine (3)[19] to the required aldehyde 2 in three steps. Yields for all three steps were above 90%, and the crude crystalline intermediates were pure enough in every case to be used directly in succeeding transformations. Thus, the pyridinium salt 4 was obtained from 3 and pyridine by stirring overnight at room temperature. Salt 4 reacted with *p*-dimethylaminonitrosobenzene in the presence of potassium carbonate to give the nitrone 5, which was then hydrolyzed to 2 with cold 6 N hydrochloric acid.

Quantitative conversion of 2 to its dimethyl acetal 6 was achieved by treatment of a methanol suspension of 2 with a catalytic amount of a strong acid, e.g., anhydrous HCl, *p*-toluenesulfonic acid, or Dowex 50W-X4 cation-exchange resin (hydrogen form). It is not necessary to isolate 6, which can be converted directly to 2,4-diamino-6-formylpteridine dimethyl acetal (7) by addition of guanidine to the dried methanol solution followed by heating overnight at reflux. Brief treatment of 7 with hot 5% sodium hydroxide gave 6-formylpterin dimethyl acetal (8), which can be hydrolyzed to 1 with either formic or trifluoroacetic acid.



The acetals 7 and 8 should find general use in the preparation of aminopterin, folic acid, and their analogues, since the respective aldehydes are readily generated in situ in the presence of acid. Thus, the UV spectrum of 8 in 1 N hydrochloric acid was identical to the reported UV spectrum of 1.[14]

Experimental Section[20]

1-[(2-Amino-3-cyano-5-pyrazinyl)methyl]pyridinium Chloride (4). A solution of 1.0 g (5.9 mmol) of 2-amino-3-cyano-5-chloromethylpyrazine[19] in 10 mL of pyridine was stirred at room temperature for 17 h. Eighty milliliters of ether was added and the salt which had precipitated was removed by filtration, washed well with ether, and air-dried to give 1.4 g (95%) of a light gray powder, mp >300 °C (dec). One recrystallization from ethanol gave pale-yellow needles: NMR (D_2O, external Me_4Si) δ 9.0–8.0 (m, 5) (pyridinium ring), 8.47 (s, 1) (6-H), 5.85 (s, 2) ($-CH_2-$); IR (KBr) 2230 cm^{-1} (CN).

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Anal. Calcd for $C_{11}H_{10}N_5Cl$: C, 53.34; H, 4.07; N, 28.28; Cl, 14.32. Found: C, 53.39; H, 4.02; N, 28.30; Cl, 14.59.

***N*-[*p*-(Dimethylamino)phenyl]-α-(2-amino-3-cyano-5-pyrazinyl)nitrone (5).** To a suspension of 2.63 g (10.6 mmol) of the pyridinium salt **4** and 1.64 g (11.0 mmol) of *p*-dimethylaminonitrosobenzene in 50 mL of ethanol was added 8.33 g (60.4 mmol) of potassium carbonate in 30 mL of water. The reaction mixture became homogeneous, changed in color from green to brown, and the orange-brown nitrone started to separate. After 30 min of stirring at room temperature followed by ice cooling, the mixture was filtered and the collected solid was washed with water followed by ethanol and then ether and air-dried: yield 2.86 g (96%) of a dull orange powder, mp 219–222 °C (dec). Recrystallization from a large volume of acetonitrile (Norite) gave dark-orange needles: mp 227–228 °C (dec); NMR (Me_2SO) δ 2.95 (s, 6), 6.68 (d, 2), 7.72 (m, 4) (2 Ar protons + $-NH_2$), 8.15 (s, 1), 9.92 (s, 1); UV λ_{max} (acetonitrile) (log ε) 237 (4.22), 258 (sh, 3.89), 338 (4.27), 376 (4.38) nm; IR (KBr) 2230 cm^{-1} (CN).

Anal. Calcd for $C_{14}H_{14}N_6O$: C, 59.56; H, 5.00; N, 29.77. Found: C, 59.44; H, 5.06; N, 30.06.

2-Amino-3-cyano-5-formylpyrazine (2). A two-phase system containing 0.96 g (3.4 mmol) of the nitrone **5**, 60 mL of cold 6 N HCl, and 50 mL of ethyl acetate was shaken in a separatory funnel for several minutes. The organic layer was separated and the aqueous layer extracted twice with 50-mL portions of ethyl acetate. Brine (50 mL) was added to the aqueous layer, which was again extracted with 50 mL of ethyl acetate. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and evaporated to give 0.48 g (96%) of a light-gray powder, mp 202–204 °C (dec). Recrystallization from benzene (Norite) gave the aldehyde **2** as a colorless, microcrystalline solid: mp 206–208 °C (dec); NMR (Me_2SO) δ 8.32 (s, 2) ($-NH_2$), 8.70 (s, 1), 9.68 (s, 1); IR (KBr) 2240 cm^{-1} (CN).

Anal. Calcd for $C_6H_4N_4O$: C, 48.65; H, 2.72; N, 37.83. Found: C, 48.44; H, 2.80; N, 37.78.

2-Amino-3-cyano-5-formylpyrazine Dimethyl Acetal (6). To a suspension of 0.48 g (3.2 mmol) of the aldehyde **2** in 30 mL of dry methanol was added 1.0 g of Dowex 50W-X4 cation-exchange resin (hydrogen form). The mixture was stirred for 15 min to give a solution which, by TLC examination, contained one fluorescent component; all starting material had disappeared. After drying over 3A molecular sieves, the solvent was removed under reduced pressure to give 0.63 g (100%) of the desired acetal **6**, mp 91–93 °C. The acetal may be recrystallized from benzene/cyclohexane: NMR (Me_2SO) δ 3.35 (s, 6), 5.30 (s, 1), 7.43 (s, 2) ($-NH_2$), 8.42 (s, 1); IR (KBr) 2225 cm^{-1} (CN).

Anal. Calcd for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.40; H, 5.30; N, 29.07.

2,4-Diamino-6-formylpteridine Dimethyl Acetal (7). A solution of guanidine in methanol was prepared by dissolving 0.10 g (4.4 mmol) of sodium in 20 mL of dry methanol, followed by the addition of 0.42 g (4.4 mmol) of guanidine hydrochloride. This was added to a solution of 0.62 g (3.2 mmol) of the acetal **6** in 30 mL of methanol, and the mixture was heated under reflux for 18 h. It was then concentrated to a small volume under reduced pressure, cooled at −20 °C, and filtered to give 0.67 g (84%) of **7** as a light yellow powder, mp 248 °C (dec). The product was obtained in the form of bright-yellow beads, mp 254–255 °C (dec) upon recrystallization from methanol (Norite): NMR (Me_2SO) δ 3.33 (s, 6), 5.35 (s, 1), 6.67 (br s, 2), 7.57 (br s, 2), 8.72 (s, 1); UV λ_{max} (MeOH) (log ε) 261 (4.37), 284 (sh, 3.73), 368 (3.85) nm.

Anal. Calcd for $C_9H_{12}N_6O_2$: C, 45.76; H, 5.12; N, 35.58. Found: C, 45.52; H, 5.02; N, 35.81.

6-Formylpterin Dimethyl Acetal (8). A mixture of 0.52 g of 2,4-diamino-6-formylpteridine dimethyl acetal (**7**) in 20 mL of 5% aqueous sodium hydroxide was heated gently at reflux for 10 min. The resulting clear solution was filtered through sintered glass and the filtrate neutralized with acetic acid. The yellow solid which separated was collected by filtration and washed with water, ethanol, and then ether and air dried to give 0.49 g (94%) of **8** as a yellow solid, mp >330 °C. The analytical sample was prepared by recrystallization from DMF: NMR (Me_2SO) δ 3.33 (s, 6), 5.37 (s, 1), 6.93 (br s, 2), 8.63 (s, 1); UV λ_{max} (0.1 N NaOH) (log ε) 256 (4.41), 282 (sh, 3.86), 360 (3.89) nm; λ_{max} (0.1 N HCl) (log ε) 248 (4.05), 318 (3.96), 335 (sh, 3.83) nm.

Anal. Calcd for $C_9H_{11}N_5O_3$: C, 45.57; H, 4.67; N, 29.53. Found: C, 45.67; H, 4.86; N, 29.66.

6-Formylpterin (1). A mixture of 0.49 g of 6-formylpterin dimethyl acetal (**8**), 10 mL of 97% formic acid, and 1 mL of water was allowed to stand at room temperature for 30 min, poured into 15 mL of water, and neutralized with concentrated ammonium hydroxide. The yellow precipitate was collected by filtration and washed with water, ethanol, and then ether to give 0.36 g (91%) of **1** as a yellow microcrystalline solid, mp >330 °C. IR and UV spectra and TLC behavior were identical with those of an authentic sample: NMR (F_3AcOH external Me_4Si) δ 8.92 (s, 1), 9.65 (s, 1).[16]

Registry No.—**1**, 712-30-1; **2**, 64440-74-0; **3**, 40127-91-1; **4**, 64440-75-1; **5**, 64440-76-2; **6**, 64440-77-3; **7**, 64440-78-4; 8, 59453-01-9; pyridine, 110-86-1; *p*-dimethylaminonitrosobenzene, 138-89-6; guanidine, 113-00-8.

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Preparation and Crystal Structure of 6-Acetyl-1-iodocodeine

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In conjunction with the development of a radioimmunoassay for morphine and related compounds[1] we were interested in preparing a sample of ring A specifically iodinated morphine. We found that the methods previously used for obtaining chloro-[2] or bromomorphine[3] or fluorocodeine[4] did not lead to the iodo derivative.

With positive iodine (ICl in Me_2SO), a trace of iodinated product was formed with both morphine and codeine as starting materials. With codeine, a trace of iodinated product was also formed when the conditions of tyrosine (protein) iodination were employed (chloramine T and sodium iodide in water buffered at pH 6.9).[5] Surprisingly, iodine monochloride in 0.1 N HCl with codeine produced a 67% yield of iodocodeine (**2**). This was later increased to 80–90% with the use of chloramine T and sodium iodide but again only when the reaction was carried out in 0.1 N HCl. While the reaction with codeine can be carried out quite smoothly, no readily defined reaction occurs with morphine under these conditions and iodomorphine (**5**) was therefore prepared by demethylation of iodocodeine. To avoid the possibility of deiodinaton, the demethylation was effected using boron tribromide.[6] Lastly, the preparation of iodocodeine-^{125}I (**4**) was readily accomplished using $Na^{125}I$ in the procedure shown below.

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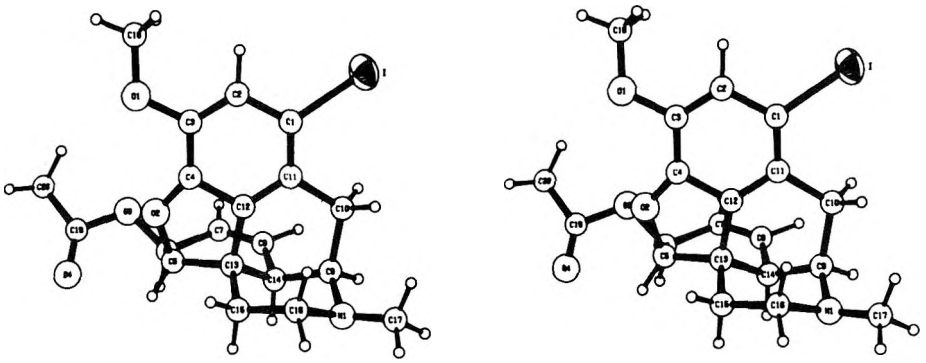
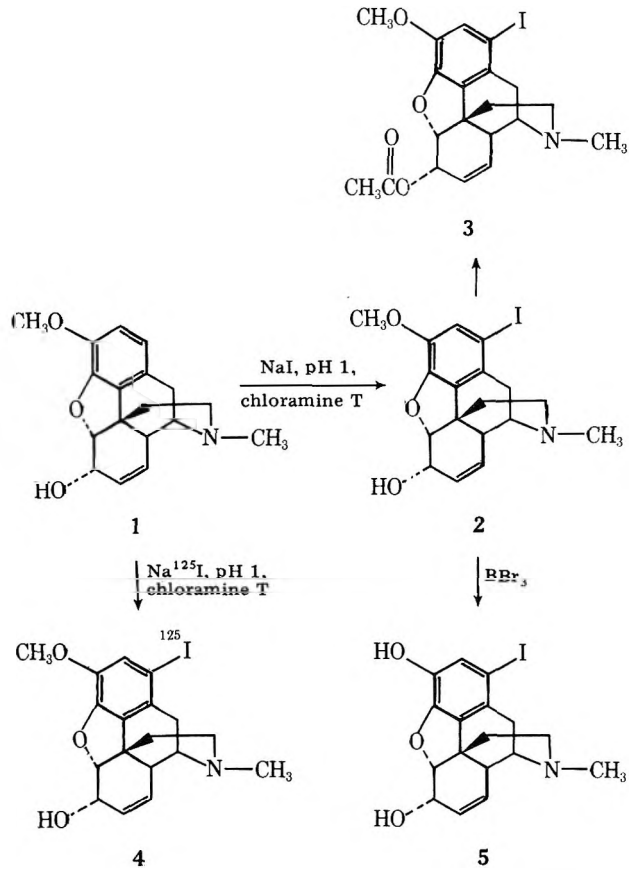


Figure 1. Stereodrawing showing the structure and conformation of **3**. The hydrogen atom positions were postulated, but they were not refined.

Table I. Crystal Data[10]

Sample	6-Acetyl-1-iodocodeine
Formula	$C_{20}H_{22}NIO_4$
Formula wt	467.30
Space group	$P2_1$
a, Å	27.127 (24)
b, Å	7.287 (8)
c, Å	9.757 (8)
β,	101.43 (4)
z	4
d_{calcd}, g cm^{-3}	1.641 g
μ(Cu Kα), cm^{-1}	137.9



We were unable to assign the position of the iodine from the NMR spectrum of **2**.[7] Accordingly, this problem was solved with a crystal structure analysis of the *O*-acetyl derivative **3**. The crystal data for **3** are given in Table I. The intensity data were measured on a Hilger-Watts diffractometer by a θ–2θ scan technique. Nickel filtered Cu Kα radiation and pulse height discrimination were used. The approximate size of the crystal used for data collection was 0.08 × 0.08 × 0.3 mm; the data were corrected for absorption. Of the 2085 accessible reflections with $\theta < 76°$, 1342 had intensities which were significantly greater than background, and these reflections were used in the analysis. The structure was solved by the heavy-atom method and was refined by full-matrix least squares. The hydrogen atoms were put in at their calculated positions. In the final refinement, the iodine atom had anisotropic thermal parameters and all other atoms had isotropic temperature factors. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final unweighted and weighted discrepancy indices are $R = 0.100$ and $wR = 0.105$ for the 1342 observed reflections. A stereoscopic drawing of **3** is shown in Figure 1.

Experimental Section

Melting points are uncorrected. Infrared spectra were taken on a Digilab-FTS-14 or Beckman IR-9 or Perkin-Elmer 621 spectrophotometer. Nuclear magnetic resonance spectra were taken on a Joelco-C-60H, or Varian HA-100, or Varian XL-100 spectrometer. The mass spectra were recorded on either a Varian-CH-5 or CEC-110 instrument at an ionizing voltage at 70 eV. Ultraviolet spectra were recorded on a Carey-14 instrument. Radiochemical purity was determined on thin-layer chromatograms with a Packard 7201 radiochromatogram scanner system. All solvents were distilled prior to use.

1-Iodocodeine (2). A solution of 30 mg (0.10 mmol) of codeine (**1**) in 5 mL of 0.1 N HCl was added to a stirred mixture of 1.0 mL of 0.10 M NaI (aqueous) and 1.2 mL of 0.10 M chloramine T (aqueous) contained in a 25 mL stoppered flask. The addition was carried out with magnetic stirring and at room temperature. After 12 min, the mixture was extracted with two 5-mL portions of chloroform then basified by the addition of 0.2 mL of concentrated ammonia solution. Extraction with five 5-mL portions of chloroform which were combined, washed with 1 mL of water, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo yielded 36 mg (85%) of product which by TLC (silica gel; acetonitrile/ammonium hydroxide, 25:2) showed only 1-iodocodeine at R_f 0.41 and no codeine which has R_f 0.32 in this system. A sample crystallized from toluene–hexane (5:1)[8] had mp 116–117 °C: IR ($CHCl_3$) 3650 (free OH), 3460 (H-bonded OH); UV (ethanol) λ_{max} 217 (E 31 500), 247 (6750), 286 nm (1510); NMR ($CDCl_3$) δ 2.40 (s, 3 H, NCH_3), 3.78 (s, 3 H, OCH_3), 5.25, 5.70 (dd, 2 H, CH=CH), 7.08 (s, 1 H, aromatic); *m/e* 425 (calcd for $C_{18}H_{20}NIO_3$, 425). Anal. Calcd for $C_{18}H_{20}NIO_3$: C, 50.9; H, 4.7. Found: C, 51.2; H, 4.9.

1-Iodocodeine-^{125}I (4). Into a serum stoppered vial containing 5 mCi of carrier-free $Na^{125}I$ solution[9] was injected 100 μL of 0.05 M sodium iodide solution followed by 120 μL of 0.05 M chloramine T (freshly prepared in water). After stirring for 2 min, a solution of 1.50 mg of codeine (**1**) in 250 μL of 0.1 N HCl was added. After stirring an additional 5 min, the reaction mixture was treated with 110 μL of 0.05 M sodium bisulfite solution, extracted with two 2-mL portions of chloroform, then basified with about 40 μL of concentrated ammonium hydroxide solution. The resulting mixture was extracted with five 2-mL portions of chloroform which were combined, washed with 1 mL of water, dried over anhydrous magnesium sulfate, filtered, and concentrated to a residue of about 1 mg. By TLC analysis, the sample was shown to be greater than 95% iodocodeine with radiochemical purity greater than 99%. A trace of codeine was detected. Specific activity was 0.86 mCi/mg.

6-*O*-Acetyl-1-iodocodeine (3). A 1-g sample of 1-iodocodeine was added to a mixture of dry pyridine (1 mL) and acetic anhydride (5 mL). The resulting solution was stirred at room temperature for 20 h then concentrated in vacuo to a residual oil which was treated twice with 5 mL each of benzene which was evaporated under reduced pressure. After the addition of 10 mL of water to the residual oil, solidification occurred after stirring for about 1 h. The product was collected by filtration, washed with water, and dried under high vacuum yielding 670 mg of **3**, mp 177–179 °C. A second crop of 360 mg (total yield is 94%) was obtained from the mother liquors. A sample for x-ray crystallographic analysis, crystallized from ethyl acetate–cyclohexane–hexane, was of mp 180–181 °C: NMR ($CDCl_3$) δ 2.13 (s, 3 H, CH_3CO_2), 2.43 (s, 3 H, NCH_3), 3.82 (s, 3 H, OCH_3), 5.40, 5.62 (dd, 2 H, CH=CH), 7.06 (s, 1 H, aromatic); *m/e* 467 (calcd for $C_{20}H_{22}NO_4I$, 467).

1-Iodomorphine (5). A solution of 2.12 g (5 mmol) of **2** in 12.5 mL of chloroform was added over a 4-min period to a stirred solution of 7.5 g of BBr_3 in 80 mL of chloroform maintained at 15–20 °C. Stirring was continued for an additional 15 min after which time the mixture was poured into 50 g of cracked ice and 10 mL of concentrated ammonium hydroxide solution. After standing 0.5 h at 0 °C, the solid was collected by suction filtration and washed successively with small portions of cold chloroform and water then dried to a constant weight of 1.14 g (54%): mp 215 °C dec; IR (KBr) 3500 (b, phenolic OH), 3350, 3255 (H-bonded OH); UV (methanol) λ_{max} 216 (E 27 070), inflection 245 (6450), inflection 288 (2100), max 293 nm (2160); NMR ($CDCl_3$ + Me_2SO) δ 2.30 (s, 3 H, NCH_3), 4.13 (m, 1 H, CHOH), 5.30, 5.53 (dd, 2 H, -CH=CH-), 7.00 (s, 1 H aromatic); *m/e* 411 (calcd for $C_{17}H_{18}NIO_3$, 411). A sample recrystallized from 0.1 N HCl was of mp 217 °C dec. Anal. Calcd for $C_{17}H_{18}NIO_3 \cdot HCl \cdot \frac{1}{2}H_2O$: C, 44.7; H, 4.3; N, 3.1; Cl, 7.8; I, 27.8. Found: C, 44.7; H, 4.9; N, 3.2; Cl, 7.5; I, 27.5.

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Registry No.—**1**, 76-57-3; **2**, 64739-74-8; **3**, 64754-11-6; **4**, 64739-75-9; **5**, 64739-76-0; **5**-HCl, 64739-77-1; NaI, 7681-82-5; $Na^{125}I$, 24359-64-6; acetic anhydride, 108-24-7.

Supplementary Material Available: Atomic and anisotropic thermal parameters for **3** (2 page). Ordering information can be found on any current masthead page.

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Rearrangement of *N*-Chloro-*N*-acetyl-1-aminoadamantane by Aluminum Chloride[1]

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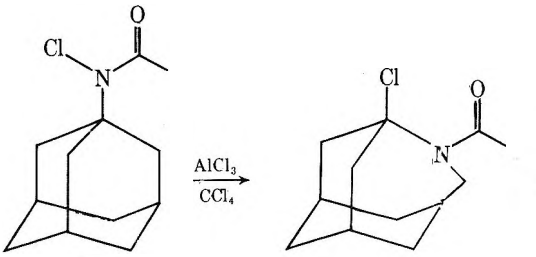
In 1971 it was reported that *N*-chloro-*N*-acetyl-1-aminoadamantane (**1**) rearranges to 3-chloro-*N*-acetyl-4-azahomoadamantane (**2**) in carbon tetrachloride with aluminum chloride catalyst,[2] eq 1. The authors assigned the structure on the basis of elemental analysis, IR, NMR, Beilstein test,



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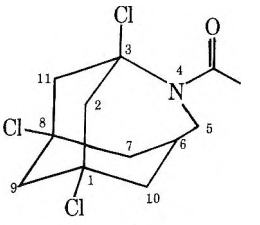

3

and chemical behavior (dehalogenation). On repeating this work, the product that we have obtained from the rearrangement is 1,3,8-trichloro-*N*-acetyl-4-azahomoadamantane (**3**). Determination of the structure was accomplished by means of elemental analysis, IR, ^1H and ^{13}C NMR, and mass spectrometry. The ^{13}C NMR spectrum contained nine peaks (as expected based on symmetry of the molecule); however, the downfield position and off-resonance decoupling splitting pattern suggested that both bridgehead carbons, 1 and 8, are quaternary. In our investigations[3] involving the ^{13}C NMR spectra of 3-substituted 4-azahomoadamantanes, a typical range for chemical shift of bridgeheads 1 and 8 is δ 26 to 28. Off-resonance decoupling shows a doublet which is characteristic of tertiary carbon atoms. In work with related models, the chemical shift for C–Cl carbon in 1-chloroadamantane is δ 67.25, for 1,3-dichloroadamantane it is δ 66.57, and for 1,3,5-trichloroadamantane it is δ 64.5[4] which is very close to the value of δ 64.97 for **3**. Mass spectrometry revealed molecular ions at *m/e* 295, 297, and 299 in about 3:3:1 ratio, as expected for the trichloro compound. The difference in melting points of the two preparations, in addition to other data,[5] suggests that the prior preparation may be a mixture derived from varying degrees of chlorination.

Investigation of reaction variables revealed (TLC and NMR) that either lowering the temperature or shortening the time below 24 h produced a complex mixture containing some starting material together with unidentified products (possibly containing a lower degree of chlorination). If the reaction is carried out for less than 4 h, most of the starting material is recovered. Reaction times of over 40 h produced good yields of product which could be easily purified by column chromatography on silica and recrystallization. The same product was obtained at 40 and 68 h but at lower yield for the shorter time.

The formation of compound **3** can be rationalized mechanistically on the basis of two known reactions: (1) the rearrangement of *N,N*-dichloro-1-aminoadamantane to the azahomoadamantyl system,[6] apparently via electron-deficient nitrogen, and (2) chlorination of C–H bonds by the alkyl halide–aluminum chloride combination. The CCl_4–$AlCl_3$ system has been used for 1,3-dichlorination of adamantane.[7] The specificity of chlorination (carbons 1 and 8, but not 6) can be rationalized by the inductive effect of amide nitrogen and by the "cage effect" (cation stabilization by unshared electrons on nitrogen).[8]

Experimental Section

Infrared spectra were obtained on a Beckman IR-8 instrument (KBr disks); ^1H NMR spectra on a Varian T60-A spectrometer and ^{13}C NMR on a Varian CFT-20 spectrometer ($CDCl_3$ as solvent and

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Me_4Si as reference); and mass spectra on a Hitachi Perkin-Elmer RMU-6E instrument (70 eV and 170 °C). Elemental analyses were performed by Baron Consulting Co., Orange, Conn. and Micro-Tech Laboratories, Skokie, Ill. Carbon tetrachloride was dried with calcium chloride. Skelly B was extracted with concentrated H_2SO_4, washed with 10% Na_2CO_3 and water, dried with $CaCl_2$, and distilled from sodium. Other materials were used without purification.

***N*-Chloro-*N*-acetyl-1-aminoadamantane (1).** The method of Sasaki et al. was used:[2] yield 99.8%;[9] mp 69–71 °C (lit.[2] mp 69–71 °C). IR and ^1H NMR spectra were similar to those reported: IR 1660, 1450, 1370, 1250, 1065, 815, 755, 675 cm^{-1} (lit.[2] 1657, 680); ^1H NMR δ 2.20 (12 H), 1.67 (6 H) (lit.[2] 2.13 (12 H), 1.65 (6 H)). Anal. Calcd for $C_{12}H_{18}ClNO$: C, 63.24: H, 7.97; N, 6.15. Found: C, 62.90; H, 7.66; N, 6.07.

Rearrangement of *N*-Chloro-*N*-acetyl-1-aminoadamantane (1). The procedure of Sasaki et al.[2] was used except for a change in reaction time (68 h instead of 40 h). Chromatography on silica with chloroform as eluent produced **3**, mp 74–76 °C dec (lit.[2] 69.5–71.5 °C). Recrystallization from dry Skelly B afforded off-white plates, mp 85–86 °C. IR and ^1H NMR were similar to those reported: IR 1670, 1370, 1320, 1270, 1120, 1015, 850, 780, 735 cm^{-1} (lit.[2] 1671, 853, 743, 713 cm^{-1}); ^1H NMR δ 2.55 (s, NCH_2), 2.22 (s, CH_3), 2.60–1.90 (m) (lit.[2,5] δ 2.55 (d, NCH_2), 2.23 (s, CH_3), 2.50–1.45 (m)); ^{13}C NMR δ 173.92 (C=O), 66.92 (3), 64.97 (1, 8), 55.20 (5), 48.17 and 44.44 (2, 11) and (7, 10), 37.53 (9), 32.50 (6), 25.67 (CH_3); mass spectrum *m/e* (relative intensity) 91 (36), 127 (28), 128 (32), 130 (20), 148 (45), 170 (30), 186 (100), 187 (23), 188 (54), 190 (21), 210 (23), 226 (100), 227 (36), 228 (59), 261 (41), 263 (27), M^+· 295 (1), (M^+· + 2) 297 (1), (M^+· + 4) 299 (0.3); (M^+·):(M^+· + 2):(M^+· + 4) = 3:3:1. Anal. Calcd for $C_{12}H_{16}Cl_3NO$: C, 48.59; H, 5.44; Cl, 35.86; N, 4.72. Found: C, 48.40; H, 5.31; Cl, 35.18;[10] N, 4.92.

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Registry No.—1, 64741-22-6; **3**, 64741-23-7; $AlCl_3$, 7446-70-0.

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Thermal Rearrangement of Halocineole to Halopinol Derivatives

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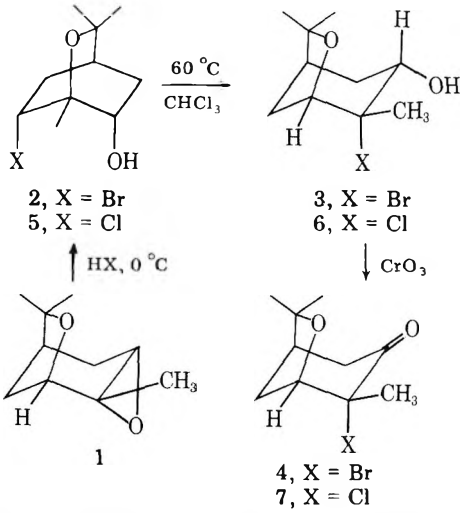
During an investigation of pinol oxide[2] (**1**) it was noted that its conversion to *endo*-6-hydroxy-*endo*-7-bromocineole (**2**) by fuming hydrobromic acid was complete after 1 h at 0 °C. Bromohydrin **2** was stable in chloroform at room temperature; however, at 60 °C it was largely transformed into pinol bromohydrin (**3**). The conversion of **2** into **3** at 60 °C was essentially complete after 20 h, at which time a mixture of 80% **3** and 20% **2** was on hand.



2, X = Br; **5**, X = Cl — **3**, X = Br; **6**, X = Cl

1

4, X = Br; **7**, X = Cl

The structure of **3** was suggested by its NMR spectrum which showed, in part, a methyl singlet at 1.87 ppm attributed to a CH_3CBr group and a doublet at 4.22 ppm characteristic of the bridgehead proton of a pinol ring.[2] An axial C-3 proton was indicated by a broad multiplet at 3.73 ppm with a half-width of 30 Hz. Chromic acid oxidation of **3** gave the bromoketone **4**. The NMR chemical shift (1.82 ppm) of the α-methyl group in **4** was not noticeably altered on changing solvent from deuteriochloroform to benzene, while its ultraviolet spectrum showed a maximum at 307 nm requiring the presence of an equatorial methyl and axial bromine atom at C-2.

endo-6-Hydroxy-*endo*-7-chlorocineole (**5**) was recovered unchanged after refluxing in chloroform or benzene for 24 h. In refluxing toluene (110 °C) chlorohydrin **5** slowly rearranged to *cis*-pinol chlorohydrin **6**. Further change was not noted after 120 h and NMR analysis of the resulting mixture indicated the presence of 78% of **6** and 22% of **5**. In refluxing xylene (140 °C) an apparent stationary state was reached in 24 h, and severe darkening was observed on more prolonged heating. Essentially the same mixture of **6** and **5** was obtained from pure **5** when it was heated in xylene for 24 h.

The structures of *cis*-pinol chlorohydrin (**6**) and the ketone **7** obtained by chromic acid oxidation were demonstrated by spectral analysis (see the Experimental Section).

endo,endo-6,7-Dibromocineole (**8**) rearranged to pinol dibromide **9** at about the same rate that chlorohydrin **5** rearranged to **6**. Refluxing in bromobenzene (154 °C) was required for completion in 5 h and despite the formation of appreciable black tar, pinol dibromide **9** could still be isolated by column chromatography. The rearrangement of **8** to **9** was also noted on passing **8** through a GLC column at 190 °C. The structural assignment to **9** is based on its NMR spectrum and the stereochemistry is suggested by analogy with that of bromohydrin **3**.

endo,endo-6,7-Dichlorocineole (**10**) similarly rearranged to pinol dichloride **11** on refluxing in bromobenzene but much more slowly than the corresponding dibromide. A 33% conversion to **11** was noted after 18 h. Heating dichloride **10** at 280 °C for 1 h furnished **11** in good yield. The methoxy chloride **13** rearranged to **14** at a rate comparable with that of dichloride **10**.

By contrast, *endo,endo*-6,7-dihydroxycineole (**12**) and its diacetate derivative **12a**[2,3] were stable at 200 °C in refluxing tetralin.

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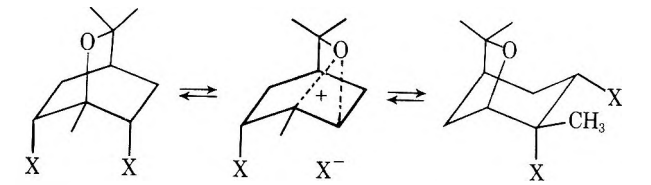
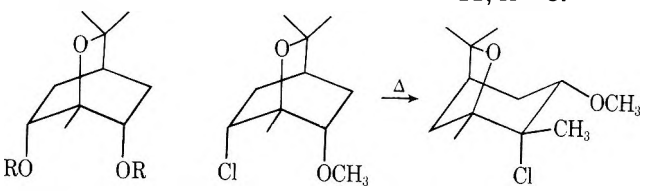


8, X = Br
10, X = Cl

8a

9, X = Br
11, X = Cl



12, R = H
12a, R = Ac

13

14

Electrophilic additions to pinol[2] involving the development of substantial positive charge in the transition state invariably proceed with oxygen migration and afford kinetically controlled cineole products derived by attack of a nucleophile at the sterically less hindered secondary carbon of the cineole (oxabicyclo[2.2.2]octane) ring system. Thermolysis of halocineole derivatives offers thefirst synthetic entry to pinol derivatives bearing a halogen at the C-4 position. The thermolysis appears to involve ionization (bromides much faster than chlorides) assisted by the favorably located neighboring oxygen atom[4,5] to form an ion pair intermediate **8a**, followed by internal return with attack of halide occurring at the more hindered tertiary position yielding the more thermodynamically stable pinol (oxabicyclo[3.2.1]octane) ring system.[6] In accord with this view is the observation that the thermolysis of dichloride **10** to **11** at 110 °C occurs 25 times faster in the more polar dimethylformamide than in toluene.

The nonrearranging substituent appears to play an important role in determining the rate of rearrangement as illustrated by the facile rearrangement of chlorohydrin **5** as compared with the dichloride **10** and methoxy chloride **13**. The accelerating effect of the hydroxyl group is most likely a consequence of intramolecular hydrogen bonding which assists in the ionization of the halide.[7]

Experimental Section

All boiling and melting points are uncorrected. Infrared spectra were measured with a Perkin-Elmer Infracord, Model 137-B. NMR spectra were recorded with Varian Associates A-60A and Perkin-Elmer R-32 spectrometers and are reported in ppm from tetramethylsilane as an internal standard. Mass spectra were determined with a Hitachi RMU-6D instrument by the Purdue University Spectral Service. Ultraviolet spectra were recorded on a Cary Model 15 spectrometer. Microanalyses were performed by Dr. C. S. Yeh and associates.

Pinol Bromohydrin (4α-Bromo-4β,7,7-trimethyl-6-oxabicyclo[3.2.1]octan-3-ol, 3). A solution of 630 mg of *endo*-6-hydroxy-*endo*-7-bromocineole (**2**) in 30 mL of chlorofrom was heated to reflux and aliquots were periodically withdrawn for NMR analysis. The ratio of the integrated areas for the 1.87-ppm singlet (CH_3CBr in **3**) and the 1.30-ppm singlet (CH_3CO in **2**) was used to determine the composition of the mixture. The proportion of **3** was ca. 35% after 6 h, reached 80% after 25 h, and remained unchanged thereafter.

A 2-g sample of **1** was refluxed in chloroform for 24 h. The solvent was removed in vacuo and the residue was chromatographed on silica gel using ether–pentane as eluant to give, after recrystallization from hexane, 940 mg of pinol bromohydrin **3**: mp 72–73 °C; NMR ($CDCl_3$) 1.19 and 1.37 (s, 6, $(CH_3)_2CO$), 1.87 (s, 3, CH_3CBr), 1.75–2.47 (m, 5), 2.51 (s, 1, OH), 3.73 (m, 1, $W_{1/2}$ = 30 Hz, CHOH), and 4.22 ppm (d, 1, J = 6 Hz, CHOC); mass spectrum (70 eV) m/e 248 (2%). Anal. Calcd for $C_{10}H_{17}BrO_2$: C, 48.19; H, 6.83; Br, 32.73. Found: C, 48.37; H, 6.65; Br, 32.68.

From 1.2 g of (−)-**2**, mp 76–77 °C, $[\alpha]^{25}D$ −9.97° (*c* 6.52, $CHCl_3$), there was obtained 760 mg of (+)-**3**, mp 50–51 °C, $[\alpha]^{25}D$ + 50.08° (*c* 4.74, $CHCl_3$).

Table I. Rate of Thermal Rearrangement of Cineol Chlorohydrin (5)

Solvent	Temp, °C	k, s^{-1}
Toluene	110	6.30×10^{-6}
Dioxane	101	4.92×10^{-6}
DMF	110	1.35×10^{-4}
DMF	90	3.50×10^{-5}

4α-Bromo-4β,7,7-trimethyl-6-oxabicyclo[3.2.1]octan-3-one (4). Approximately 2 mL of Jones reagent was added slowly to a solution of 1 g (4 mmol) of pinol bromohydrin (**3**) in 25 mL of acetone. Isopropyl alcohol (0.25 mL) was added to destroy the excess oxidant and the salts were removed by filtration and washed thoroughly with ether. The ether solution was washed with 5% sodium bicarbonate, dried (Na_2SO_4), and evaporated to leave 890 mg of light-yellow oil. The oil was chromatographed on silica gel using ether–pentane as eluant and then evaporatively distilled to yield 693 mg of pure **4**: IR 5.81 μm; UV λ_{max} (MeOH) 307 nm (E = 83); NMR 1.17 and 1.22 (s, 6, $CH_3)_2CO$), 1.82 (s, 3, CH_3CBr), 2.32 (m, 2), 2.72 (m, 3), and 4.23 ppm (d, 1, CHO); NMR (C_6H_6) 1.02 (s, 6, $CH_3)_2CO$), 1.83 (s, 3, CH_3CBr), 1.92–2.97 (m, 5), and 4.17 ppm (d, 1, –CHO–); mass spectrum m/e (rel intensity) 246 (33), 167 (48), and 97 (100). Anal. Calcd for $C_{10}H_{15}O_2Br$: C, 48.58; H, 6.07; Br, 32.39. Found: C, 48.43; H, 6.29; Br, 32.60.

Pinol Chlorohydrin (4α-Chloro-4β,7,7-trimethyl-6-oxabicyclo[3.2.1]octan-3α-ol, 6). A solution of 2 g of cineol chlorohydrin (**5**) in 25 mL of *p*-xylene was refluxed for 20 h and the solvent was removed under reduced pressure to leave a brown oil whose NMR indicated the presence of an 80:20 mixture of **6** and **5**. Column chromatography on silica gel using ether–pentane, followed by recrystallization from hexane, afforded 980 mg of pinol chlorohydrin **6**: mp 77–78 °C; NMR ($CDCl_3$) 1.18 and 1.35 (s, 6, $(CH_3)_2CO$), 1.63 (s, 3, CH_3CCl), 1.85–2.55 (m, 5), and 4.12 ppm (d, 1, –CHO–).

From 1.0 g of (+)-**5**, mp 72–73 °C, $[\alpha]^{25}D$ +11.14° (*c* 4.72, $CHCl_3$), there was obtained 575 mg of (+)-**6**, mp 81–82 °C, $[\alpha]^{25}D$ + 78.52° (*c* 3.1, $CHCl_3$).

The rate of rearrangement of **5** to **6** was followed by dissolving 300–400 mg of **5** in 25 mL of the appropriate solvent and the resulting solution was heated in an oil bath. Aliquots were periodically withdrawn, the solvent was evaporated under reduced pressure, and the NMR spectrum of the residue was determined in $CDCl_3$. The ratio of the area of the signal at 1.63 ppm to the area of the signal at 1.37 ppm was used to determine the composition of the mixture.

4α-Chloro-4β,7,7-trimethyl-6-oxabicyclo[3.2.1]octan-3-one (7). To a solution of 1.6 g of pinol chlorohydrin (**5**) in 25 mL of acetone was added Jones reagent until the red-orange color persisted. The mixture was worked up in the usual manner to afford 1.4 g of oil. Chromatography on silica gel followed by evaporative distillation gave 1.0 g of chloroketone **7**: IR 5.80 μm; UV λ_{max} (MeOH) 298 nm (E = 40); NMR ($CDCl_3$) 1.15 and 1.20 (s, 6, $CH_3)_2CO$), 1.63 (s, 3, CH_3CCl), 2.0–3.0 (m, 5), and 4.20 ppm (d, 1, –CHO–); NMR (C_6H_6) 0.97 (s, 6, $CH_3)_2CO$), 1.70 (s, 3, CH_3CCl), 1.8–2.2 (m, 5), and 4.02 ppm (d, 1, –CHO–); mass spectrum m/e 202 (39), 167 (15), 125 (22), 123 (18), and 97 (100). Anal. Calcd for $C_{10}H_{15}ClO_2$: C, 59.26; H, 7.41; Cl, 17.53. Found: C, 59.19; H, 7.52; Cl, 17.40.

***endo*-6-Methoxy-*endo*-7-chlorocineole (13).** An ethereal solution of diazomethane, prepared from 36 g of *N,N'*-dimethyl-*N,N'*-dinitrosoterephthalamide, 120 mL of 30% NaOH, 90 mL of carbitol, and 600 mL of ether, was distilled into a receiver containing 1 g of cineal chlorohydrin (**5**) and 0.3 mL of boron trifluoride etherate in 10 mL of ether. The solution was kept at ambient temperature overnight and was then washed with water and 5% sodium bicarbonate solution and dried (Na_2SO_4). The solvent was removed and the residue was chromatographed on silica gel using ether–pentane as eluant to afford 350 mg of chloro methyl ether **13**, followed by 75 mg of 4α-chloro-3α-methoxy-4β,7,7-trimethyl-6-oxabicyclo[3.2.1]octane (**14**) and 450 mg of starting cineole chlorohydrin (**5**). The analytical sample of **13** was obtained by evaporative distillation: NMR ($CDCl_3$) 1.21 (s, 6, $CH_3)_2CO$), 1.31 (s, 3, CH_3CO), 1.4–2.1 (m, 3), 2.3–3.1 (m, 2), 3.33 (s, 3, CH_3O), 3.40 (m, 1, CHO), and 3.96 ppm (d of q, 1, CHCl); mass spectrum m/e 218 (15), 160 (12), 126 (49), 125 (78), 124 (21) and 43 (100). Anal. Calcd for $C_{11}H_{19}ClO_2$: C, 60.39; H, 8.77; Cl, 16.20. Found: C, 60.35; H, 8.88; Cl, 16.20.

Chloromethoxypinol (**14**) was an oil and showed NMR ($CDCl_3$) 1.20 and 1.36 (s, 6, $CH_3)_2CO$), 1.63 (s, 3, CH_3CCl), 1.8–2.6 (m, 5), 3.43 (s, 3, CH_3O), 3.62 (q, 1, $CHOCH_3$) and 4.04 ppm (d, 1, CHO).

A sample of **13** in *p*-xylene at 110 °C showed no change after 24 h. At 140 °C, 13% rearrangement to **14** had occurred in 14 h, 26% in 23 h, and 32% in 39 h.

Pinol Dibromide (3α,4α-Dibromo-4β,7,7-trimethyl-6-oxabicyclo[3.2.1]octane, 9). *endo,endo*-6,7-Dibromocineole (8) was unchanged after refluxing in toluene for 24 h. In 48 h a 10% conversion to **9** was noted. In *p*-xylene (140 °C) 45% rearrangement was observed in 8 h and 75% after 24 h. In bromobenzene (154 °C) the rearrangement of **8** to **9** was essentially complete in 5 h.

The black bromobenzene solution resulting from heating 638 mg of dibromide **8** in bromobenzene for 5 h was chromatographed on 50 g of silica gel using hexane, 2% ether–hexane, and 4% ether–hexane as eluants to give 300 mg of pinol dibromide (**9**). After two sublimations in vacuo, dibromide **9** displayed mp 58–60 °C: NMR ($CDCl_3$) 1.22 and 1.41 (s, 6, $(CH_3)_2CO$), 1.83 (s, 3, CH_3CBr), 2.0–2.8 (m, 8), 4.30 (d, 1, –CHOC–), and 4.40 ppm (d of d, 1, $W_{1/2}$ = 30 Hz, CHBr); mass spectrum, *m/e* 310 (2.5), 231 (100), 133 (67), 125 (56), 123 (28), 93 (56), 81 (41) and 69 (36). Anal. Calcd for $C_{10}H_{16}Br_2O$: C, 38.46; H, 5.13; Br, 51.28. Found: C, 38.54; H, 5.21; Br, 51.40.

Pinol Dichloride (3α,4α-Dichloro-4β,7,7-trimethyl-6-oxabicyclo[3.2.1]octane, 11). Aliquots were periodically withdrawn from a refluxing solution of *endo,endo*-6,7-dichlorocineole (**10**) in bromobenzene and analyzed by NMR. After 18 h. 33% rearrangement to **11** had occurred. The mixture darkened appreciably after 100 h and even after 134 h (60% **11**) the conversion to **11** was not complete.

A 534-mg sample of dichloride **10** was heated at 260–270 °C for 1 h with considerable foaming and discoloration. The mixture was cooled and washed through a short plug of Florisil with hexane and ether. A total of 380 mg of brown oil was recovered and GLC analysis using a 10% Carbowax column at 170 °C indicated the presence of 82% of **11** (retention time 14 min) and 18% of **10** (retention time 19 min).[9] A pure sample of dichloride **11** was obtained by GLC and showed: NMR ($CDCl_3$) 1.21 and 1.39 (s, 6, $(CH_3)_2CO$), 1.65 (s, 3, CH_3CCl), 1.8–2.8 (m, 5), 4.20 (d, 1, J = 6 Hz, CHO), and 4.35 ppm (m, 1, CHCl); mass spectrum (70 eV) *m/e* (rel intensity) 222 (24), 187 (100), 180 (14), 178 (18), 171 (7), 169 (17), 151 (21), 145 (24), 143 (48), 97 (38), 93 (43), 81 (37), and 43 (45). Anal. Calcd for $C_{10}H_{16}Cl_2O$: C, 58.81; H, 7.17; Cl, 31.87. Found: C, 54.11; H, 7.15; Cl, 32.03.

Registry No.—**1**, 5718-71-8; (±)-**2**, 64665-45-8; (−)-**2**, 64665-46-9; (±)-**3**, 64611-57-0; (+)-**3**, 64611-58-1; **4**, 64611-59-2; (±)-**5**, 60760-99-8; (+)-**5**, 64665-47-0; (±)-**6**, 60705-69-3; (+)-**6**, 64611-60-5; **7**, 60705-71-7; **8**, 32207-49-1; **9**, 64611-61-6; **10**, 32221-12-8; **11**, 64611-62-7; **13**, 64611-63-8; **14**, 64611-64-9.

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Carbon-13 Nuclear Magnetic Resonance Study of Iodine–Sulfide Charge-Transfer Complexes

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Charge-transfer complexes between iodine and alkyl or aryl sulfides have been known for some time now.[1b,c] Most of the studies hitherto have been concerned with the measurement of the formation constants utilizing spectrophotometric methods,[2] although one proton NMR study has been reported.[3] While these investigations have presented useful information concerning the structural features which affect the strength of the charge-transfer interaction, they have not dealt with the gross molecular reorganization in these complexes. Since carbon-13 NMR chemical shifts are sensitive to changes in electron density[4] and the stereochemical relationship of atoms in a molecule,[5] it was felt that this spectroscopic method would provide additional insight into the electronic reorganization of the sulfides. In fact, Roberts has already shown that carbon-13 NMR spectroscopy can be utilized in the study of charge-transfer complexes.[6]

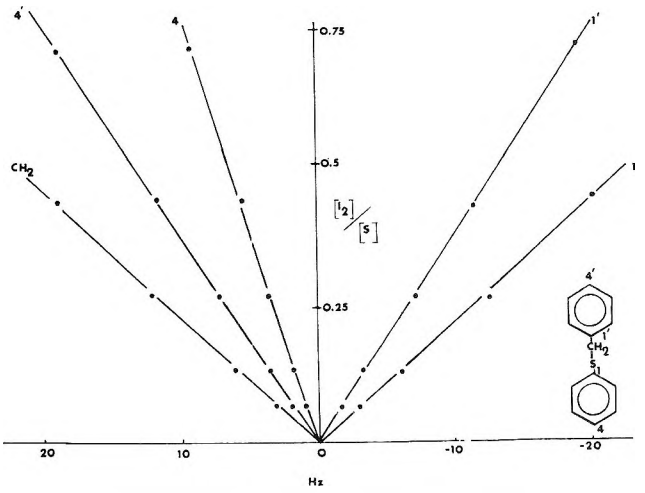

Figure 1. Plot of the ratio of iodine to sulfide concentration against the magnitude of the iodine-induced shift for benzyl phenyl sulfide.

It is generally agreed that the sulfide–iodine charge-transfer interaction is a 1:1 species[2d] and that the sulfur–iodine bonds all lie in a straight line.[7] For the purpose of this report, all other species will be ignored. It has also been shown that in aromatic sulfides only the sulfur atom is complexed by the iodine.[2d]

A typical set of data is illustrated by the plot given in Figure 1. The plot is clearly monotonic, at least to molar concentrations less than 0.75, and this is a good indication that only one complexed species is present in solution.[8] Attempts at obtaining the limiting shift of the complex were not performed due to the insolubility of iodine under the experimental conditions. Attempts at decreasing the sulfide concentration (thus increasing the accumulation time significantly) facilitated some oxidation to the corresponding sulfoxide.

Given in Figure 2 are the carbon chemical shifts and iodine-induced chemical shifts (in parentheses) for the sulfides studied. The iodine-induced shifts were obtained directly from the plotted data by extrapolation of the $\Delta\delta$ vs. concentration curve to a 1:1 ratio. The value obtained by this method should be proportional to the limiting shift of the sulfide–iodine complex.[9]

The iodine-induced shifts in the aliphatic sulfides I, V, VI, and VII appear quite unexceptional. The α-carbon resonances suffer a large downfield shift due to the increase of the electron withdrawing nature of the sulfide–iodine complex vs. that of the free sulfide. The β-carbon resonances are shifted to higher field and this most likely results from a polarization of the C–H bond, the well known γ effect.[10] For the remaining sulfides II, III, and IV, the aliphatic α-carbon resonances are also shifted to lower field but to a lesser extent than the above compounds. However, for a directly bonded aromatic α-carbon the direction of shift is to *higher* field. An upfield shift is also observed for all ipso aromatic carbon resonances β to the sulfur atom. In aromatic systems there is a good correlation between the direction of the shift and electron density at a carbon site.[4]

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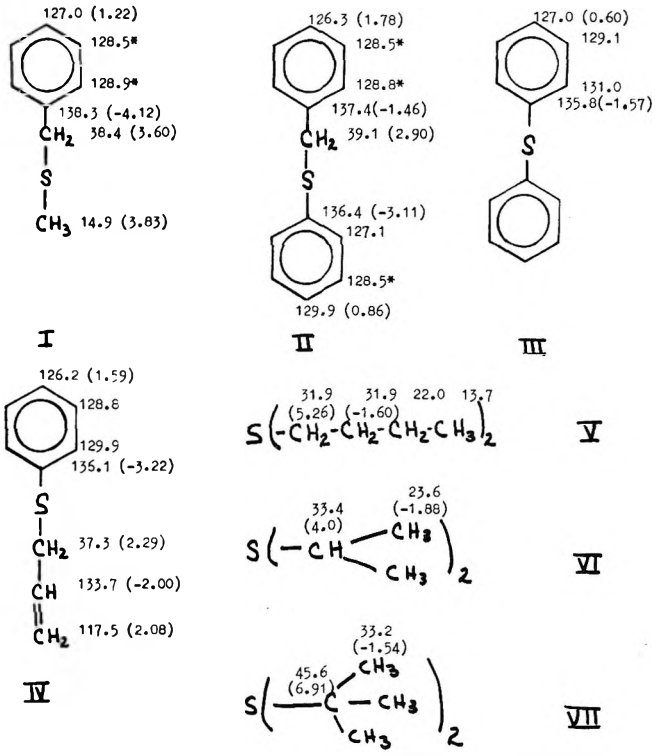


Figure 2. Carbon-13 chemical shifts and iodine-induced chemical shifts (slope of the δ_{obsd} vs. molar concentration plot) for the sulfides. *Assignments may be reversed.

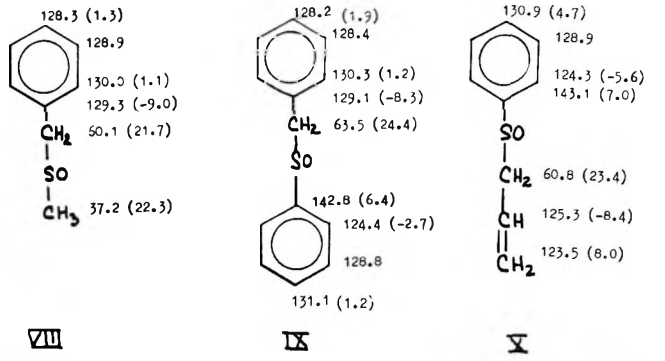
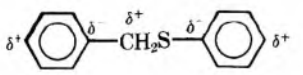


Figure 3. Carbon-13 chemical shifts and substituent chemical shifts (where negative values indicate upfield shifts) for the sulfoxides as compared to the sulfides.

An upfield shift would indicate an increase of electron density as compared to the parent sulfide. Except for compound IV, the only iodine-induced shift of any magnitude occurs for the para-aromatic ring carbons which invariably are shifted to lower field.

The net result of the iodine-induced shifts illustrated for compound II is shown below. The type of electronic interac-



tion found in the sulfide–iodine complex is best explained by a π-bond polarization mechansim.[11] Strong evidence supporting the π-bond polarization of these systems can be found in the induced shifts for the olefinic carbons in XI. Clearly, both of these carbon resonances are affected to the same degree but in opposite directions, as predicted by the π-bond polarization mechanism. Further support for the π-bond polarization mechanism can be seen in the substituent shifts of the sulfoxides VIII, IX, and X; see Figure 3.[12]

Experimental Section

All of the sulfides were commercially available and are estimated by VPC to be greater than 99% pure. The sulfoxides were obtained from C. G. Venier, Texas Christian University, and were used as received. The iodine-induced shifts were obtained by an incremental addition of iodine to a 0.5 M solution of the sulfide in deuteriochloroform contained in a 10-mm o.d. NMR tube.

The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a JEOL FX-60 spectrometer system equipped with a 24K memory Texas Instruments computer. The spectra were obtained at an observing frequency of 15.03 MHz. General NMR spectral parameters were: internal lock to the deuterium containing solvent; a spectral width of 2500 Hz; a pulse width of 4 μm corresponding to a 36° pulse angle; and a pulse repetition time of 2.1 s. All shifts are estimated to be accurate to ±0.05 ppm and are referenced to internal Me_4Si.

Acknowledgments. The financial support of this work by the Robert A. Welch Foundation is gratefully acknowledged. The author also thanks the National Science Foundation and the National Institutes of Health for their grants to Professor P. D. Bartlett which enabled the purchase of the JEOL FX-60 spectrometer system. In addition, the author thanks Professor P. D. Bartlett for the opportunity to engage this project and Professor C. G. Venier for the sulfoxides used and for helpful discussions.

Registry No.—I, 766-92-7; II, 831-91-4; III, 139-66-2; IV, 5296-64-0; V, 544-40-1; VI, 625-80-9; VII, 107-47-1; VIII, 824-86-2; IX, 833-82-9; X, 19093-37-9; iodine, 7553-56-2.

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(9) The "limiting shift" obtained by this method is dependent upon the absolute concentration of the sulfide. Experimentally this can be resolved by performing the experiment keeping the iodine concentration constant and varying the sulfide concentration. Since an accurate limiting shift or equilibrium constants were not of prime importance in this study, this experiment was not performed. See: I. Armitage, L. D. Hall, and A. G. Marshall, *Can. J. Chem.*, **50**, 2119 (1972).
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Studies on Friedel–Crafts Chemistry. 3. A New Preparative Method of 2-*tert*-Butyl-*p*-xylene by the $AlCl_3$–CH_3NO_2 Catalyzed *tert*-Butylation of *p*-Xylene with 2-*tert*-Butyl- and 2,6-Di-*tert*-butyl-*p*-cresol[1]

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There are few preparatively useful procedures for the synthesis of 2-*tert*-butyl-*p*-xylene (**4**) by the *tert*-butylation of *p*-xylene (**1**). The desired compound **4** was only obtained as

Table I. The $AlCl_3$–CH_3NO_2 Catalyzed *tert*-Butylation of *p*-Xylene with 2-*tert*-Butyl- and 2,6-Di-*tert*-butyl-*p*-cresol [a]

Run	Alkylating reagent	Time, min	Product, mol % [b]			
			2	3	4	5
1	2	1	2.8	36.7	19.3	60.5
2	2	2	0	30.6	16.4	69.4
3	2	5	0	22.6	41.4	77.4
4	2	10	0	20.7	44.8	79.3
5	2	15	0	8.2	39.9	91.8
6	2	20	0	4.1	28.8	95.9
7	2	30	0	3.9	25.0	96.1
8 [c,d]	2	17	0	0	60.0 [e]	70 [e]
9	3	1	0	24.8	20.2	75.2
10	3	2	0	16.4	23.4	83.6
11	3	5	0	6.0	32.7	94.0
12	3	10	0	5.6	36.6	94.4
13	3	15	0	5.5	32.1	94.5
14	3	20	0	4.7	23.7	95.3
15	3	30	0	5.3	26.2	94.7
16 [c,f]	3	17	0	16 [d]	40.1 [e]	77.6 [e]

[a] **1/2** or **3**: 5 mol/mol. $AlCl_3$–CH_3NO_2/2 or **3**: 1.5 mol/mol. Reaction temperature was 1 °C unless otherwise indicated. [b] The yields were determined by GC analyses. [c] In the scale of 53.08 g (0.5 mol) of **1**, this reaction was carried out in order to isolated the desired compound **4**. [d] Reaction temperature, −15 °C. [e] The yields isolated are shown. [f] Reaction temperature, 5 °C.

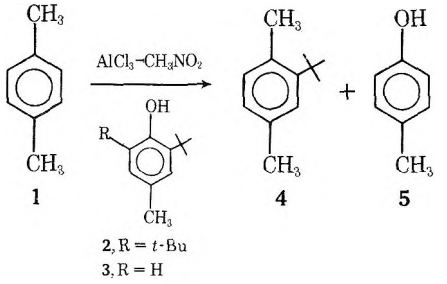
a by-product in low yield in the Friedel–Crafts *tert*-butylation of **1**.[2-4]

It was previously reported that[5] a *tert*-butylating system of $AlCl_3$–CH_3NO_2 catalyst and 2,6-di-*tert*-butyl-*p*-cresol (**2**) was a powerful reagent affording *tert*-butylbenzenes from the corresponding aromatics under very mild conditions (at room temperature, for only 1 min) in good yields.

The above results prompted us to reinvestigate the $AlCl_3$–CH_3NO_2 catalyzed *tert*-butylation of **1** with **2** and 2-*tert*-butyl-*p*-cresol (**3**) in order to obtain **4**, which has never been isolated in good yield, from the Friedel–Crafts *tert*-butylation of **1** as described above.

Results and Discussion

The $AlCl_3$–CH_3NO_2 catalyzed *tert*-butylations of **1** with **2** and **3** were carried out under various conditions, and the results are summarized in Table I.



These reactions were carried out at lower temperature since it was previously shown[5] that when a mixture of three isomers of xylenes was treated with **2** at room temperature in the presence of $AlCl_3$–CH_3NO_2 catalyst, the corresponding *tert*-butyl derivatives of *o*- and *m*-xylene were obtained in good yield, but no **4** was formed and **1** was recovered in almost quantitative yield.

As is shown in Table I, the $AlCl_3$–CH_3NO_2 catalyzed *tert*-butylation of **1** with **2** at 1 °C for 10 min afforded **4** in 44.8 mol % yield,[6] which decreased with increasing reaction time after 10 min. Similarly, the maximum yield of **4** in the reaction with **3** appeared in 10 min reaction time. These results suggest that **4** should be unstable under the conditions used. Indeed, when **1** was treated with **2** at −15 °C in the presence of $AlCl_3$–CH_3NO_2 catalyst, **4** was isolated in 60 mol % yield.

It should be noted that although **2** has two *tert*-butyl groups, the yields of **4** in the reaction with **2** were only somewhat higher than that of the reaction with **3**. These results might suggest that of the two *tert*-butyl groups of **2** only one might mainly act as an alkylating reagent, and the other might be lost as isobutylene. For the practical preparation of **4**, the $AlCl_3$–CH_3NO_2 catalyzed *tert*-butylation of **1** with **3** was carried out on a large scale; **4** was isolated in 40.1 mol % yield.[7]

Although besides the desired product **4** small amounts of the lower and higher boiling products[8] were also detected by gas chromatographic analyses in the respective cases, the detailed determination of the compounds was not carried out. As mentioned above, **4** was isolated first in good yields by the $AlCl_3$–CH_3NO_2 catalyzed *tert*-butylation of **1** with **2** and **3**, respectively.

Experimental Section

All boiling points are uncorrected. NMR spectra were determined at 60 MHz with a Hitachi R-20 NMR spectrometer with Me_4Si as an internal reference.

Analytical Procedures. The analyses were carried out by gas chromatography using a Yanagimoto gas chromatograph, Yanaco YR-101; column, 30% high-vacuum silicon grease, 75 cm; increase rate of column temperature, 8 °C/min; carrier gas, helium at 25 cm^3/min.

From the areas of individual peaks, mole percent figures were calculated for each product after the relative response data had been determined by the internal standard method. Bromobenzene was used as an internal standard.

General Procedure. To a solution of 5 equiv of **1** and 1 mol of **2** or **3** was added a solution of 1.5 equiv of $AlCl_3$ catalyst/equiv of **2** in nitromethane (1 g/2 mL) at a desired and constant temperature. After the reaction mixture was stirred for a specified reaction time at the same temperature, it was poured into a large amount of ice–water. The organic layer was separated and dried over sodium sulfate. A definite amount of bromobenzene was added into the organic layer as an internal standard substance for the gas chromatographic analyses.

Isolation of 4. (a) The *tert*-Butylation with 2. To a solution of 53.08 g (0.5 mol) of **1**, 22 g (0.1 mol) of **2** in 10 mL of nitromethane was added at −15 °C (bath temperature, −17 °C; the catalyst, $AlCl_3$, 19.8 g (0.15 mol) in 40 mL of nitromethane) over a period of 2 min. After the reaction mixture was stirred for an additional 15 min, it was poured into 500 mL of ice–water. The organic layer was separated and washed with 10% sodium hydroxide solution and then with the Claisen alkaline reagent[9] in order to separate **5** and **3** which were formed, respectively.

The remaining organic layer was dried over sodium sulfate and evaporated in vacuo to leave the residue which was distilled under reduced pressure to afford 9.74 g (60 mol %; 30% yield) of **4**: colorless liquid, bp 95–98 °C (18 mm); IR (NaCl) cm^{-1} 2960, 2880, 1465, 1360, 810; NMR (CCl_4) δ 1.36 [9 H, s, $C(CH_3)_3$], 2.26 (3 H, s, CH_3), 2.44 (3 H, s, CH_3), 6.70–7.10 (3 H, m, aromatic protons). The NMR data

agreed well with those reported.[4] The washed 10% sodium hydroxide solution was acidified with 10% hydrochloric acid to afford 7.56 g (70 mol %; 70% yield) of **5**.

(b) The *tert*-Butylation with 3. Similarly, to a mixture of 53.08 g (0.5 mol) of **1** and 16.4 g (0.1 mol) of **3** was added at 5 °C the $AlCl_3$–CH_3NO_2 catalyst (19.8 g/40 mL). The reaction mixture was stirred for 15 min and it was treated and worked up as described above to afford 6.5 g (40.1 mol %, 40.1% yield) of **4**, 3.42 g (16%) of the recovered **3**, and 8.38 g (77.6%) of **5**.

Registry No.—**1**, 106-42-3; **2**, 128-37-0; **3**, 2409-55-4; **4**, 42861-84-7; **5**, 106-44-5; $AlCl_3$, 7446-70-0; CH_3NO_2, 75-52-5.

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Novel Photochemically Induced Carbon Monoxide Insertion of an Enone–Iron Tetracarbonyl Complex to Yield a Lactone

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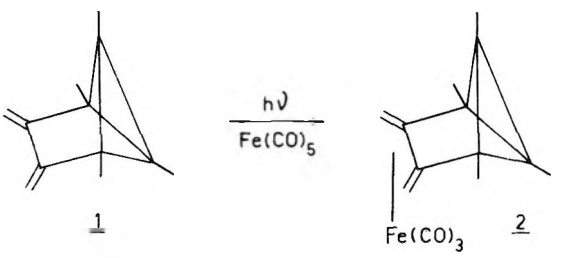
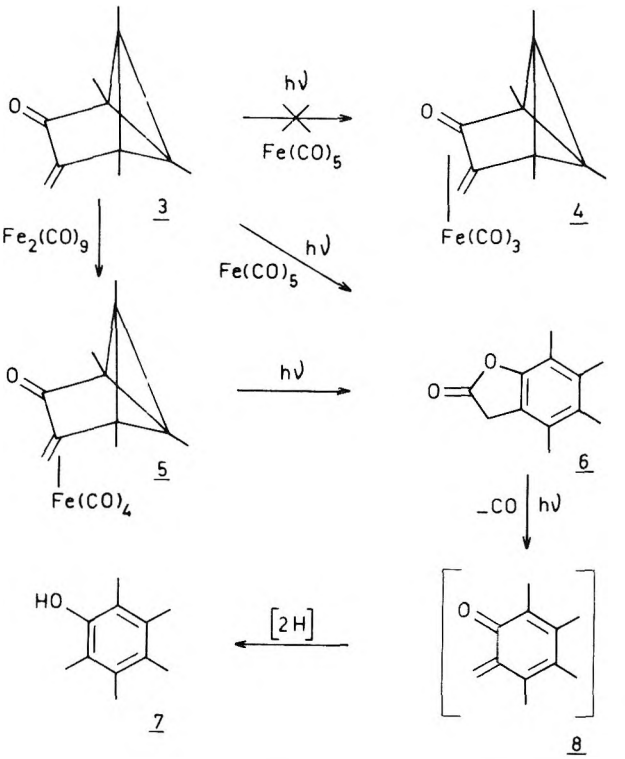
Recently, we reported the synthesis of the bicyclobutane-bridged diene–iron tricarbonyl complex **2** from the corresponding diene **1**[1] (Scheme I). Because both diene **1** and enone **3**[2] show an unexpected reactivity toward the $[Rh(CO)_2Cl]_2$/CO catalyst system[3] and, moreover, because the extremely high reactivity (e.g., in Diels–Alder cycloadditions[4]) of diene **1** can be suppressed by complex formation to iron tricarbonyl, we undertook to prepare the related enone–iron tricarbonyl complex **4**. Unexpectedly, this proved to be impossible and a different reaction, viz., intramolecular CO insertion to yield a lactone, was observed. In view of the current interest in the preparation and properties of enone–iron tetra- and tricarbonyl complexes,[5-8] an account of the results obtained is given herewith.

Following the usual procedure for formation of enone–iron tricarbonyl complexes,[5] enone **3** and iron pentacarbonyl were irradiated in THF solution. However, no iron tricarbonyl complex **4** was isolated, but instead we obtained lactone **6** in 28% yield. IR and ^1H NMR measurements performed during the irradiation showed the presence of small amounts of iron tetracarbonyl complex **5**. Prolonged irradiation in the presence of excess iron pentacarbonyl did not increase the yield of **6**, but formation of substantial amounts of phenol **7**[9] was observed, probably via intermediacy of *o*-quinone methide **8**.[10] (See Scheme II.) Iron tetracarbonyl complex **5** was prepared independently as a yellow oil in 51% yield by treating **3** with diiron nonacarbonyl in THF. On warming at temperatures above 40 °C complex **5** decomposes back to enone **3**. Irradiation of **5** in THF or benzene solution gave lactone **6** in 45% yield but no **4**.[11]

Scheme I

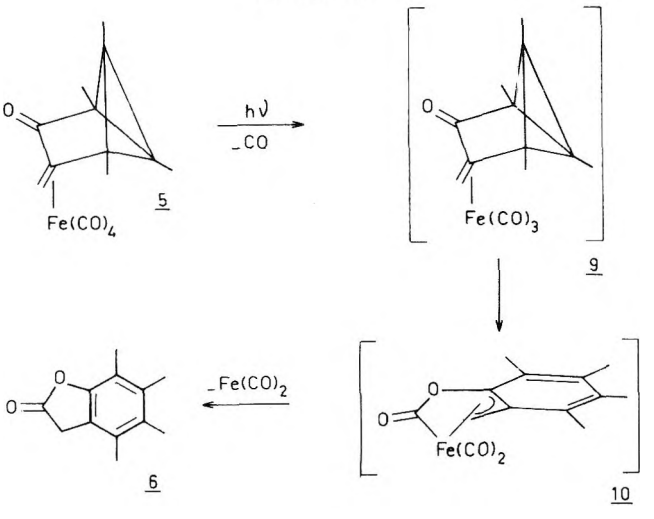


Scheme II



A satisfactory explanation for the unusual photochemically induced reaction of **5** → **6** in comparison with the normal conversion of enone–iron tetracarbonyl into iron tricarbonyl complexes must involve the special nature of the organic ligand. It is conceivable that on irradiation a coordinatively unsaturated complex **9** is formed, which—rather than to complex to the ketone moiety—gives the CO-inserted σ,π-complex **10**, followed by extrusion of the $Fe(CO)_2$ moiety to yield lactone **6** (Scheme III). Subtle differences between the chemical behavior of the iron tetracarbonyl complexes of diene **1** and **3** result in formation of diene complex **2**, on the one hand, and lactone **6**, on the other hand. This may be related to the difference in thermodynamic stability of enone–iron tricarbonyl and diene–iron tricarbonyl complexes.[17]

Scheme III



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Experimental Section

General. The IR spectra were taken on a Perkin-Elmer 257 spectrophotometer. Mass spectra were obtained on a AEI MS-902 by Mr. A. Kiewiet. ^{1}H NMR spectra were recorded using a Varian A-60 D or Hitachi-Perkin-Elmer R24B spectrometer with Me_4Si as internal standard. ^{13}C NMR spectra were recorded using a Varian XL-100 spectrometer operating at 25.2 MHz. All reactions were carried out under a dry nitrogen atmosphere. Irradiations were performed with a Hanau Q-81 high-pressure mercury arc.

Irradiation of Enone 3 and Iron Pentacarbonyl. Enone **3** (310 mg, 1.9 mmol) and iron pentacarbonyl (390 mg, 2.0 mmol) in 100 mL of THF were irradiated for 2 days. Solvent, excess iron pentacarbonyl, and enone were removed in vacuo (room temperature, 0.001 mmHg pressure) and the residue was extracted with *n*-pentane. After recrystallization from *n*-pentane at −40 °C, lactone **6** was obtained in 28% yield (100 mg, 0.5 mmol). Compound **6** was characterized by comparison with an authentic sample.[3] During the irradiation, samples were taken from the solution, the solvent was evaporated, and the residue was analyzed by IR and ^{1}H NMR, showing absorptions due to complex **5**. When the irradiation was performed for 3 days a mixture of lactone **6**, phenol **7**, and starting material was obtained. Extraction of this mixture with aqueous KOH solution and acidification with HCl gave phenol **7** as a white solid, which was purified by recrystallization from *n*-pentane at −40 °C. Phenol **7** was characterized by spectral data and melting point (125–127 °C, lit.[18] 129 °C).

Enone–Iron Tetracarbonyl Complex 5. Enone **3** (630 mg, 3.9 mmol) was treated with 1.46 g (4.0 mmol) of diron nonacarbonyl in 50 mL of THF at room temperature during 2 h. Solvent and starting material were removed in vacuo. The residue was extracted with *n*-pentane, leaving after removal of the solvent in vacuo iron complex **5** in 51% yield (based on ^{1}H NMR) as a yellow oil. Attempts to crystallize **5** from *n*-pentane at −50 °C were unsuccessful. Compound **5** could not be completely freed from small amounts of enone **3** (to an extent of about 10%): MS *m/e* 330 (M^+), 302 (found 302.020; calcd 302.024[19]), 274, 246, 218, 162 (successive loss of CO groups and Fe); IR absorptions at 2090, 2020, and 1975 [$Fe(CO)_4$] and 1710 (C=O) cm^{-1}; ^{1}H NMR (C_6D_6, 35 °C) δ 2.86 (d, J = 1.8 Hz, 1 H), 2.43 (d, J = 1.8 Hz, 1 H), 1.27 (s, 3 H), 1.05 (s, 3 H), 1.01 (s, 3 H), 0.67 (s, 3 H); ^{13}C NMR (C_6D_6, 10 °C) δ 212.8[19] (s, C=O), 210.1[19] (s, FeC≡O), 85.8 (s), 50.7 (s), 42.9 (s), 40.7 (s), 31.5 (t, J = 156 Hz), 31.2 (s), 8.0:4.8:3.3:3.0 (q, $J \simeq$ 125 Hz).

Irradiation of Complex 5. Complex **5** (200 mg, 0.63 mmol) was irradiated in THF solution for 4 h, during which evolution of gas took place and insoluble material deposited on the lamp. After removal of the solvent the residue was recrystallized from *n*-pentane at −40 °C, giving lactone **6** in 45% yield (53 mg, 0.28 mmol).

Registry No.—**3**, 56745-77-8; **5**, 64314-99-4; **6**, 60998-59-6; iron pentacarbonyl, 13463-40-6; diiron noncarbonyl, 15321-51-4.

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(19) The intensity of the parent peak was too low to be used for an exact mass determination. Therefore, the exact mass of the (M^+ − CO) fragment was taken. In the ^{13}C NMR spectrum the CO absorptions have an intensity of about 4:1, which allows the assignment given.

Acid-Catalyzed Isomerization of 2-Protoadamantenone to 8,9-Dehydro-2-adamantanone

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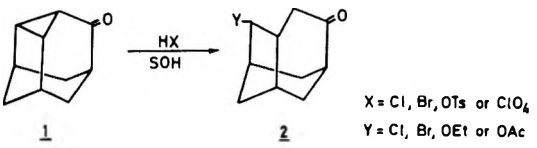
Rearrangements of the dehydroadamantyl and the protoadamantenyl cations are quite complex.[1-7] The course of these rearrangements depends highly on the reaction conditions. While the 8,9-dehydro-2-adamantyl cation undergoes rapid degenerate equilibrium under stable ion conditions,[7] 8,9-dehydro-2-adamantanol isomerizes in the presence of perchloric acid to 2-*exo*-protoadamantenol.[1,2] Under similar conditions, 8,9-dehydro-2-adamantanone (**1**) rearranges



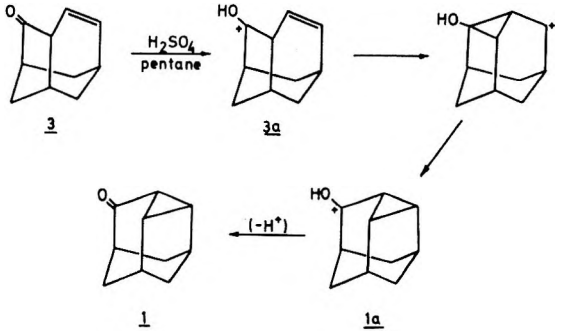
1 **2**

smoothly to 2-exo-substituted 5-protoadamantanones (**2**).[3] This rearrangement probably proceeds via the enol form of the 5-protoadamantanon-2-yl cation.

We report now an example of the reverse rearrangement: the acid-catalyzed isomerization of 2-protoadamantenone (**3**) to 8,9-dehydro-2-adamantanone (**1**). Treatment of **3** with 96% sulfuric acid in the presence of pentane at 22 °C afforded **1** in 30–40% yield. The product was stable under the reaction conditions used and was identified by IR,[1,6] ^{1}H NMR,[1,6] and ^{13}C NMR spectroscopy, mass spectrometry, and GLC comparison with an authentic sample which was prepared by the previously reported[1] procedure. The mechanism of this isomerization probably involves the initial protonation of the carbonyl group in **3** to give homoallyl cation **3a**, which then rearranges by the homoallyl–cyclopropylcarbinyl rearrangement to cation **1a** and ketone **1** (Scheme I).

This reaction provides the only example of the "solvolytic" π-route isomerization of 2-protoadamantenone (**3**) to 8,9-dehydro-2-adamantanone (**1**) and could be synthetically useful as an alternative to the photoisomerization[1] of **3** to **1**. Ketone **1** is a convenient starting material for the preparation of not only 2-substituted 8,9-dehydroadamantanes[1,6] but also

Scheme I



3 **3a** **1** **1a**

0022-3263/78/1943-0746$01.00/0

a variety of 2,5-disubstituted protoadamantanes,[3] 2-substituted protoadamantenes,[2] and 2-substituted isotwistanes.[3]

Experimental Section

The ^{13}C NMR spectra were taken on a JEOL FX-100 spectrometer, the ^1H NMR spectra on a Varian A-60A spectrometer, the IR spectra on a Perkin-Elmer 257 spectrophotometer, and the mass spectra on a Varian CH-7 mass spectrometer. The GLC analyses were carried out on a Varian Aerograph 1800 gas chromatograph.

2-Protoadamantenone (3). Following the reported procedure,[8] a 1:1 mixture of 2-protoadamantenone (3) and 10-protoadamantenone (4) was obtained by thermal cyclization of 7-allyloxycycloheptatriene. The ketones were not satisfactorily separated either by column chromatography or preparative GLC. We found, however, that ketone 4 formed the ethylene ketal much faster than 3.

A solution of the sublimed crude mixture of ketones 3 and 4 (1.5 g) was stirred in ethylene glycol (10 mL) in the presence of TsOH (2.1 g) at 80–85 °C for 2 h and then poured into a mixture of KOH (0.7 g) and crushed ice. The resulting mixture was extracted with ether (3 × 25 mL), and the combined extracts were washed with water and dried. Evaporation of ether gave 1.3 g of a crude oily product which contained two GLC-detectable components (10% Carbowax 20M, 150 °C): ketone 3 and the ethylene ketal of 4 (less than 5% of unreacted 4 was present). Pure ketone 3 (0.3 g) was obtained by column chromatography on silica gel using 1:49 ether–benzene as eluent. The physical and spectral properties of 3 agree with those previously reported for this compound.[8]

8,9-Dehydro-2-adamantanone (1). A typical experiment is described. Ketone 3 (75 mg, 0.5 mmol) was stirred with 0.5 mL of 96% sulfuric acid and 2 mL of pentane at 22 °C for 3 h. Ether (10 mL) and crushed ice were added, and the layers were separated. The aqueous layer was extracted with ether (2 × 5 mL), and the combined ether extracts were washed with saturated aqueous $NaHCO_3$ and dried. Evaporation of the solvent yielded crystalline crude product which contained 15% of unreacted 3 and 85% of 8,9-dehydro-2-adamantanone (1) (by GLC; 10% Carbowax 20M, 150 °C). Pure ketone 1 (≥98% by GLC; 26 mg, 35% based on 3) was easily obtained by column chromatography on Al_2O_3 (neutral, activity II) using ether as an eluent. Its melting point (205–206 °C), IR, ^1H NMR, and the mass spectral data were in complete agreement with those previously reported[1,6] for this compound; the ^{13}C NMR spectrum [δ_{Me_4Si} ($CDCl_3$) 32.2, 34.2, 37.7, 39.6, 44.0, 51.4, and 214.4 ppm] of 1 was identical to that of an authentic sample prepared by the reported[1] photoisomerization of 3.

Ketone 1 was also obtained in 10–20% yield directly from the crude (sublimed) product mixture of the thermal cyclization of 7-allyloxycycloheptatriene by the procedure described above.

A sample of pure 1 was subjected to the same reaction conditions as 3. Essentially no rearranged products were detected by GLC.[9]

Acknowledgment. This work was supported by a grant from the Research Council of the Republic of Croatia. We thank Professor Y. E. Rhodes for helpful discussions and Mrs. Lj. Vulić for the technical assistance.

Registry No.—1, 10497-56-0; 3, 28673-75-8; 4, 28673-76-9; 4 ethylene ketal, 64345-72-8; 7-allyoxycycloheptatriene, 28673-74-7.

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(9) This is consistent with the formation of the stable 2-hydroxy-8,9-dehydro-2-adamantyl cation by protonation of ketone 1 in FSO_3H–SO_2ClF.[7]

Protecting Groups. 6. Interaction of 2-Picoline 1-Oxides with Acylating and Phosphorylating Agents. A Case of Product Distribution Control[1]

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Previous reports from our laboratory show that the 2-picolyl 1-oxide group is potentially a useful protecting group in organic chemistry in general[2] and in oligonucleotide syntheses in particular.[1,3] The picolyl 1-oxide group can be removed from an ether, thioether, or amine (1, Scheme I) or from an ester 6 by treatment with an acid anhydride. The reaction may proceed by the following mechanism: O-acylation to the *N*-acyloxypyridinium salt 2 and subsequent proton abstraction from the α-methylene group of 2 by the conjugate base to afford 3, followed by intramolecular electron transfer to complete the rearrangement from 3 to 4.[4b]

In order to determine the scope and limitations of this protecting group, we undertook systematic studies on the interaction between picolyl 1-oxide acetate (6) and various acylating agents (Table I).[4] An acylating agent (3 equiv) was added portionwise to a solution of 6 in deuterated chloroform. Little spectral change of 6 occurred upon addition of acetic anhydride (8) or benzoyl fluoride (13). The spectrum of 6, however, rapidly changed upon addition of acyl halide (except 13), indicating the formation of the *N*-acyloxypicolinium salt 2. A large paramagnetic shift of the H-6 signal of 6 was observed. The α-methylene signal of 2 also appeared in a lower field than that of 6 (Table I). The degree of this low-field shift of H-6 in 2 was found to be dependent upon the nature of the counterion. The largest shift was observed when the picolinium ion was associated with a hard base (Cl^-) and the smallest shift was observed when a soft base (I^-) was the counterion. The shape of the H-6 signal suggested that the strongest virtual coupling occurred with chloride and little virtual coupling was observed with iodide counterion. When bromide was the conjugate base, the long-range virtual coupling was medium.

Addition of acetyl iodide (11) to a preformed *N*-acetoxypicolinium chloride (2a, X = Cl) resulted in the formation of *N*-acetoxypicolinium iodide (2a, X = I) as observed by ^1H NMR spectroscopy. The bromide counterion of 2a (X = Br) was also replaced by iodide by treatment of 2a (X = Br) with 11. The reverse (exchange of iodide by chloride or bromide)

Scheme I

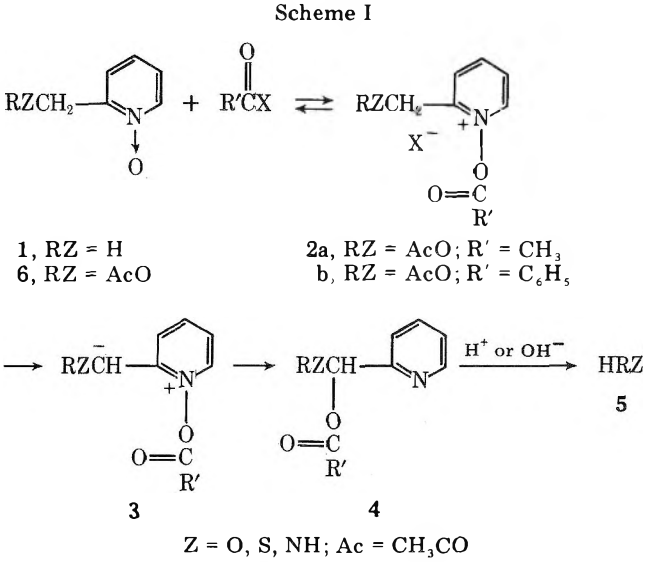

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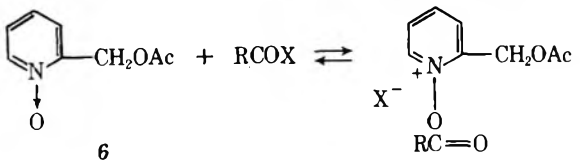
Table I. Reaction of 2-Picolyl 1-Oxide Acetate (6) with Acylating Agents



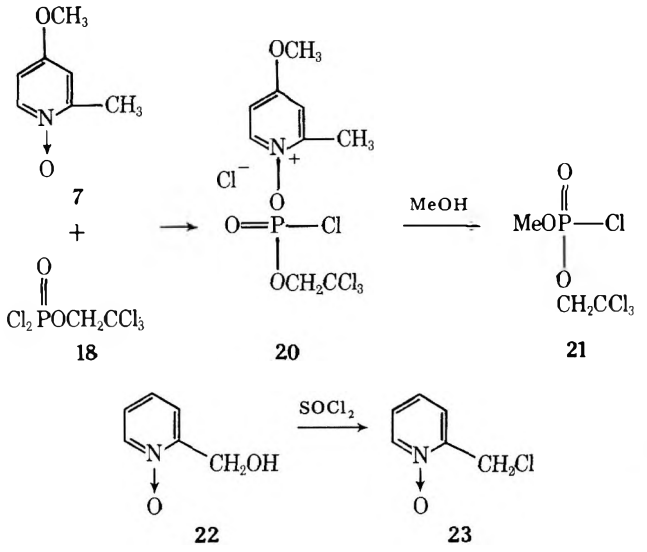
6

2a, R = CH_3
b, R = C_6H_5

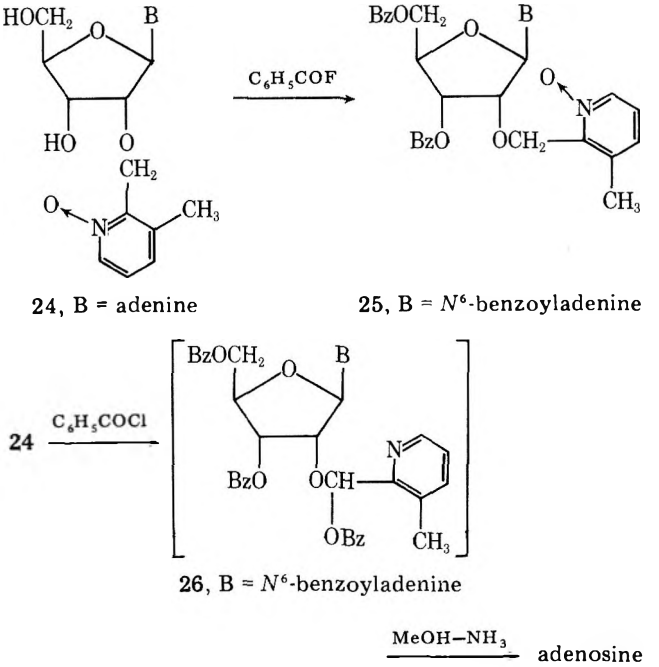
Acylating agent	Registry no.	Chemical shift (δ) of product 2[a] H-6	α-Methylene	Registry no.
Acetic anhydride (8)	108-24-7	8.25 t	5.35 s	64332-63-4
Acetyl chloride (9)	75-36-5	10.54 br s	5.62 s	64314-78-9
Acetyl bromide (10)	506-96-7	10.27 br d	5.61 s	64314-79-0
Acetyl iodide (11)	507-02-8	9.96 d	5.60 s	64314-80-3
Chloroacetyl chloride (12)	79-04-9	9.98 d	5.56 s	64314-81-4
Benzoyl fluoride (13)	455-32-3	8.19 t	5.34 s	64314-82-5
Benzoyl chloride (14)	98-88-4	Undetd	5.22 br s	64314-83-6
Benzoyl bromide (15)	618-32-6	10.24 d	5.75 s	64332-61-2

[a] Relative to the internal Me_4Si signal. and $CDCl_3$ was used as the solvent. Signals are quoted as s (singlet), d (doublet), br d (broad doublet), and t (triplet).

Scheme II



Scheme III



could not be effected. These experiments established that the *N*-acetoxypicolinium ion is a soft acid and forms a most stable salt with a soft base, such as iodide, and it cannot form a stable salt with a very hard base such as fluoride.

The effect of halide ion (counterion) upon the rate of overall rearrangement (1 → 4) was examined by taking advantage of the unique chemical shift of a sharp singlet due to the lateral α-methylene group of **2**. As the rearrangement proceeded the methylene signal decreased. It was found that only acyl chlorides were effective. Benzoyl fluoride (**13**) and acyl bromides were even less effective than acetic anhydride (**8**). The ineffectiveness of **13** in overall rearrangement (1 → 4) is apparently due to the inability of **13** to react with **6** to form **2**. Acetyl bromide (**10**) or benzoyl bromide (**15**) forms a stable *N*-acyloxypicolinium salt **2**. The conjugate base (Br^-), however, is less basic so that it does not abstract a proton as effectively from the α-methylene group as the chloride ion does. It was also found that benzoyl chloride (**14**) is several orders more efficient than acetyl chloride (**9**) in promoting the rearrangement. This may be explained by the difference of ease with which intramolecular electron transfer (from **3** to **4**) takes place. The carbonyl group of the *N*-benzoyloxy derivative **2b** is a better electron acceptor than that of the *N*-acetoxy analogue **2a** due to high conjugation of the benzoyl system. Anisoyl chloride or *p*-nitrobenzoyl chloride (**16**) was found as effective as **14**. Thus, the electronic nature of the para substituent is much less significant than conjugation of the system in the rearrangement.

Ethyl phosphorodichloridate[5] (**17**) or 2,2,2-trichloroethyl phosphorodichloridate[6] (**18**) did not react with **6**. Treatment of 4-methoxy-2-picoline 1-oxide[7] (**7**) with **18**, however, gave rise to *N*-(2,2,2-trichloroethylchlorophosphoryl)picolinium chloride (**20**) as judged by the ^1H NMR spectrum. Addition of methanol to **20** led to an immediate displacement of the spectrum of **20** by that of the hydrochloride salt of **7** with the concomitant appearance of a methyl signal [at δ 3.99 (J = 14.4 Hz)] due to the methyl group of methyl 2,2,2-trichloroethyl phosphorochloridate (**21**) (see Scheme II).

These results clearly showed that the electron-releasing methoxy group at position 4 favors the formation of quaternary salt **20**, and the phosphorus in **20** is sufficiently electrophilic to phosphorylate methanol. Thus, compound **20** has

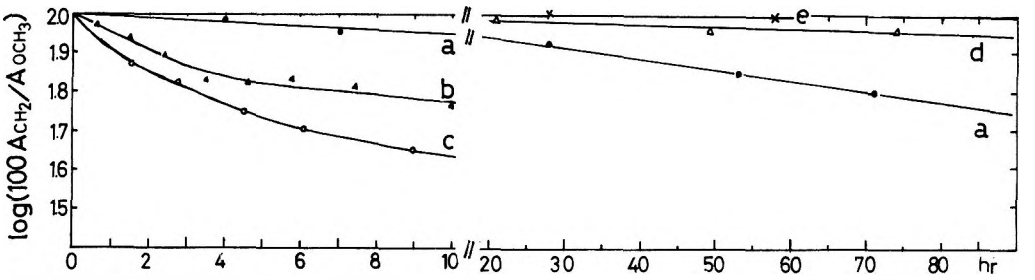


Figure 1. Rearrangement rate of the *N*-acyloxy group to the side chain. Time course of the integration of lateral methylene protons of **6** with reference to methyl protons of an internal standard (*p*-nitrotoluene or *p*-bromoanisole) on treatment of **6** with a variety of acylating agents. A_{CH_2} and A_{OCH_3}, the integration of lateral methylene protons of **6** and that of methyl protons of an internal standard, respectively. (a) 2-Pyridinemethanol 1-oxide (**6**) and Ac_2O (**8**); (b) **6** and $ClCH_2COCl$ (**12**); (c) **6** and BzCl (**14**); (d) **6** and AcBr (**10**); (e) **6** and BzF (**13**). For details of the reaction conditions, see the Experimental Section.

characteristics of an "active" ester and is a good acyl transfer agent with a reasonably electrophilic phosphorus.

Treatment of 2-pyridylmethanol 1-oxide (**22**) with thionyl chloride (**19**) afforded 2-picolyl chloride 1-oxide[2a] (**23**) which was isolated in crystalline form as its hydrochloride salt in good yield. It was not possible, however, to establish whether or not this chlorination reaction proceeded via the cyclic intermediate involving the *N*-oxide group.

In summary, we wish to emphasize that the present work[8] suggests that it may be possible for us to control the competing pathways (rearrangement, nonrearrangement, or acylating pathways) that a combination of 3-methyl-2-picolyl 1-oxide protected substrate, e.g., **24**, with an acylating agent undergoes. For example, to remove the 3-methyl-2-picolyl 1-oxide group, benzoyl chloride (**14**) may be an appropriate reagent. On the other hand, to introduce any acyl group without affecting the protecting group already present, acyl fluoride may be a reagent of choice. Thus, treatment of 2′-*O*-(3-methyl-2-picolyl 1-oxide)adenosine (**24**) in DMF–pyridine with excess benzoyl fluoride afforded $O^{3'},O^{5'},N^6$-tribenzoyl-2′-*O*-(3-methyl-2-picolyl 1-oxide)adenosine (**25**) in 89% yield. Analogous reaction of **24** and **14** failed to give **25** but instead presumably an *N*-benzoyloxy-rearranged product (**26**), because on deblocking with methanolic ammonia the latter gave rise to adenosine in excellent yield rather than 2′-*O*-(3-methyl-2-picolyl 1-oxide)adenosine (see Scheme III).

Experimental Section

General. Melting points and boiling points are uncorrected. UV spectra were determined on a Hitachi spectrometer, type T4. NMR spectra were determined on a Hitachi R24 instrument. Unless otherwise specified, the chemical shifts are reported in parts per million downfield from tetramethylsilane. Thin-layer chromatography (TLC) was run on glass plates coated with silicic acid. Elemental analysis was performed by Misses Chizuko Ohara and Hiroko Matsumoto of our Faculty of Pharmaceutical Sciences to whom our thanks are due. Solvents were evaporated on a rotary evaporator under water-aspirator pressure using a water bath at ca. 40 °C. The progress of reactions was routinely followed by either TLC or NMR spectrometry.

Reaction products were characterized or determined by TLC. Samples were spotted on precoated silica gel plates and developed to a distance of ca. 15 cm with a solvent system, $CHCl_3$–EtOH, whose composition depends on the cases.

Benzoyl fluoride was obtained from Aldrich Chemical Co., Milwaukee, Wis. Benzoyl bromide, benzoyl iodide, and other acylating agents are of analytical grade and were obtained from Wako Pure Chemical Co.

2-Picolyl 1-oxide acetate [**6**, mp 142–143 °C (crystallized from MeOH–AcOEt)],[9] 4-methoxy-2-picoline 1-oxide [mp 77–78 °C (crystallized from acetone)],[7] and ethyl phosphorodichloridate [bp 63–64 °C (19 mm)][5] were prepared according to reported methods. 2,2,2-Trichloroethyl phosphorodichloridate (**18**) [bp 116–118 °C (14 mm)] was also prepared by a reported method.[6]

Interaction between 2-Picolyl 1-Oxide Acetate (6) and Acylating Agents. NMR spectra of a mixture of **6** (100 mg, 0.598 mmol) and 3 equiv of acetylating agent (AcX: X = OAc, **8**; Cl, **9**; Br, **10**; or I, **11**) in 0.3 mL of chloroform-d_6 were taken at 29 °C. In the case of aroyl halide (BzX: X = F, **13**; Cl, **14**; or Br, **15**), the spectra were similarly determined, except that *p*-bromoanisole (0.179 mmol, 0.3 equiv) was used as the internal standard. δ values of signals arising from H-6 are listed in Table I.

Reactions of Aromatic Amine *N*-Oxides (6 or 7) with Phosphorylating Agents. Interaction of **6** or **7** with **18**, as well as the reaction of *N*-(2,2,2-trichloroethylchlorophosphoryl)picolinium chloride (**20**) with methanol were similarly followed as above.

Determination of the Relative Areas under the Signal Arising from the α-Methylene of 6 Interacting with Acylating Agents. An aromatic amine *N*-oxide **6** (103 mg, 0.616 mmol, 1 equiv), *p*-bromoanisole (83.8 mg, 0.448 mmol, 0.72 equiv), and 3 equiv of acylating agent (**13**, **8**, **12**, or **14**) were dissolved in 0.3 mL of chloroform-d_6. NMR spectra of the mixture were determined at 36 °C. A two-proton signal arising from the α-methylene of **6** appeared at δ 5.5, whereas a three-proton singlet due to the methyl group of *p*-bromoanisole appeared at δ 4.0. The areas under the signal of the former relative to that of the latter were determined at intervals (from 10 min to 80 h after the mixing, see Figure 1).

With aroyl chloride such as *p*-nitrobenzoyl or *p*-anisoyl chloride, the same results were obtained as with **14**. Acetyl chloride (**9**) gave the same time profile as chloroacetyl chloride (**12**). With acetyl bromide (**10**) the relative area remained virtually constant throughout the determination for up to 48 h, showing that rearrangement of the acyloxy group to the side chain did not take place under the above conditions.

Reaction of 2-Pyridinemethanol 1-Oxide (22) with Thionyl Chloride (19). To a suspension of **22** (5.0 g) in chloroform (70 mL) was added, with stirring at −15 °C, a solution of **19** (6.3 g) in chloroform (30 mL). A complete solution soon resulted and then a white precipitate deposited. The mixture was added to dry *n*-hexane (200 mL). The solid was collected by filtration and dried in vacuo. TLC and NMR examination showed that 2-picolyl chloride 1-oxide (**23**) HCl salt was formed (rather than free 2-picolyl chloride). The yield was 4.6 g (63%).[2a]

Reaction of 2′-*O*-(3-Methyl-2-picolyl 1-oxide)-N^6-benzoyladenosine (24) with Benzoyl Fluoride (13). Synthesis of $O^{3'},O^{5'},N^6$-Tribenzoyl-2′-*O*-(3-methyl-2-picolyl 1-oxide)adenosine (25). A suspension of 2′-*O*-(3-methyl-2-picolyl 1-oxide)adenosine[3] (2 g, 5.15 mmol) in a mixture of DMF (20 mL) and pyridine (20 mL) was treated with **13** (10 g, 80.6 mmol) at 40 °C for 2 days. The resulting solution was concentrated to dryness. The residue was partitioned between 30 mL of a saturated Na_2CO_3 solution and 30 mL of chloroform. This process was repeated twice. The combined chloroform solution was dried over Na_2SO_4. The salt was filtered off. The filtrate was concentrated to dryness. The residue was chromatographed over silica gel (100 g). The band corresponding to **25** was collected: yield, 3.2 g (89%); NMR ($CDCl_3$) δ 2.08 (s, 3 H, 3″-CH_3),[10] 6.36 (d, J = 5.6 Hz, $H_{1'}$), 8.30 (s, H_8 or H_2), 8.60 (s, 1 H, H_8 or H_2). Anal. Calcd for $C_{38}H_{33}N_6O_8 \cdot {}^1/_3H_2O$: C, 64.58; H, 4.72; N, 11.89. Found: C, 64.75; H, 4.48; N, 11.71.

To a solution of **25** (479 mg, 0.68 mmol) in pyridine (20 mL) was added 10 mL of 2 N sodium hydroxide solution. The solution then became turbid and ethanol was added until a homogeneous solution was obtained. It required 35 mL of ethanol. The solution was kept at room temperature for 5 min and then neutralized with cooling with 15 mL of acetic acid and concentrated to dryness in vacuo. The residue was purified with TLC to afford 2′-*O*-(3-methyl-2-picolyl 1-oxide)-N^6-benzoyladenosine (ca. 330 mg). Without further purification, this sample was dissolved in 20 mL of pyridine and treated with trityl chloride (300 mg, 1.07 mmol) at 30 °C for 2 days. The solvent was removed. The residue was neutralized with saturated Na_2CO_3 solution

(20 mL). The product was extracted with chloroform (30 mL × 3). The dried (Na_2CO_3) solution was concentrated to dryness and the residue was purified by TLC [silica gel, 4 g; $CHCl_3$–EtOH (100:3)] to give 2′-*O*-(3-methyl-2-picolyl 1-oxide)-5′-*O*-trityl-N^6-benzoyladenosine: yield, 276 mg (55.3%). On the criterion of the NMR spectra [NMR ($CDCl_3$) δ 2.26 (s, 3 H, 3″-CH_3[10]), 6.05 (d, J = 4.0 Hz, 1 H, $H_{1'}$), 8.04 (s, 1 H, H_8 or H_2)] this sample was indistinguishable with an authentic sample, prepared by an alternate route.

Synthesis of 2′-*O*-(3-Methyl-2-picolyl 1-oxide)-5′-*O*-trityl-N^6-benzoyladenosine (Alternate Route). A DMF solution (200 mL) of N^6-benzoyladenosine[11] (12 g, 32.8 mmol) was alkylated as reported[3] with 3-methyl-2-pyridyldiazomethane 1-oxide,[2] prepared from 16.8 g (55.1 mmol) of the *p*-tosylhydrazone of 2-formyl-3-methylpyridine 1-oxide in the presence of $SnCl_2 \cdot 2H_2O$ (900 mg). After workup as reported, the residue was dissolved in chloroform (200 mL) and applied to a silica gel column. The eluate corresponding to 2′-*O*-(3-methyl-2-picolyl 1-oxide)-N^6-benzoyladenosine was tritylated with 3 g (10.1 mmol) of triphenylchloromethane in pyridine (300 mL). After removal of the solvent, the residue was partitioned between saturated Na_2CO_3 solution (30 mL) and chloroform (30 mL). This process was repeated twice. The combined chloroform layer was dried (Na_2CO_3) and concentrated to dryness. A homogeneous sample of the title compound was isolated by TLC: NMR ($CDCl_3$) δ 2.26 (s, 3 H, 3″-CH_3[10]), 6.05 (d, J = 4.0 Hz, 1 H, $H_{1'}$), 8.04 (s, 1 H, H_8 or H_2). Anal. Calcd for $C_{43}H_{38}N_6O_6 \cdot H_2O$: C, 66.67; H, 5.55; N, 12.96. Found: C, 66.58; H, 5.34; N, 12.54.

Reaction of 24 with Benzoyl Chloride. Analogous reaction of **24** (2 g, 5.15 mmol) and 3 equiv of benzoyl chloride in pyridine–DMF (1:1, v/v, 40 mL) afforded after workup presumably the *N*-benzoyloxy-rearranged product **26**, because on deblocking with methanolic ammonia the latter gave rise to adenosine rather than 2′-*O*-(3-methyl-2-picolyl 1-oxide)adenosine.

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Registry No.—**6**, 2683-69-4; **7**, 6890-60-4; **7**·HCl, 64314-84-7; **18**, 18868-46-7; **19**, 7719-09-7; **20**, 64314-85-8; **21**, 64314-86-9; **22**, 10242-36-1; **23**·HCl, 20979-34-4; **24**, 54657-22-6; **25**, 64314-87-0; ethyl phosphorodichloridate, 1498-51-7; trityl chloride, 76-83-5; 2′-*O*-(3-methyl-2-picolyl 1-oxide)-5′-*O*-trityl-N^6-benzoyladenosine, 64314-88-1; N^6-benzoyladenosine, 4546-55-8.

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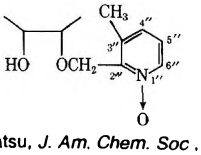

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Organofunctional Alkylstannanes via Michael-Type Additions[1]

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Organostannanes have been shown to be useful as intermediates in a variety of organic syntheses such as the preparation of vinyl-[2,3] and allylalkalis[4] and other species.[5,6] Their utility could be increased with the availability of organofunctional organotins which can be easily synthesized. To this end, in part, we have been studying the scope and mechanisms of reactions of organostannylalkalis with functional organic compounds and have reported some results recently.[7,8] We wish to report preliminary observations on Michael-type additions of trimethylstannylsodium to α,β-unsaturated esters, ketones, and nitriles. Gilman and Rosenberg[9] reported that triphenylstannyllithium fails to react with either benzophenone or benzalacetophenone in ether.[9] Recently, Hudec reported the addition of trimethylstannyllithium in the presence of copper(I) iodide in THF to α,β-unsaturated ketones.[10] Tri-*n*-butylstannylmagnesium chloride has been shown to undergo Michael-type addition to unhindered α-β-unsaturated ketones, but 1,2 addition occurred if the β-carbon was dialkylated.[11] Still has observed that either 1,2 addition or Michael addition can be brought about using only trialkylstannyllithium without copper(I) iodide.[12]

When 50 mmol of trimethylstannylsodium in THF was added to 50 mmol of ethyl cinnamate and 100 mmol of ethanol in THF, a rapid reaction ensued to yield 60–75% ethyl 3-phenyl-3-(trimethylstannyl)propionate: IR 1730 cm^{-1}; ^{13}C NMR (C β to CO 29.96 ppm; $^3J(^{119}Sn-^{13}C{=}O)$ = 30.8 Hz indicated that the trimethylstannyl group was β rather than α to the carbonyl.[13,14] If the trimethylstannylsodium and the ester were first combined and the alcohol added after 1 min, none of the adduct was obtained; polymeric material and hexamethylditin were the major products. These observations show that, under the conditions used, the addition of trimethylstannylsodium to the ester (eq 1) and the reaction of the resulting enolate with ethyl alcohol (eq 2) are extremely fast compared with the reaction between ethyl alcohol and stannylsodium. A further transformation of the stannane formed in eq 3 results in the formation of hexamethylditin (eq 4). Prolonged standing of the initial reaction mixture before workup resulted in the ethanolysis of adduct **2** to ethyl 3-phenylpropionate, due to the lability of the benzylic trimethylstannyl group.

$$PhCH{=}CHCOOEt + Me_3SnNa \rightarrow \underset{\mathbf{1}}{[(Me_3Sn)C(Ph)HCHCOOEt]^-Na^+} \quad (1)$$

$$\mathbf{1} + EtOH \rightarrow EtONa + \underset{\mathbf{2}}{(Me_3Sn)C(Ph)HCH_2COOEt} \quad (2)$$

$$Me_3SnNa + EtOH \rightarrow Me_3SnH + EtONa \quad (3)$$

$$2Me_3SnH \rightarrow (Me_3Sn)_2 + H_2 \quad (4)$$

The reaction of ethyl acrylate with trimethylstannylsodium under similar conditions provided 48–53% yields of ethyl 3-trimethylstannylpropionate. If the reaction was carried out at −78 °C with workup after warming to room temperature, the yield of adduct was 45%.

The reaction of trimethylstannylsodium with mesityl oxide

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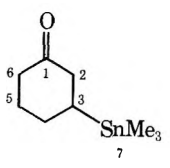
in THF with 2-propanol as the proton source at ambient temperature provided 49% 4-methyl-4-(trimethylstannyl)-2-pentanone.[11] The results obtained with mesityl oxide contrast strikingly with the formation of the 1,2 adduct when tri-*n*-butylstannylmagnesium chloride is used and suggest a means of controlling the direction of addition.

The reaction of 2-cyclohexenone with trimethylstannylsodium at −78 °C using ethanol as a proton source provided 3-(trimethylstannyl)cyclohexanone (**3**) contaminated with a small amount of 3-(trimethylstannyl)cyclohexanol (**4**). The yield of ketone was 50%. When a twofold excess of trimethylstannylsodium was used, the ratio of **4** to **3** increased to 3:1. Separation by high pressure liquid chromatography (HPLC) provided pure **4**, apparently a single geometrical isomer.[14] Treatment of 1 equiv of cyclohexanone and 2 equiv of ethanol with 1 equiv of trimethylstannylsodium in THF at ambient temperature led to 90% reduction of the ketone to cyclohexanol in 44 h. Hexamethylditin was the major tin-containing product.



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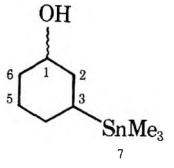

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Under conditions similar to those described above, methyl vinyl ketone, isophorone, and divinyl sulfone gave little or no adduct.

The observations recorded and cited above demonstrate that Michael-type acceptors can undergo 1,4 addition, 1,2 addition, and reduction of the 1,4 adduct upon treatment with trialkylstannylanionoids. They also reflect the importance of the various reaction parameters in directing the course of the reactions and yields of products.

Experimental Section

The IR spectra were recorded on Beckman IR-8 and IR-10 instruments. The C NMR spectra were recorded at 25.15 MHz on a Varian HA-100D spectrometer interfaced to a Digilab FTS-3 pulse and data system. The spectra were 8K or 14K Fourier-transformed, recorded at bandwidths of 2000 Hz. ^{1}H NMR spectra were recorded on a Varian A-60A instrument. All chemical shifts are recorded in ppm downfield from internal $(Me_4)Si$. Multiplicities are indicated by the first letters of the descriptives singlet, doublet, triplet, quartet, or multiplet, and relative areas are indicated in parentheses. Coupling constants are for ^{119}Sn if not specified.

Solutions of trimethylstannylsodium were prepared by stirring hexamethyldistannane for 12 h with 4 equiv of the metal cut into small pieces in THF, which had been dried by distillation from potassium benzophenone ketyl, an atmosphere of nitrogen or argon being maintained throughout the preparation and subsequent reaction of the alkali-metal derivative. Solutions for further use were removed by syringe through a serum cap, or the entire solution was filtered into the reaction flask through a small wad of cotton which retained unreacted metal.

General Reaction Procedure. The procedure described here for ethyl acrylate was generally used for synthetic scale preparations. To a solution of 6.1 g (61 mmol) of ethyl acrylate and 5.5 g (120 mmol) of ethanol in 200 mL of tetrahydrofuran (THF) cooled to −78 °C was added 66 mmol of trimethylstannylsodium in 33 mL of THF over about 30 min with stirring. The reaction mixture was allowed to warm to room temperature. The mixture was quenched with 60 mL of water and extracted with two 60-mL portions of pentane, which were combined and concentrated and the product distilled: bp 36 °C (0.26 Torr); yield 7.1 g (45%). The ^{1}H NMR spectrum was in accord with that reported for ethyl 3-(trimethylstannyl)propionate.[16]

Ethyl cinnamate was used in a similar procedure, but the product decomposed on distillation. However, GLPC using 15% Apiezon L on 60–80 mesh Chromosorb W provided pure product. Yields were estimated at 65–75%: IR 1730 and 520 cm^{-1} (C=O and Sn–C); ^{13}C NMR phenyl C 145.6 ($^2J(^{119}Sn-^{13}C)$ = 31.25 Hz), 125.7 ($^3J(^{119}Sn-^{13}C)$ = 22.25 Hz), 123.9, 128.3; $CH(SnMe_3)$ 30.0; CH_2 36.8 ($J(^{119}Sn-^{13}C)$ = 727 Hz); C=O 172.7 ($^3J(^{119}Sn-^{13}C)$ = 30.8 Hz); CH_2O 59.9; CH_3 14.2; CH_3Sn 9.68 ($^1J(^{119}Sn-^{13}C)$ = 322 Hz); ^{1}H NMR −0.04 (J = 52.0 Hz, 9); $(CH_3)_3Sn$ 1.15 (t, 3, 2.85 (s, 3), 4.07 (q, 2, 7.0 (m, 5),

Anal. Calcd for $C_{14}H_{22}O_2Sn$: C, 49.30; H, 6.51. Found: C, 49.41; H, 6.41.

Acrylonitrile yielded 3-(trimethylstannyl)acrylonitrile (81%) identical with a sample prepared by the addition of trimethylstannane to acrylonitrile.[16]

Mesityl oxide yielded 4-methyl-4-(trimethylstannyl)-2-pentanone (49%): bp 40 °C (0.05 Torr), ^{1}H NMR −0.06 (s, J = 52.0 Hz, 9, $(CH_3)_3Sn$), 1.00 (s, J = 62 Hz, $(CH_3)_2CSn$), 2.02 (s), 2.42 (J = 68 Hz, CH_2Sn).

Anal. Calcd for $C_9H_{20}SnO$: C, 41.11; H, 7.67. Found: C, 41.11; H, 7.83.

Cyclohexenone provided 40% of the expected adduct and 7% of its reduction product if workup was conducted after 2 h of reaction time. If the reaction was allowed to proceed for 44 h, equal amounts of alcohol and ketone were obtained. Use of 2 equiv of trimethylstannylsodium also gave this latter distribution after 2 h and a 3:1 ratio of alcohol to ketone after 44 h.

The products were separated by HPLC using 4 ft × 1/8 in Porasil columns with chloroform as an eluant.

3-(Trimethylstannyl)cyclohexanone: ^{13}C NMR (210.6 ($^3J(^{119}Sn-^{13}C)$ = 58 Hz, C_1), 45.7 ($^2J(^{119}Sn-^{13}C)$ = 15 Hz, C_2), 25.3 ($^1J(^{119}Sn-^{13}C)$ = 376 Hz, C_3), 29.5 (^2J (not defined), C_4), 30.8 ($^3J(^{119}Sn-^{13}C)$ = 69 Hz, C_5), 42.1 ($^1J(^{119}Sn-^{13}C)$ = 316 Hz, C_6), −11.6, (J = 320 Hz, $SnCH_3$).[15]

Anal. Calcd for $C_9H_{18}SnO$: C, 41.43; H, 6.95. Found: C, 40.98, H, 6.98.

3-(Trimethylstannyl)cyclohexanol: ^{13}C NMR (insufficiently pure sample for determination of J values) 71.6 (C_1), 40.2 (C_2), 22.6 (C_3), 29.9 (C_4), 27.5 (C_5), 36.2 (C_6), −11.8 (CH_3Sn).

Anal. Calcd for $C_9H_{20}SnO$: C, 41.11; H, 7.67. Found: C, 40.83; H, 7.53.

Registry No.—Ethyl acrylate, 140-88-5; trimethylstannylsodium, 16643-09-7; ethyl 3-(trimethylstannyl)propionate, 17490-11-8; ethyl cinnamate, 1103-36-6; ethyl β-(trimethylstannyl)cinnamate, 64010-80-6; mesityl oxide, 141-79-7; 4-methyl-4-(trimethylstannyl)-2-pentanone, 63831-56-1; cyclohexanone, 930-68-7; 3-(trimethylstannyl)cyclohexanone, 63831-50-5; 3-(trimethylstannyl)cyclohexanol, 64010-81-7; acrylonitrile, 107131; 3-(trimethylstannyl)acrylonitrile, 64010-82-8.

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Synthesis of Enol Chloroformates

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In a recent series of communications from this laboratory, vinyl chloroformate (VOC-Cl) was introduced as a useful reagent for the selective N-dealkylation of tertiary amines[1-3] and for the masking of amino[4] and hydroxyl[3] groups in synthesis. N-Dealkylation with VOC-Cl has already permitted the development of much improved preparative routes to the important narcotic antagonists, naloxone and naltrexone, as well as the potent mixed agonist–antagonist analgesics, *N*-cyclobutylmethylnoroxymorphone and nalbuphine.[1,2,5] An efficient process for the construction if the heptapeptide sequence H-Ser-Phe-Leu-Pro-Val-Asn-Leu-OH (all L) has been used to show the utility of VOC-Cl in amino protection.[4,5] To illustrate the advantages of VOC-Cl in hydroxyl protection, a facile synthesis of the classic narcotic antagonist, nalorphine, has been reported.[3] The scope and limitations of other uses of VOC-Cl as a reagent and precursor are presently under investigation.[5]

The demonstrated value of VOC-Cl and VOC groups in synthetic chemistry has provided substantial incentive for initiating a comparative study of the utility of other enol chloroformates in similar applications. Can more effective reagents be developed by appropriate substitution of the vinyl unit? Certainly an α-alkyl-VOC moiety (**1**) should be more reactive than VOC toward electrophilic cleavage due to the increased stability of the intermediate cation (**2**).

$$\underset{\mathbf{1}}{CH_2{=}C(R')OC(O)XR} \xrightarrow{E^+} \underset{\mathbf{2}}{[ECH_2{}^+C(R')OC(O)XR]}$$

XR is OR, SR, NR_2

Inductive and steric factors should reduce the sensitivity of **1** (vs. VOC-XR) toward base hydrolysis, another potentially attractive feature. Similar and other variations in the vinyl substitution pattern could induce greater crystallinity and, thus, more facile isolation of the modified VOC compounds.

The literature records only two enol chloroformate syntheses. VOC-Cl itself is made[6] by the gas-phase pyrolysis of the bis(chloroformate) **3**.

$$HOCH_2CH_2OH + COCl_2 \rightarrow \underset{\mathbf{3}}{ClC(O)OCH_2CH_2OC(O)Cl} \xrightarrow{480\ ^\circ C} \underset{\text{VOC-Cl}}{H_2C{=}CHOC(O)Cl}$$

(35% overall)

In the other publication, the combination of acetone with phosgene is claimed to yield isopropenyl chloroformate.[7] However, this work could not be reproduced and has since been disproved.[8] Thus, since substituted enol cholorformates are previously unknown and obviously not accessible by the pyrolytic route to VOC-Cl, the development of a general synthesis would be required before their merits could be appraised.

Acylation of enolates with phosgene would seem a simple and direct route to enol chloroformates. However, complications caused by the ambident nature of enolates would be anticipated as would problems caused by reaction of the enolate-forming base and its conjugate acid with phosgene and the product chloroformate. Still several potential schemes of this kind are tested. Enolate-forming bases used included NaH, $NaNH_2$ (with NH_3 removal prior to $COCl_2$ addition), lithium 2,2,6,6-tetramethylpiperidide,[9] and hexamethylphosphoric triamide radical anion[10] (as Li^+ salt). Processes involving other potential enolate-forming reactions such as the *n*-BuLi initiated fragmentation of THF[11] and the oxygenation of alkenyllithiums[12] were also examined. All of these schemes failed entirely; no enol chloroformate was found.

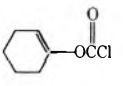
Success was finally achieved by using bis(keto)mercurials as the enolate equivalents. Motivation for testing this approach was provided by reports[13,14] that treatment of α-mercuri ketones with simple acyl halides yields only the *O*-acyl products.

The enol chloroformates which have been prepared are listed in Table I along with IR and NMR data of structural importance. Most thoroughly studied was the synthesis of isopropenyl chloroformate (**4**), which was best made by adding diacetonylmercury[15] to excess phosgene in CH_2Cl_2 (86% distilled yield).

$$(MeCOCH_2)_2Hg + COCl_2 \rightarrow \underset{\mathbf{4}}{H_2C{=}C(Me)OC(O)Cl} + \underset{\mathbf{5}}{MeCOCH_2HgCl}$$

Though there is some evidence that **5** can also serve as a source of **4** (see Experimental Section), chloromercuri ketones are generally so insoluble in reaction-compatible solvents that they are not usable precursors.[16] In the syntheses of the enol chloroformates of cyclohexanone, acetophenone, and pinacolone (38–64% yield), the product distillation fractions were contaminated by starting ketone (15–30%). Since this impurity is only an inert diluent in the uses contemplated for these chloroformates, its removal by high efficiency fractionation or chromatography was not attempted. However, as a further structure proof, all chloroformates were analyzed as the crystalline anilides or cyclohexylamides. Though the expected chloroformate is obtained from cyclopropyl methyl ketone,

Table I. Enol Chloroformates: Selected Spectral Data

Registry no.	Chloroformate	IR stretch (CCl_4), μm		NMR (CCl_4), δ[b] vinyl H
		C=O	C=C[a]	
57933-83-2	$H_2C{=}C(CH_3)OC(O)Cl$	5.60	6.03	4.7–5.0 (m)
64294-76-4	$H_2C{=}C(Ph)OC(O)Cl$	5.58	6.09	5.12 (d, 3.5) 5.40 (d, 3.5)
64294-77-5	$H_2C{=}C(t\text{-}Bu)OC(O)Cl$	5.59	6.03	4.91 (s)
64294-78-6	$H_2C{=}C(c\text{-}C_3H_5)OC(O)Cl$	5.61	6.01	4.5–5.0 (m)
64294-79-7		5.59	6.08	5.1–6.0 (m)
5130-24-5	$H_2C{=}CHOC(O)Cl$	5.60	6.07	4.79 (q, 2.5, 6) 5.09 (q, 2.5, 14) 7.11 (q, 6, 14)

[a] Carbonyl stretch band much stronger than C=C stretch. [b] Coupling constants in hertz, multiplet = m, quartet = q, etc.

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the process was not practical because of difficulties in isolating pure the volatile $(C_3H_5COCH_2)_2Hg$. Volatility problems also hampered the isolation of VOC-Cl from treatment of $(HCOCH_2)_2Hg$ with phosgene.

From preliminary tests involving **4**, it is already apparent that enol chloroformates from ketones could have substantial impact as synthetic reagents.[5,17] However, for some of the processes envisioned to be practical, the synthesis outlined here must first be superceded by a more economical route.

Experimental Section

Melting points were taken in a Thomas-Hoover apparatus equipped with a calibrated thermometer. Infrared spectra were obtained on a Perkin-Elmer Model 257 spectrophotometer, NMR spectra on a Varian A60-A spectrometer, and mass spectra on an AEI MS-902 spectrometer.

Isopropenyl Chloroformate. (Hood!) A 250-mL three-neck flask equipped with a magnetic stirrer was fitted with a pressure-equalizing dropping funnel topped by a rubber septum, a dry-ice-jacketed volume-calibrated pressure-equalizing dropping funnel topped by a dry ice–acetone condenser connected to phosgene and N_2 tanks, and a dry ice–acetone condenser connected to a series of four traps (empty, concentrated H_2SO_4, empty, concentrated NH_4OH) and vented to hood exhaust. The system was flushed with N_2 to remove trace moisture. The reaction vessel was charged with anhydrous CH_2Cl_2 (25 mL) and cooled in an ice bath. Phosgene (Matheson; 10 mL, 0.14 mol) was condensed in the jacketed funnel and then added to the CH_2Cl_2. Then diacetonylmercury (13.1 g, 0.042 mol; from ethyl isopropenyl ether in 99% yield, mp 67–69 °C, lit.[15] 68 °C) in 15 mL of CH_2Cl_2 was added (15 min) to the stirred mixture, which was kept at 0 °C for another 2 h and then at 25 °C for 2 h while a white solid precipitated. Next the dropping funnels were replaced by stoppers and a take-off valve, connected to a hood aspirator via a dry ice–acetone trap, was inserted in the third neck of the reaction flask. Volatiles were evaporated at reduced pressure and collected in the trap. This condensate was warmed to 25 °C and fractionally distilled through a 10-cm Vigreux column (hood). The first fraction of bp ≤47 °C was collected in another trap and this CH_2Cl_2 solution of phosgene and other volatiles was disposed of. Simple distillation of the remaining liquid afforded 4.37 g (86% or 43% if two available isopropenyl units) of isopropenyl chloroformate, bp 74–75 °C.

Anal. Calcd for $C_4H_5ClO_2$: C, 39.9; H, 4.2; Cl, 29.4. Found: C, 39.9; H, 3.9; Cl, 29.6.

When this reaction was repeated in THF (distilled from $LiAlH_4$), the yield was 104% (or 52%, NMR analysis). Because the product and solvent were not readily separable, the THF solution was used in subsequent synthetic chemistry. The yield did not change if the reaction was left for 24 h prior to workup.

With THF as the reaction solvent, 1-*tert*-butylvinyl chloroformate was similarly synthesized from mercury bispinacolone (see below) and phosgene. Fractional distillation of the material contained in the trap afforded a fraction, bp 73–75 °C (65 mm), which analyzed (NMR) as a mixture of the desired chloroformate (38% yield) and pinacolone in a ratio of 6:1.

Vinyl chloroformate was similarly prepared by reaction of mercury bisacetaldehyde[15] in diglyme (distilled over sodium) with phosgene in anhydrous ether. The product codistilled with the ether, but was identified by NMR comparison with an authentic sample and by derivative preparation (see below).

1-Cyclohexenyl Chloroformate. Using the apparatus design already described, mercury biscyclohexanone[13] (28.0 g, 0.071 mol) in 200 mL of $CHCl_3$ (distilled from P_2O_5) was added (3 h) to the stirred, cooled solution of phosgene (11 mL, 0.15 mol) in $CHCl_3$ (50 mL). Stirring was continued overnight and much of the excess phosgene then was blown out of the system with N_2. Next the desired solution was separated from solid by-products using a filter stick (sealed system) connected to a filter flask which in turn was connected to a hood aspirator via a trap and $CaCl_2$ drying tube. The filtrate was distilled first at atmospheric pressure (H_2SO_4–NH_4OH traps) and later at reduced pressure. The fraction bp 79–85 °C (22 mm) contained the product chloroformate and cyclohexanone in a ratio of 7:3 (NMR analysis, chloroformate yield 64%).

The similar reaction of mercury bisacetophenone (mp 170–171.5 °C, lit.[13] 171–172.5 °C) with phosgene afforded a distillation fraction of bp 64–66 °C (0.9 mm) which contained 1-phenylvinyl chloroformate (45% yield) and acetophenone in a ratio of 6:1.

The analogous reaction of impure $(C_3H_5COCH_2)_2Hg$ (see below) afforded a small amount of distillation fraction containing 1-cyclopropylvinyl chloroformate and $C_3H_5COCH_3$ in a ratio of 3:2, bp 73–77 °C (60 mm).

Enol Carbamate Derivatives. Isopropenyl chloroformate (3.5 g, 0.029 mol) in anhydrous 1,2-dichloroethane was added to a stirred solution (0 °C) of cyclohexylamine (5.75 g, 0.058 mol) in the same solvent. The next day precipitated amine hydrochloride was filtered off and the filtrate was concentrated. Isopropenyl *N*-cyclohexylcarbamate was isolated from the residue by vacuum sublimation [57 °C (0.1 mm)]: yield 5.21 g (98%); mp 95.5–96.5 °C; NMR ($CDCl_3$) δ 0.9–2.1 (13 H, br m with s at 1.95), 3.2–3.8 (1 H, br m), 4.52–4.64 (1 H, m), 4.68 (1 H, s) 4.8–5.2 (1 H, m); IR ($CHCl_3$) 2.93, 5.78, 5.99 μm; mass spectrum *m/e* (rel intensity) 183 (2), 126 (7), 125 (10), 83 (57), 58 (100).

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.5; H, 9.4; N, 7.6. Found: C, 65.8; H, 9.3; N, 7.8.

The following enol carbamates were similarly prepared from the appropriate chloroformates and amines.

Vinyl *N*-cyclohexylcarbamate: sublimed at 50 °C (1 mm), mp 83–84 °C; NMR ($CDCl_3$) δ 0.8–2.3 (10 H, m), 3.1–3.9 (1 H, m), 4.34 (1 H, q, J = 1, 6 Hz), 4.63 (1 H, q, J = 1, 14 Hz), 4.9–5.4 (1 H, m), 7.14 (1 H, q, J = 6, 14 Hz); IR ($CHCl_3$) 2.93, 5.78, 6.06 μm; mass spectrum *m/e* (rel intensity) 169 (0.5), 126 (35), 83 (94), 55 (100).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.9; H, 8.9; N, 8.3. Found: C, 64.0; H, 8.9; N, 8.2.

1-Cyclohexenyl *N*-phenylcarbamate: triturated with pentane, mp 119.5–120 °C; NMR ($CDCl_3$) δ 1.3–2.4 (8 H, m), 5.3–5.6 (1 H, m), 6.8–7.5 (6 H, m); IR ($CHCl_3$) 2.90, 5.79, 6.03 μm; mass spectrum *m/e* (real intensity) 217 (1), 119 (100), 98 (41), 91 (39).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.9; H, 7.0; N, 6.5. Found: C, 71.9; H, 7.2; N, 6.3.

1 Phenylvinyl *N*-cyclohexylcarbamate: triturated with pentane, mp 104–105 °C; NMR ($CDCl_3$) δ 0.8–2.3 (10 H, m), 3.1–3.9 (1 H, m), 5.04 (1 H, d, J = 2 Hz), 5.40 (1 H, d, J = 2 Hz), 4.9–5.4 (1 H, m), 7.0–7.7 (5 H, m); IR ($CHCl_3$) 2.90, 5.79, 6.05 μm; mass spectrum *m/e* (rel intensity) 245 (1), 120 (85), 105 (100), 77 (69).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.4; H, 7.8; N, 5.7. Found: C, 73.1; H, 8.1; N, 5.6.

1-Cyclopropylvinyl *N*-phenylcarbamate: crystallized from pentane, mp 104–105 °C; NMR ($CDCl_3$) δ 0.6–0.9 (4 H, m), 1.3–1.9 (1 H, m), 4.76 (2 H, s), 6.8–7.6 (6 H, m); IR ($CHCl_3$) 2.90, 5.76, 6.03 μm; mass spectrum *m/e* (rel intensity) 203 (1), 119 (100), 91 (42), 84 (32), 69 (58).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.9; H, 6.5; N, 6.9. Found: C, 70.9; H, 6.3; N, 6.7.

1-*tert*-Butylvinyl *N*-cyclohexylcarbamate: sublimed at 85 °C (0.1 mm), mp 79–80 °C; NMR ($CDCl_3$) δ 1.05 (9 H, s), 1.1–2.2 (10 H, m), 3.2–3.8 (1 H, m), 4.68 (1 H, d, J = 2 Hz), 4.79 (1 H, d, J = 2 Hz), 4.7–5.3 (1 H, m); IR ($CHCl_3$) 2.93, 5.78, 6.04 μm; mass spectrum *m/e* (rel intensity) 225 (10), 126 (15), 125 (31), 124 (10), 100 (100).

Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.3; H, 10.3; N, 6.2. Found: C, 69.1; H, 10.5; N, 6.1.

Mercury Bispinacolone: This was made by the general method of House[13] from the trimethylsilyl enol ether of pinacolone (bp 140–143 °C) and yellow HgO with $Hg(OAc)_2$ as catalyst, and crystallized from benzene–hexane (94% yield): mp 102–103 °C; NMR ($CDCl_3$) δ 1.33 (9 H, s), 2.62 (2 H, s); IR ($CHCl_3$) 6.09 μm.

The analogous reaction of 1-cyclopropyl-1-trimethylsilyoxyethylene [bp 83–84 °C (95 mm)] afforded a product too volatile to separate from the reaction solvent by vacuum evaporation. However, material collected in the evaporation trap could be partly purified by dissolution in EtOH, filtration to remove a gray flocculence, and slow evaporation at 25 °C. Several crops of precipitated powder were collected and the $(C_3H_5COCH_2)_2Hg$ was crystallized from CH_2Cl_2–pentane: mp 106–108 °C; NMR ($CDCl_3$) δ 0.6–1.2 (m), 1.5–2.3 (m), 2.60 (s), 3.02 (s), 4.0–4.2 (m) (ratio: 6.54:1.84:2:0.46:0.15; contains cyclopropyl methyl ketone impurity); IR ($CHCl_3$) 6.08 μm.

An attempt to obtain mercury bisisobutyraldehyde from $Me_2C{=}CHOSiMe_3$ (bp 97–99 °C) failed. The product was too volatile to separate from the reaction solvent.

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Registry No.—Phosgene, 75-44-5; diacetonylmercury, 6704-33-2; mercury bispinacolone, 16004-47-0; mercury bisacetaldehyde, 4387-13-7; mercury biscyclohexanone, 37160-46-6; mercury bisacetophenone, 37160-45-5; $(C_3H_5COCH_2)_2Hg$, 64294-80-0; cyclohexylamine, 108-91-8; isopropenyl *N*-cyclohexylcarbamate 64294-81-1; vinyl *N*-cyclohexylcarbamate, 64294-82-2; 1-cyclohexenyl *N*-phenylcarbamate, 64294-83-3; benzamine, 62-53-3; 1-phenylvinyl *N*-cy-

clohexylcarbamate, 64294-84-4; 1-cyclopropylvinyl *N*-phenylcarbamate, 64294-85-5; 1-*tert*-butylvinyl *N*-cyclohexenylcarbamate, 64294-86-6; pinacolone trimethylsilyl enol ether, 17510-46-2; 1-cyclopropyl-1-trimethylsilyloxyethylene, 42161-96-6.

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(17) However, the methodology to be developed should complement and not parallel chemistry with VOC-Cl because the derivatives (**1**, R′ = Me) are so different in reactivity vs. VOC amides and VOC esters. For example, titration of VOC-NR_2 with Br_2 yields $BrCH_2CHBrOCONR_2$, while the same reaction of $H_2C{=}CMeOCONR_2$ gives $BrCONR_2$.[5]

Synthesis of 4-Amino-3-hydroxy-6-methylheptanoic Acid by a Modified Reformatsky Reaction

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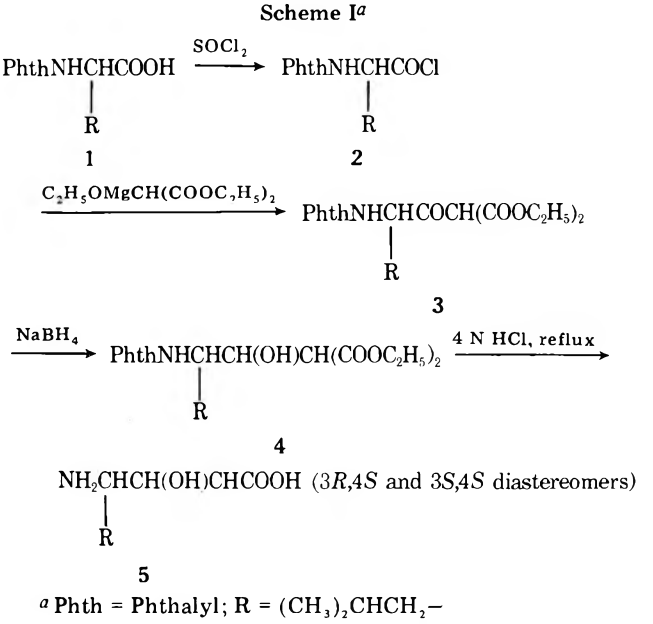
Pepstatin is a naturally occurring low-molecular-weight peptide that is a potent inhibitor of acid proteases.[1] The natural pentapeptide contains two residues of (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid (AHMHA), although a tripeptide containing only one residue of AHMHA at the C terminus retains its potency as an inhibitor of pepsin.[1] Since pepstatin is an effective inhibitor of renin, pepsin, and tissue cathepsin D's, there is a need for synthesis of analogues and derivatives that might be selective among these enzymes. The only derivatives reported have been prepared from AHMHA isolated from acid hydrolysates of pepstatin. AHMHA is unstable under conditions of acid hydrolysis, so it is not a good method for obtaining this amino acid. Synthesis of the 3*S*,4*S* and 3*R*,4*S* diastereomers (**5**) has been reported.[2] No yields or experimental details were given, but the yields were undoubtedly low (vide infra). All four of the possible stereoisomers have been synthesized by a method unsuitable for preparative work.[3] We report below the preparation of AHMHA in greatly improved yield via a modified Reformatsky reaction.

Results and Discussion

As a starting point, we repeated the reported[2] method for the preparation of AHMHA (Scheme I). We obtained an approximately equimolar mixture of diastereomers in 3.2% overall yield estimated by amino acid analysis of the crude

Scheme I[a]



[a] Phth = Phthalyl; R = $(CH_3)_2CHCH_2$–

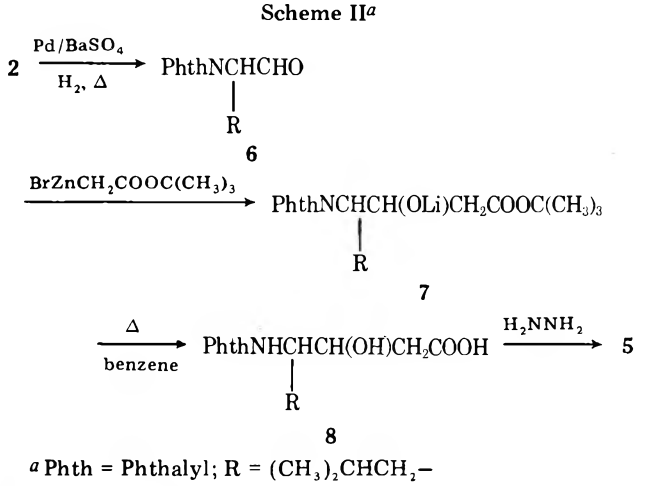
product. The intermediates **3** and **4** were obtained in good yield; their structures were confirmed by NMR analysis and by the fact that **3** is acidic and can be purified by extraction. Nearly all of **5** is lost during the hydrolysis step. The instability of **5** to acid-hydrolysis conditions was confirmed by heating a purified sample in 6 N HCl at 110 °C for 24 h which resulted in a loss of 58%. The yield of AHMHA from hydrolysis of pepstatin was about 50%.

The problem with Scheme I could have been solved by changing to *tert*-butyl ester blocking groups which could be removed by anhydrous acid, allowing removal of the phthalyl blocking group by hydrazinolysis. However, the Reformatsky reaction sequence in Scheme II was appealing in view of the reported success in obtaining β-hydroxy acids using the zinc enolate of *tert*-butyl acetate.[4]

The acid chloride **2** was obtained in quantitative yield as an oil that was used without further purification. Reduction gave the aldehyde **6** in 85% yield after removal of unreacted **2** by stirring the mixture with aqueous sodium bicarbonate and was used without further purification. Performing the Reformatsky reaction in the usual manner gave **8** in only 20% yield, due primarily to reaction of the enolate at the phthalyl carbonyl groups. The yield of **8** was improved to 40% with no side reaction at the blocking group by preparing the enolate separately and adding it to a cooled solution of the aldehyde. Hydrazinolysis proceeded in quantitative yield, giving a 55:45 mixture of **5** (3*S*,4*S*:3*R*,4*S*).

Although separation of the diastereomers **5** was reported

Scheme II[a]



[a] Phth = Phthalyl; R = $(CH_3)_2CHCH_2$–

0022-3263/78/1943-0754$01.00/0

using ion-exchange chromatography,[2] we have not been successful in separating them by this technique. We are investigating separations of the mixtures with 7 (alcohol) and 8 or at the stage of peptides prepared from the mixture **5**.

It is likely that the yield of **8** can be optimized, but even without a higher yield this synthesis is applicable to the preparation of AHMHA in quantity. In addition, the optical rotation of the mixture **5** indicates no more than 2% racemization, an important consideration in the preparation of enzyme inhibitors.

Experimental Section

Amino acid analyses were performed on a Beckman 120-C amino acid analyzer using standard short and long columns and pH 4.25, 0.2 M sodium citrate buffer.[5] The mixture **5** eluted as a single symmetrical peak on the short (33 min) or long (308 min) columns as did natural AHMHA in hydrolysates from pepstatin. The ninhydrin constant is 36% of that of L-leucine.

4-Amino-3-hydroxy-6-methylheptanoic Acid (5). Under anhydrous conditions, 48.7 g (0.25 mol) of *tert*-butyl α-bromoacetate[4] and 19.6 g (0.3 mol) of activated zinc[6] were refluxed in 100 mL of dry tetrahydrofuran for 1.5 h. The solution was cooled, decanted into a dropping funnel, and added dropwise during 45 min, with stirring, to a solution of 41.7 g (0.17 mol) of *N*-phthalyl-L-leucinal[7] maintained at 0–5 °C. After an additional 30 min of stirring, the solvent was removed by distillation and the residue was refluxed in 200 mL of dry benzene for 5 h. The solvent was removed in vacuo, 200 mL of 2 N hydrochloric acid was added, and the solution was extracted with three 150-mL portions of ethyl acetate. The combined organic extracts were extracted with two 100-mL portions of 5% sodium bicarbonate. The basic extracts were acidified to pH 1 with hydrochloric acid and the product was extracted with two 100-mL portions of ether. The extracts were dried over sodium sulfate and evaporated to give 20.7 g (40% yield) of crude **8**. Deblocking was effected by refluxing the product (0.068 mol) with 2.3 g (0.068 mol) of 95% hydrazine hydrate for 1.5 h in 100 mL of ethanol. The solvent was removed in vacuo, the residue was stirred with 200 mL of 2 N hydrochloric acid, the phthalylhydrazide was filtered off, and the filtrate was evaporated to dryness. The residue was taken up into 200 mL of water and amino acid analysis of the solution indicated a quantitative yield in the deblocking step. The solution was applied to a 2.5 × 79 cm column of Dowex 50-X8 ion-exchange resin equilibrated with 0.1 M pyridine adjusted to pH 5 with acetic acid. Elution with this buffer yielded 11.5 g (38%) of the mixture **5**. The NMR spectrum agrees with that reported[2,8] for the 3*R*,4*S* and 3*S*,4*S* diastereomers and revealed a 45:55 mixture of the two: $[\alpha]^{21}_{365}$ −47.9° (Cl, H_2O) [reported[3] for 3*R*,4*S* and 3*S*,4*S* $[\alpha]^{21}_{365}$ −49° (Cl, H_2O)].

Anal. Calcd for $C_8H_{17}NO_3$: C, 54.83; H, 9.77; N, 7.99. Found: C, 54.77; H, 9.68; N, 7.89.

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Registry No.—(3*R*,4*S*)-**5**, 49642-13-9; (3*S*,4*S*)-**5**, 49642-07-1; **6**, 64490-39-7; (3*R*,4*S*)-**8**, 64490-38-6; (3*S*,4*S*)-**8**, 64490-37-5; *tert*-butyl α-bromoacetate, 5292-43-3.

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Metal–Ammonia Reduction of *cis*-8,10-Dimethyl-1(9)-octal-2-one[1]

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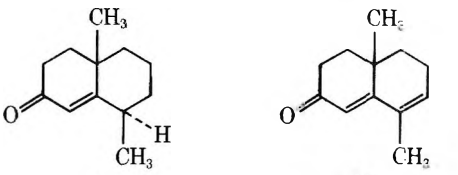
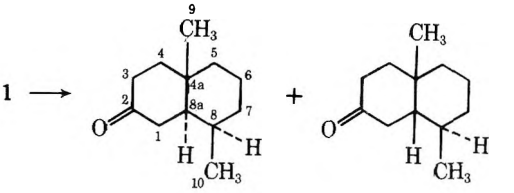
Recently, we reported the synthesis of *cis*-8,10-dimethyl-1(9)-octal-2-one (**1**) by transfer hydrogenation of the bicyclic dienone **2**.[2] The continued interest in the influence of substituents upon the metal–ammonia reductions of 1(9)-octal-2-ones[3] has prompted us to investigate the stereochemistry of the reduction of **1** with lithium and other metals in liquid ammonia.



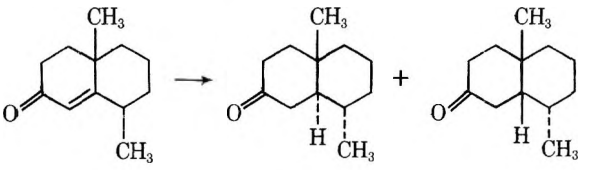
1 **2**

Reduction of **1** with lithium in liquid ammonia containing 1 equiv of *tert*-butyl alcohol under the usual conditions gave a 6.4:1 mixture of the known *trans*-decalone **3**[4] and an isomer which has been assigned the *cis*-decalone structure **4** in 85–91% yield. It was also found that catalytic hydrogenation of **1** using 10% paladium on carbon in 95% ethanol gave a 65:35 mixture of **3** and **4** in essentially quantitative yield.[5]



	3	**4**
Li/NH_3, ether, 1 equiv *t*-BuOH	87%	13%
H_2, Pd(C), 95% EtOH	65%	35%

In order to ascertain that isomerization of **1** into the thermodynamically more stable *trans*-octalone **5**[6] was not occurring prior to chemical (or catalytic) reduction, the latter enone was converted to the corresponding decalone derivatives. As expected lithium–ammonia reduction of **5** gave exclusively the *trans*-decalone **6**[4b] and a 5:95 mixture of **6** and the cis isomer **7**[7] was produced by catalytic hydrogenation of **5** in acidic 95% ethanol using 5% palladium on carbon as the catalyst. The isomeric decalones **3**, **4**, **6**, and **7** were readily separated from each other by GLC using a Carbowax column. Thus no significant isomerization of **1** into **5** occurred under either set of reduction conditions.[5]



	5	**6**	**7**
Li/NH_3, ether 1 equiv *t*-BuOH	100%	—	
H_2, Pd(c), 95% EtOH, HCl	5%	95%	

The structural assignment of **4** is based upon the fact that

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Table I. Natural Abundance ^{13}C Chemical Shifts of *trans*- and *cis*-2-Decalones[a]

Registry no.	Decalone	Chemical shifts of C atoms[b]											
		1	2	3	4	4a	5	6	7	8	8a	9	10
941-23-1	3	(43.8)	211.6	(40.6)	(43.7)	33.4	(38.2)	17.2	(32.8)	32.8	46.4	18.6	14.1
64281-62-5	4	(39.6)	211.6	(37.6)	(39.6)	33.0	(35.9)	21.4	(31.4)	31.4	51.6	27.7	20.1
64281-60-3	6	(41.2)	212.0	(40.9)	(40.9)	33.2	(37.8)	21.4	(35.6)	32.3	50.6	19.6	15.9
52305-17-6	7	(41.1)	212.4	(36.9)	(37.5)	33.2	(28.7)	21.6	(27.7)	29.9	47.6	26.2	19.3

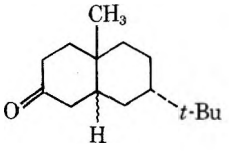
[a] For the numbering system of the decalones, see structure 3. [b] Chemical shifts are in ppm relative to internal Me_4Si.

Table II. Reduction of Enone 1 with Metals in Liquid Ammonia Containing 1 Equiv of *tert*-Butyl Alcohol at −33 °C

Metal	% 3[a]	% 4[a]	3/4 ratio	% yield[b]
Li	86.5 ± 2.3	13.6 ± 2.3	6.4	85–91
Na	80.4 ± 0.4	19.6 ± 0.4	4.1	88–98
K	78.6 ± 0.8	21.4 ± 0.8	3.7	78–90
Ca	93.2 ± 0.6	6.8 ± 0.6	13.7	96–97
Ba	88.1 ± 2.3	11.9 ± 2.3	7.4	93–95

[a] Percentages are an average of two or more runs. [b] Range of isolated yields of decalone mixtures after GLC analysis.

it is formed along with 3 in both the chemical and catalytic reduction of 1 and upon a comparison of its ^{13}C NMR spectrum with those of the other three isomeric decalones. The natural abundance ^{13}C chemical shifts of decalones 3, 4, 6, and 7 are recorded in Table I. These chemical shift assignments are consistent with off-resonance decoupling measurements. However, the assignments in parentheses are tentative. A significant feature of these ^{13}C spectra is that the angular carbon atoms (C-9) in the two cis-fused isomers 4 and 7 occur at 6–10 ppm lower field than the corresponding absorptions in the trans isomers 3 and 6. The latter compounds have a greater number of γ interactions[8] which contribute to the shielding of the angular carbon atoms. The angular carbon atoms in the cis- and trans-fused decalones 8a and 8b have

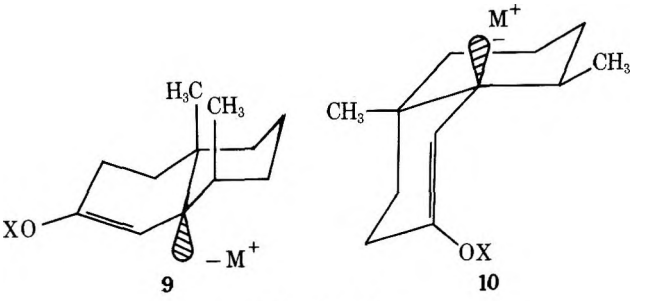


8a, cis-ring fusion
b, trans-ring fusion

been reported to have chemical shifts of 27.0 and 17.2 ppm.[3b] This provides another example of a pair of 2-decalones in which the angular carbon of the cis isomer absorbs at lower field.

Systematic studies on the influence of the nature of the metal on the course of metal–ammonia reductions of α,β-unsaturated ketones are rare and have not been reported for 1(9)-octalones.[3c] Therefore, since enone 1 gave a mixture of isomers using lithium in liquid ammonia, we have determined the ratio of the reduction products obtained using other alkali and alkaline-earth metals under the same conditions. These results and the lithium–ammonia reduction results are recorded in Table II.

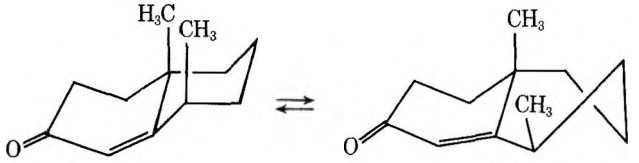
Decalones 3 and 4 may be considered to arise via protonation of β-carbanionic intermediates 9 or 10, respectively, in which the oxygen atom is either protonated[9] or associated with a metal cation.[3c] Intermediate 9 is favored over 10 on stereoelectronic grounds and as predicted by the Stork–Darling axial protonation rule[10] the *trans*-decalone 3 is the favored reduction product with all metals investigated. On the basis of estimates of nonbonded interactions alone, species



X = H or M

10 which leads to the cis product should be 2–3 kcal/mol more stable than 9. Therefore, the ratios of 3/4 observed under various conditions support the previous suggestion that the orbital overlap (stereoelectronic) factor provides a stabilization energy of 3–5 kcal/mol.[3c]

The amount of cis product 4 obtained from 1 was small with lithium and the other metals studied, but it was significantly greater than has been observed for other ring B substituted octalones except those having exceptionally bulky groups at the 6β or 7α positions.[3b,c] It seems to be generally true that when the B ring of the 1(9)-octal-2-one system is forced into an unusual conformation by substituent effects, cis reduction products are observed.[3b] In the case of 1 conformation **1B**, in which the B ring is in a twist-boat and the 1,3-diaxial methyl–methyl interaction is relieved, may be in equilibrium with conformation **1A**, in which the B ring is in a normal chair. On addition of two electrons, conformation **1B** may be converted into the cis β-carbanionic species 10 with a minimum



1A 1B

amount of motion of atoms and solvent-shell reorganization.

The magnitude of the change in the stereochemistry of the reduction with the change in metal cation is small but outside the range of experimental error. The results show that within the alkali metal and alkaline-earth metal series the smaller cations, i.e., Li^+ and Ca^{2+}, respectively, yield less of the cis-fused product 4 than the larger cations. At first sight this is surprising, since the β-carbanion–metal complex seems to be in a slightly more crowded environment in configuration 10 than 9. Also, since the charge is more localized at the β position in 10 a closer approach of the metal to the carbanionic center might be expected to be necessary in this case. However, the literature contains a number of suggestions that the smaller metal cations are more extensively solvated by ammonia than larger cations.[3c] If the metal–ammonia complex is actually larger for the smaller than for the larger metal cations, this could account for the greater amounts of trans product obtained in the reductions using lithium and calcium. Also, if the species undergoing β protonation is a dianion rather than a

hydroxyallyl anion, it might be expected that **9** would be stabilized relative to **10** when metal cations such as Li^+ and Ca^{2+} are involved. These cations should form more covalent bonds with the oxygen atom than the more electropositive metal cations, thus allowing more favorable overlap of the β-carbanion with the π-electron system of the metal enolate.

Experimental Section[11]

General Procedure for the Metal–Ammonia Reduction of Octalone 1.[3c] Anhydrous liquid ammonia (300 mL, distilled from sodium) was distilled under nitrogen into a flame-dried three-necked flask fitted with a mechanical stirrer, an addition funnel, and a Claisen adaptor holding a dry-ice condenser and a gas inlet tube. Freshly cut metal, 0.022 g-atom of alkali metal or 0.011 g-atom of the alkaline-earth metal, was then added and the mixture was stirred until the metal had completely dissolved (15–45 min). A mixture of 1.78 g (0.010 mol) of octalone **1** and 0.74 g (0.010 mol) of *tert*-butyl alcohol in 70 mL of anhydrous ether (distilled from $LiAlH_4$) was added dropwise with stirring over 30 min at −33 °C. Stirring was continued for 3 h and then 3.14 g of solid ammonium chloride was added as rapidly as possible. The ammonia was allowed to evaporate and the residue was dissolved in 200 mL of a 1:1 ether–water mixture. The layers were separated and the aqueous layer was saturated with sodium chloride and extracted with three 50-mL portions of ether. The ethereal extracts were combined and dried over magnesium sulfate. After removal of the solvent in vacuo the residue was analyzed by GLC and distilled to give a mixture of decalones **3** and **4** in the yields given in Table I.

Pure samples of ketones **3** and **4** were collected by preparative GLC. Ketone **3** showed identical IR, ^1H NMR, and mass spectral properties and GLC behavior to an authentic sample.[4] Its ^{13}C chemical shifts are recorded in Table I. Compound **4** showed: mp 51.0–52.0 °C; IR (CCl_4) 1711, 1460, 1442, 1379, 1330, 1305, 1157, 1142, 1110 cm^{-1}; NMR (CCl_4) δ 0.89 (d, 3 H, J = 3.8 Hz), 1.25 (s, 3 H); MS (70 eV) m/e 180 (28), 109 (100).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.19. Found: C, 79.85; H, 11.18.

The ^{13}C chemical shifts of **4** are recorded in Table I. It formed a semicarbazone, mp 182.0–183.0 °C.

Anal. Calcd for $C_{13}H_{20}N_3O$: C, 65.79; H, 9.77. Found: C, 65.70; H, 9.81.

Preparation of Ketone 6. Ketone **6** was prepared in ~90% yield by lithium–ammonia reduction of the enone **5** according to the general procedure described for the enone **1**. Ketone **6** [bp 110–112 °C (0.1 mm); lit.[4b] 80 °C (0.01 mm)] showed identical IR, ^1H NMR, and mass spectral properties with those reported for the optically active material.[4b] It formed a semicarbazone: mp 203–204 °C (lit.[7] mp 202.5–203.0 °C). The ^{13}C chemical shifts are shown in Table I.

Catalytic Hydrogenation of Enone 1. To a solution of 0.32 g of octalone **1** in 6 mL of 95% ethanol was added 0.056 g of 10% palladium on carbon. The mixture was hydrogenated in a Parr apparatus for 2 h at 35 psi of hydrogen pressure. Removal of the catalyst by filtration and removal of the solvent in vacuo gave a mixture of decalones **3** and **4** [bp 110–115 °C (bath temperature) (0.1 mm)] in essentially quantitative yield. Analysis of the mixture by GLC showed that it contained ~65% **3** and ~35% **4**. A trace (<3%) of decalone **6** was also present.[5]

Catalytic Hydrogenation of Enone 5 in Acidic Medium. To a solution prepared from 0.80 g of octalone **5**, 1.5 mL of 3.2 N hydrochloric acid, and 15 mL of 95% ethanol was added 0.15 g of 5% palladium on carbon. The mixture was hydrogenated in a Parr apparatus for 2 h at 35 psi of hydrogen pressure. On removal of the catalyst by filtration and removal of the solvent in vacuo, GLC analysis of the residue showed that it was composed of a 5:95 mixture of decalones **6** and **7**. Distillation of the mixture under reduced pressure gave 0.403 g (49%) of pure **7**: bp 108–112 °C (0.10 mm); IR (film) 1713, 1462, 1447, 1430, 1379, 1355, 1340, 1284, 1266, 1243, 1217, 1185, 1155, 1133, 1109, 1072, 1022, 1005, 934, 826, 755 cm^{-1}; NMR (CCl_4) δ 0.81 (d, 3 H, J = 6.6 Hz), 1.06 (s, 3 H); MS (70 eV) m/e 180 (37), 109 (100), 108 (88), 95 (65), 81 (58), 67 (54), 55 (84), 41 (79); semicarbazone mp 202.0–203.0 °C (lit.[7] 202.2–202.5 °C).

Registry No.—**1**, 64281-61-4; **4** semicarbazone, 64215-98-1.

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(1) This investigation was supported by Grant No. CA12193, awarded by the National Cancer Institute, DHEW. The research was also assisted by Institutional Research Grants from the National Science Foundation for the purchase of a mass spectrometer and a Fourier transform NMR spectrometer.

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(4) (a) The major reduction product **3** showed identical NMR, IR, and mass spectral properties and chromatographic behavior to an authentic sample of racemic **3** which had identical spectral and chromatographic properties to the optically active material obtained by oxidative degradation of dihydroeudesmanol (ref 4b). We are grateful to Dr. B. Maurer for providing us with a generous supply of authentic racemic **3**. (b) B. Maurer, M. Fracheboud, A. Grieder, and G. Ohloff, *Helv. Chim. Acta*, **55**, 2371 (1972).
(5) A trace (<3%) of the decalone **6** was obtained in the catalytic reduction of **1**. This product may have arisen because **1** was slightly contaminated with the trans isomer **5** or a slight amount of isomerization of **1** into **5** may have occurred under the reaction conditions.
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(11) Melting points and boiling points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 457 infrared spectrophotometer. The ^1H NMR spectra were obtained on a Varian T-60 NMR spectrometer and the ^{13}C NMR spectra were determined at 25 MHz with a Jeol Fourier transform spectrometer, Model PFT-100. The chemical shifts are expressed in δ values (ppm) to Me_4Si as an internal standard. The mass spectra were obtained with a Hitachi (Perkin-Elmer) Model RMU-7. Gas–liquid chromatography was carried out using a Perkin-Elmer 881 or an Aerograph A-90-P3 gas chromatograph. A 6 ft × 0.125 in. aluminum column packed with 20% Carbowax K-20M on acid washed Chromosorb W was employed for analytical work and a 10 ft × 0.25 in. stainless steel column containing the same packing material was used for preparative work. Microanalyses were obtained by Atlantic Microlab, Inc., Atlanta, Ga.

A Convenient Method for the Stereoselective Reduction of Alkynes to Alkenes by the New Reagents MgH_2–CuI and MgH_2–CuO-*t*-Bu

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The most common method of reducing alkynes to cis olefins is by catalytic hydrogenation, whereas the most common method of reducing alkynes to trans olefins is by liquid ammonia reduction.[1] In catalytic hydrogenation, usually some trans olefin is also produced with the cis olefin and quite often the two isomers are difficult to separate completely. A more recent method of reducing alkynes to cis olefins is based on the work of Normant.[2,3] Normant has shown that organocopper reagents (RMgBr + CuBr) add to unactivated terminal alkynes (eq 1) to produce the alkyl addition product. More

$$RMgBr + CuBr \longrightarrow RCu\cdot MgBr_2 \xrightarrow{RC{\equiv}CH} \underset{R'}{\overset{R}{\diagdown}}C{=}C\underset{H}{\overset{Cu\cdot MgBr}{\diagup}} \quad (1)$$

recently, Crandall reported that when the reagent 2RMgX–CuI is added to disubstituted alkynes, reduction is the predominant reaction (eq 2).[4] These reactions are potentially important because of their stereospecificity and versatility in organic synthesis.[5–10] However, the main re-

$$RC{\equiv}CR' + 2R''MgX\text{-}CuI \xrightarrow{THF} \underset{H}{\overset{R}{\diagdown}}C{=}C\underset{H}{\overset{R'}{\diagup}} + \underset{H}{\overset{R}{\diagdown}}C{=}C\underset{R''}{\overset{R'}{\diagup}} \quad (2)$$

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Table I. Reduction of Alkynes by MgH_2–CuI and MgH_2–CuOBu-*t* in THF[a]

Alkyne	Registry no.	Reagent	Recovered starting material, %	Products, %		
			1-Hexyne	1-Hexene		Hexane
1-Hexyne	693-02-7	A[b]	0	80		0
		B[c]	5	78		0
				2-Hexene		Hexane
			2-Hexyne	cis	trans	
2-Hexyne	764-35-2	A	0	80	0	0
		B	7	81	0	0
			1-Octyne	1-Octene		Octane
1-Octyne	629-05-0	A	5	84		0
		B	0	92		0
			Phenylacetylene	Styrene		Phenylethane
Phenylacetylene	536-74-3	A	0	98		0
			Diphenylacetylene	Stilbene		1,2-Diphenylethane
				cis	trans	
Diphenylacetylene	501-65-5	A	0	95	0	0

[a] Mole ratio of MgH_2/CuI(CuOBu-*t*)/alkyne = 1.00:1.00:0.25 and the reaction time was 48 h except in the case of phenyl- and diphenylacetylene when the reaction time was 24 h. [b] Reagent A, MgH_2–CuI. [c] Reagent B, MgH_2–CuOBu-*t*.

duction product is accompanied by a side alkylation product, sometimes in substantial yield. This report encourages us to report our own findings using the reagent MgH_2–CuI and MgH_2–CuOBu-*t* which reduces alkynes stereoselectively to the corresponding cis olefins in the complete absence of trans olefin or alkane by-product. The advantages of this method over catalytic hydrogenation lie in the purity of the product formed and in the convenience of the method once the reagent is prepared.

Results and Discussion

Results of alkyne reduction by the reagents MgH_2–CuI or MgH_2–CuOBu-*t* are summarized in Table I. The terminal alkynes, 1-hexyne, 1-octyne, and phenylacetylene, were reduced to the corresponding alkene with 100% selectivity (0% alkane) in 80–98% yield (eq 3). The internal alkynes, 2-hexyne and diphenylacetylene, were reduced to the cis alkene as the only product (no trans alkene or alkane was detected) in 80–95% yield. The alkene, 1-octene, was not affected by either reagent. The high stereospecificity of the reaction of MgH_2–CuI (or CuOBu-*t*) reveals that these reagents are very promising for the conversion to alkynes to alkenes, especially interal alkynes to cis alkenes.

$$RC{\equiv}CH \xrightarrow[MgH_2\text{–}CuOBu\text{-}t]{MgH_2\text{–}CuI} RCH{=}CH_2 \quad (80\text{–}90\%\ \text{yield}) \qquad (3)$$

(where R = *n*-C_4H_9, *n*-C_6H_{13}, or Ph)

$$RC{\equiv}CR' \xrightarrow[\text{or } MgH_2\text{–}CuOBu\text{-}t]{MgH_2CuI} \underset{H}{\overset{R}{}}\!\!>C{=}C<\!\!\overset{R'}{}_{H} \qquad (4)$$

(80–95% yield)

(where R = *n*-C_4H_9 and R′ = CH_3 or R = R′ = C_6H_5)

$$n\text{-}C_8H_{17}\text{–}CH_2{=}CH_2 \xrightarrow[48\ h]{MgH_2\text{–}CuI} \text{no reaction} \qquad (5)$$

The Normant reagent (RMgBr + CuBr) is believed to have a composition expressed by the empirical formula RCu·$MgBr_2$. By analogy one might propose that the reagent MgH_2–CuI has a similar composition, namely, CuH–HMgI; however, we have no evidence to support this idea and it would be difficult to obtain support. For example, the MgH_2 and CuI are mixed at −78 °C in THF. The solution does not become clear and a brownish mixture results. The alkyne is then added and the solution allowed to warm to room temperature, at which time the mixture turns black. Reagent decomposition is obviously taking place at room temperature, since H_2 is being slowly evolved; thus, a spectroscopic analysis of the reaction mixture is not possible.

Experimental Section

Apparatus. All operations were performed under a nitrogen atmosphere using either a nitrogen-filled glove box equipped with a special recirculating system to remove oxygen and moisture[11] or on the bench using Schlenk tube techniques.[12] All glassware were flash flamed and flushed with dry nitrogen prior to use.

Analyses. Gas analyses were carried out by hydrolyzing samples with hydrochloric acid on a standard vacuum line equipped with a Toepler pump. Magnesium was determined by EDTA titration, at pH 10, using Eriochrome Black as an indicator. Copper was determined electrolytically. GLPC analyses were performed on an F and M Model 720 or 700 gas chromatograph.

Materials. Tetrahydrofuran was distilled over $NaAlH_4$ prior to use. Diphenylacetylene, phenylacetylene, 2-hexyne, 1-octyne, 1-octene (Chemical Sample Co.), and 1-hexyne (Beacon Chemical Industries, Inc.) were purchased commercially and used without further purification.

Preparation of Cuprous *tert*-Butoxide.[13] Fifty millimoles of BuLi in *n*-hexane was added dropwise to a solution of *tert*-butyl alcohol (50 mmol) in THF and stirred for 1 h. This solution of 50 mmol of LiOBu-*t* was added to a slurry of cuprous chloride (4.95 g; 50 mmol) in THF and stirred for another hour, and the solvent was removed under vacuum. The residue was sublimed in vacuo at 160 °C (0.1 mm) to give yellowish crystals (yield 70%). Anal. Found: Cu/*t*-BuOH, 1.00:1.03.

Preparation of Active Magnesium Hydride in THF. When 15.0 mmol of $LiAlH_4$ solution in diethyl ether (30 mL) was added dropwise to a magnetically well-stirred solution of Et_2Mg (15.0 mmol) in diethyl ether (35 mL), an exothermic reaction occurred and an immediate precipitate appeared. This reaction mixture was allowed to stir for 1 h at room temperature followed by centrifugation of the insoluble white solid. The supernatant solution was separated by syringe and the insoluble white solid was washed with diethyl ether three to four times and finally made a slurry in THF. The analysis of this slurry showed that it contained Mg and H in ratios 1.00:2.02.

General Reaction. The experiments were carried out by the following procedure. A slurry of MgH_2 in THF was syringed into the mixture of alkyne and CuI (or CuOBu-*t*) at −78 °C. Then, the temperature was allowed to increase to room temperature by removing the cooling bath; a deep black color and slight gas evolution were observed at room temperature. After an indicated period (24 or 48 h), the reaction mixture was quenched with distilled water, dried over $MgSO_4$, and extracted with several portions of THF. Product analyses and percent yield were carried out either by NMR or GLC using an internal standard.

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Registry No.—*t*-BuOH, 75-65-0; CuCl, 7758-89-6; CuOBu-*t*, 35342-67-7; $LiAlH_4$, 16853-85-3; Et_2Mg, 557-18-6; MgH_2, 7693-27-8; CuI, 7681-65-4.

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Facile Ring Cleavage of Prostaglandin Epoxy Ketones

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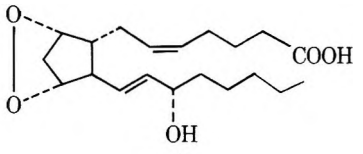
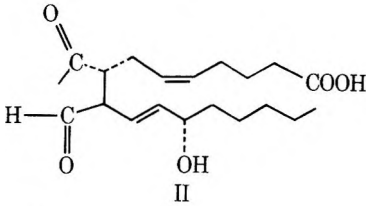
Received July 8, 1977

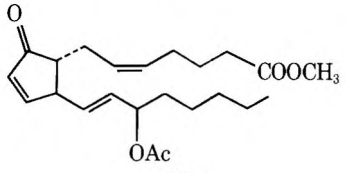
The suggestion of Salomon and Salomon[1] that prostaglandin endoperoxides (I) may rearrange to ring-opened keto aldehydes (II) prompts us to report another reaction in the prostaglandin field which we observed some years ago in connection with the epoxidation of (15*R*)-prostaglandin A_2 esters[2] [(15*R*)-PGA_2 esters, III], resulting in the facile opening of the 5-membered ring.



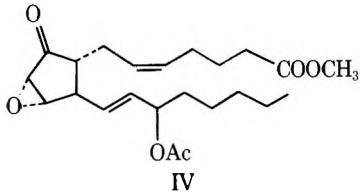
I



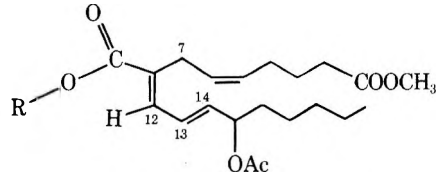
II



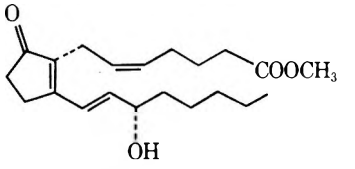
III



IV



Va, R = H
b, R = CH_3



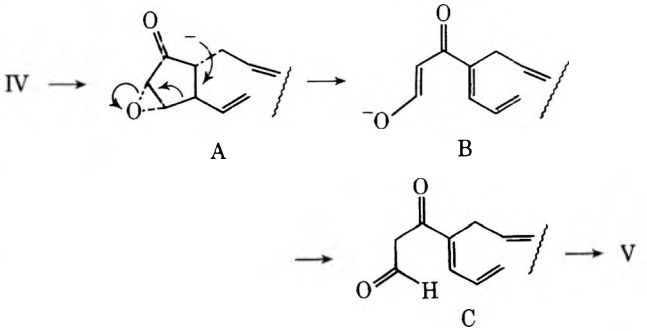
VI

The epoxidation of III to produce IV was accomplished by hydrogen peroxide and catalytic amounts of alkali metal hydroxides in cold methanol or other alcohols. If larger amounts of base or longer times are used for the reaction, an increasing amount of an acidic byproduct was formed which was shown to be the acid ester Va. The NMR spectrum of this showed the original C-1 methyl ester was still intact (OCH_3 at δ 3.67). This material was more easily isolated by chromatography as the diester Vb after diazomethane treatment, when it now showed an additional methyl ester function by NMR at δ 3.75.

The conjugated diene ester system for Vb was evident by the UV spectrum (λ_{max}(EtOH) 265 nm) and the NMR spectrum, which was particularly definitive in structure determination. It strongly resembled that of PGB_2 methyl ester VI except for an additional vinyl proton (C-12, PG numbering system) as a doublet at δ 7.15 (J = 11 Hz) coupled with the C-13 proton, now a doublet of doublets centered at δ 6.54 ($J_{12,13}$ = 11, $J_{13,14}$ = 14.5 Hz). The C-14 proton was also coupled to the proton at C-15 by 6.5 Hz at δ 5.96. By decoupling at 100 MHz, these couplings were shown to be correct, and also the presence of long-range coupling from C-15 to C-13 protons and from C-7 to C-12 protons was detected. The doubly allylic protons at C-7 occurred at δ 3.16 as a doublet with long-range coupling. The infrared and mass spectra were completely consistent with this formulation, the latter confirming the empirical formula $C_{22}H_{34}O_6$ for Vb and giving the expected fragmentation ions (see Experimental Section). The double bond at C-8(12) (PG numbering) is shown in the *E* configuration in structure V to show its relationship to its parent prostaglandin, and this seems consistent with its UV maximum.[3]

The same product, Vb, was formed when the epoxide mixture (IV and its 10β, 11β isomer)[2] was first isolated, freed of starting enone III by chromatography, and then retreated as above. The epoxide mixture used was about 5:1 α- to β-epoxides, but the epoxide recovered after the reaction (12%) was essentially all the 10β,11β-epoxide, perhaps reflecting a slower removal of the 8β-proton from the β-epoxide. These epoxides can be distinguished by NMR, the α-epoxide having a proton at δ 3.43 (d, J = 3 Hz) and the C-13,14 protons between δ 5.5 and 5.68. The β-epoxide has a proton at δ 3.38 (d, J = 3 Hz) with the C-13,14 protons between δ 5.65 and 5.88.

Structure V may arise by some such mechanism as below, followed by the cleavage of β-keto aldehyde by base.[7]



Experimental Section

Methyl (5*Z*,8*E*,10*E*,12*R*)-8-Carboxy-12-acetoxyheptadeca-5,8,10-trienoate. A solution of 4.0 g of (15*R*)-PGA_2 methyl ester acetate[2] in 75 mL of methanol was cooled to 0 °C, and then 5 mL of 30% H_2O_2 was added, followed over a period of 20 min by 10 mL of 1 N NaOH. The reaction mixture was stirred at 0 °C for 2.5 h, 12 mL of 1 N HCl was added, and the methanol was largely removed in vacuo. The products were extracted with ethyl acetate, and the extracts were washed with water and brine, dried with Na_2SO_4, and evaporated. The

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residue was treated briefly with excess ethereal diazomethane, concentrated in vacuo, and chromatographed in 300 g of silica gel, eluting with 5 L of a gradient 20–70% ethyl acetate–Skellysolve B solution. Fractions were assayed by thin-layer chromatography (AIX[5] system), and the first material eluted was combined to give 1.05 g of Vb, followed by 1.343 g of a mixture of epoxides (IV and its 10β,11β isomer). Vb was characterized as follows: IR (neat) 1745, 1715, 1650, 1615, 1440, 1375, 1240, 1210, 1160, 1100, 1070, 1020, 975, 840 cm^{-1}; NMR ($CDCl_3$) δ 7.15 (d, J = 11 Hz), 6.54 (dd, J = 14.5, 11 Hz), 5.96 (dd, J = 14.5, 6.5 Hz), 3.75 (s, 3 H), 3.67 (s, 3 H), 3.16 (d, 2 H), 2.03 (s, 3 H), 0.89 (t, 3 H); mass spectrum, m/e 394 (M^+), 362, 352, 334, 330, 320, 302, 291, 288, 284, 281, 274, 270, 259, 251, 245, 243, 221, 199, 189, 99, 71, 55, 43. In the ^{13}C NMR spectrum, absorptions were seen at 13.9, 21.1, 22.5, 24.7 (2 carbons), 25.4, 26.7, 31.5, 33.5, 34.3, 51.4, 51.8, 74.0, 126.7, 127.6, 129,7, 131.2, 137.6, 139.5, 168.1, 170.1, and 173.9 ppm downfield from Me_4Si (Varian CFT-20 instrument at 20 MHz).

If the diazomethane treatment was omitted, the acid Va was isolated by chromatography on acid-washed silica gel, eluted with 25–50% EtOAc–Skellysolve B, followed by rechromatography of combined fractions on a reversed-phase column (C-18 Porasil B[6]), and eluted with 80% acetonitrile–20% water. The NMR spectrum was very similar to that of the diester Vb except that the 3-proton singlet at δ 3.75 was absent, and the proton which in Vb occurred at δ 7.15 was shifted downfield to δ 7.3. Esterification of this material with diazomethane gave the diester Vb, identical with that described above.

Analogous products were produced from (15S)-PGA_2 methyl ester acetate.[2]

Registry No.—III, 35730-43-9; IV, 38310-83-7; 10β,11β-IV, 38344-07-9; Va, 64200-85-7; Vb, 64200-84-6; H_2O_2, 7722-84-1.

References and Notes

(1) R. G. Salomon and M. F. Salomon, *J. Am. Chem. Soc.*, **99**, 3501 (1977).
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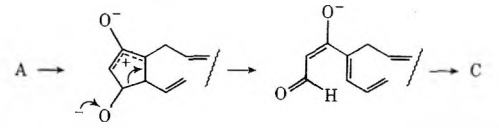
(3) A. J. Scott, "Interpretation of the UV Spectra of Natural Products", MacMillan, New York, N.Y., 1964.
(4) We are indebted to S. A. Mizsak of these laboratories for the 100-MHz NMR spectrum and decoupling data and to J. A. Woltersom for isolation of Va.
(5) M. Hamberg and B. Samuelsson, *J. Biol. Chem.*, **241**, 257 (1966).
(6) Waters Assoc., Milford, Mass.
(7) A referee has suggested the following as an alternative mechanism:



He suggested that facile electrocyclic cyclopentenyl to pentadienyl cation rearrangement would be promoted by concomitant C=O bond formation and charge neutralization.

Reaction of *cis*- and *trans*-4-*tert*-Butyl-1-methoxy-1-phenylphosphorinanium Hexafluorophosphate with Aqueous Hydroxide. Axial vs. Equatorial Displacement of Methoxide

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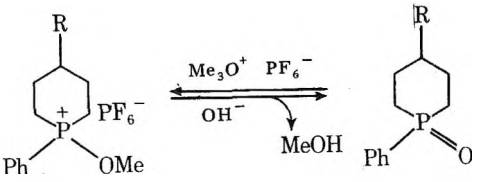
Received August 19, 1977

Nucleophilic displacement of methoxide by aqueous hydroxide on phosphorus in cis and trans isomers of 4-methyl-1-methoxy-1-phenylphosphorinanium hexafluorophosphate (**1a**)[1] was observed to occur with 100% inversion of configuration at the phosphorus atom (eq 1).[2] Labeled oxygen studies showed 8–9% retention of configuration due to attack at carbon.[2] We have recently synthesized *cis*- and *trans*-4-*tert*-butyl-1-phenylphosphorinane 1-oxide (**2b**),[3a] and wished to investigate the rates at which axially vs. equatorially P-bonded alkoxide was hydrolyzed from **1b** in these conformationally biased systems derived from **2b**. We were also interested in determining ratios of stereoisomeric phosphine oxide products

Table I. Some Results of Heterogeneous Cleavage of *cis*- and *trans*-4-*tert*-Butyl-1-methoxy-1-phenylphosphorinanium Hexafluorophosphate at 24 °C

Wt of salt, g	Solvent	% retention Cis salt	% retention Trans salt
0.284	9 mL of 0.50 N NaOH	11.3	4.0
0.140	4.5 mL of 0.50 N NaOH[a]		2.7
0.284	30 mL of 0.50 N NaOH[b]	5.8	
0.284	32 mL of 1.00 N NaOH in 25% dioxane	13.7	12.9

[a] Solution was refluxed. [b] 15 mL of 1.00 N NaOH added to a suspension of **1b** in 15 mL of water.



(1)

1a, R = Me
b, R = *t*-Bu

2a, R = Me
b, R = *t*-Bu

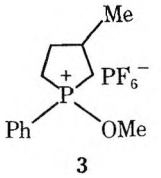
obtained by base cleavage. Configurational assignments for *cis*- and *trans*-**1b** and -**2b** were previously made[3a] and were based upon proton NMR spectra. These assignments have been subsequently verified through an x-ray structure analysis of *cis*-**2b**.[4]

The configurationally pure 4-*tert*-butyl oxides were converted by a previous procedure[2] into their alkoxy salts (eq 1) with complete retention of configuration. The salts were characterized by proton NMR spectroscopy and elemental analysis.

Unlike the 4-methyl analogues (**1a**), these salts were ideally suited to careful isomeric oxide product studies by proton NMR spectroscopy because of the presence of separated *tert*-butyl proton signals for the isomeric phosphorinane derivatives. Initially, cleavage of *cis*- and *trans*-**1b** was carried out under heterogeneous conditions because of the sparing solubility of the hexafluorophosphate salts in water. Inability to reproduce product ratios led to the belief that nucleophilic attack by hydroxide on methoxy carbon, as previously demonstrated with **1a**,[2] was influenced in some way by the heterogeneous nature of the reaction. Some results are shown in Table I.

However, when the reaction was conducted homogeneously by dissolving the salts in 50% aqueous dioxane and then adding aqueous sodium hydroxide, *no* retention was detected either by NMR or oxygen-18 labeling experiments.

Previous work on the phosphorinanium system, **1a**, and the cis and trans phospholanium salts (**3**) was conducted under



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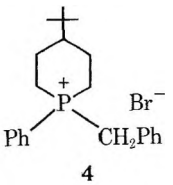

4

heterogeneous conditions and retention of configuration at phosphorus due to attack at methoxy carbon was found to be 9 and 11%, respectively.[2] We are now convinced that attack at carbon could have been obviated by homogeneous treatment with base. From the results in Table I it seems very reasonable that attack of hydroxide at carbon is the result of a phase phenomenon and not a solvent effect.

Luckenback has reported different stereochemical results with homogeneous vs. heterogeneous reaction conditions in base-promoted cleavage reactions at chiral phosphorus in

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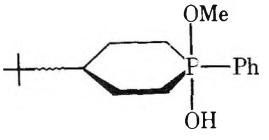
Table II. Phosphine Oxide Formation upon Hydroxide Cleavage of *cis*- and *trans*-4

	trans-4	*cis*-4
Heterogeneous results	23.4 trans	65.0 trans
(% *cis*- or *trans*-2b)	76.6 cis	35.0 cis
Homogeneous results	20.6 trans	65.6 trans
(% *cis*- or *trans*-2b)	79.4 cis	34.4 cis

acyclic phosphonium salts,[5] although attack at carbon is obviously not occurring in these salts. This work promoted us to reexamine homogeneous vs. heterogeneous cleavage of isomeric benzylphosphorinanium salts[2,3a] (4) with aqueous NaOH. In this case we observed no significant differences in the distribution of isomeric oxides (2b) formed as seen in Table II.

The pseudo-first-order rate constants for the cleavage of *cis*- and *trans*-1b were determined in 50% dioxane/standard pH 7 buffer at 25 °C and calculated to be as shown in Chart I.

That the rate constants are nearly identical indicates virtually no influence on reaction velocity by the *tert*-butyl group or the orientation of the methoxy substituents at phosphorus (axial or equatorial). This supposes the unlikelihood of compensating effects on reaction rate by interaction of the *tert*-butyl group and methoxy substituent for the two isomers. The transition states probably do not resemble products because the oxides are known to differ in thermodynamic stability.[3a] Evidently the ground-state energies of the two disastereomeric salts are comparable, since stabilities of the presumed diastereomeric pentacovalent intermediates (5) would be expected to be very similar. Where the leaving group is benzyl (4), in an otherwise identical system, the rate constants for inversion of the two isomers were also found to be nearly equal,[3b] probably for the same reasons.



5

Alkaline cleavage of alkoxyphosphorinanium salts under homogeneous conditions provides an excellent synthetic method for complete stereospecific transformations of cis or trans phosphorinane 1-oxides, via their alkoxy salts, into opposite configuration.

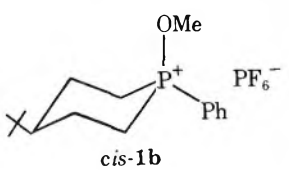
Experimental Section[7]

Melting points are uncorrected and were determined in sealed tubes in a Thomas Hoover melting point apparatus. NMR spectra were obtained by use of a Perkin-Elmer R12-B spectrometer. Oxygen-18 analyses were performed by West Coast Technical Service, Inc., Cerritos, Calif.

***cis*-4-*tert*-Butyl-1-methoxy-1-phenylphosphorinanium Hexafluorophosphate (*cis*-1b).** *cis*-4-*tert*-Butyl-1-methoxy-1-phenylphosphorinane 1-oxide (*cis*-2b) (0.50 g, 0.0020 mol) dissolved in 5 mL of dry methylene chloride was added in a dry atmosphere to a suspension of 0.439 g (0.00213 mol) of trimethyloxonium hexafluorophosphate in 10 mL of dry methylene chloride. The mixture was magnetically stirred overnight at room temperature and any insoluble residue was removed by centrifugation and decantation. After removal of the solvent in vacuo the resulting white residue was extracted with five 10-mL portions of dry ether, and the solid residue was dried overnight in vacuo to give a 64% yield of *cis*-1b. Recrystallization was accomplished by dissolving the dried material in dry methylene chloride, removal of insoluble material by centrifugation, and addition of petroleum ether to the decantate to the cloud point. The resulting solution was cooled and the crystals were removed by filtration in a dry atmosphere: mp 140–142 °C; NMR ($CDCl_3$) δ 0.93 (s, 9, *t*-Bu), 3.83 (d, OCH_3), 7.85 (m, C_6H_5).

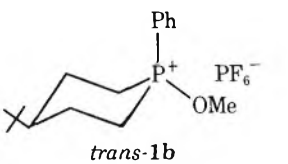
Anal. Calcd for $C_{16}H_{26}OP_2F_6$: C, 46.84; H 6.39. Found: C, 46.79; H, 6.65.

Chart I



cis-1b

2.71×10^{-3} s^{-1}



trans-1b

2.92×10^{-3} s^{-1}

***trans*-4-*tert*-Butyl-1-methoxy-1-phenylphosphorinanium Hexafluorophosphate (*trans*-1b).** The preparative procedure was the same in all respects as for the cis salt: mp 158.3–159.8 °C; NMR ($CDCl_3$) δ 0.83 (s, *t*-Bu), 3.81 (d, OCH_3), 8.70 (m, C_6H_5).

Anal. Calcd for $C_{16}H_{26}OP_2F_6$: C, 46.84; H, 6.39. Found: C, 47.10; H, 6.44.

Heterogeneous Base Cleavage of *cis*-1b and *trans*-1b in Aqueous Base. The cis or trans hexafluorophosphate salt (1b) (0.284 g) was added to 9.0 mL of 0.50 N NaOH and the mixture was stirred for 3 h at room temperature. The resulting reaction mixture was extracted with five 25-mL portions of methylene chloride and the combined extracts were flash evaporated. A Kugelrohr distillation was performed on the residue: bp 205 °C (0.15 mm); overall yields, 88.2% from *cis*-1b and 83.6% from *trans*-1b. Compositions of product mixtures are given in Table I. Other reactions listed in Table I followed essentially the same procedure. NMR analysis of the residue prior to distillation yielded the same oxide composition as the distillate in every case.

Homogeneous Base Cleavage of *cis*-1b and *trans*-1b. The cis or trans hexafluorophosphate salt (1b) (0.149 g) was dissolved in 10 mL of dioxane in a 50-mL round-bottom flask with the aid of magnetic stirring. Water (10 mL) was then added with stirring until the salt dissolved. This was followed by the addition of 20 mL of 1.00 N NaOH, and the mixture was stirred for 3 h at room temperature. The reaction mixture was extracted with five 25-mL portions of methylene chloride, the combined extracts were evaporated, and an NMR spectrum was recorded on the residue dissolved in $CDCl_3$. Only the oxide isomer corresponding to inversion of configuration could be detected in each case. NMR analysis of the distillate resulting from distillation of the residue gave the same results.

Preparation of Isotopically Labeled *cis*-1b and *trans*-1b. A mixture of *cis*- and *trans*-2b (1 g; 9.7% trans/90.3% cis) was placed in an ampule with 5 mL of 10% $D_2{}^{18}O$ which had had hydrogen chloride gas introduced to a pH of 2. The ampule was sealed and the contents were heated to 125 °C in an oil bath for 24 h. The $D_2{}^{18}O$ was then removed by distillation and the residue was vacuum distilled to afford an 82% recovery of the oxide (24.5% trans/74.5% cis). The labeled oxides were separated by preparative thin-layer chromatography[3a] and each was alkylated with trimethyloxonium hexafluorophosphate as described above. [Two separate runs with $D_2{}^{18}O$ (under nonidentical conditions) were necessary in order to obtain sufficient amounts of labeled *trans*-2b.] Mass spectral analysis of the labeled salts (1b) gave the following results: *trans*-1b, 1.173 atom % ^{18}O; *cis*-1b, 0.220 atom % ^{18}O.

Homogeneous Base Cleavage of Oxygen-18 Labeled *cis*- and *trans*-1b. The same procedure was followed as detailed above for homogeneous cleavage of nonlabeled 1b. Mass spectral analysis of product oxides showed: *trans*-2b, 0.204 atom % ^{18}O; *cis*-2b, 0.202 atom % ^{18}O; natural abundance, 0.204 atom %.

Heterogeneous Cleavage of *cis*- and *trans*-4. A published procedure was followed.[6]

Homogeneous Clevage of *cis*- and *trans*-4. The *cis*- or *trans*-4 salt (0.250 g) was dissolved in 4.5 mL of 1.00 N NaOH and the solution was heated under reflux for 9 h. The remainder of the procedure was identical with literature instructions (see ref 6). Results are given in Table II. Isomer composition is unaffected by distillation.

Pseudo-First-Order Rate Constant Determinations for Cleavage of *cis*- and *trans*-1b. The rate constants for the hydrolysis of these salts were determined at 275.0 nm and 25 °C in a standard pH 7 buffer in 50% water–50% dioxane (v/v). Under conditions of the stereochemical experiment the reaction was too rapid for rate constant determination.

Acknowledgments. We are grateful for financial support from the National Science Foundation (Grant GP 38756X) and for helpful suggestions from Dr. James L. Jensen.

Registry No.—*cis*-1b, 64457-45-0; *trans*-1b, 64457-47-2; *cis*-2b, 61332-82-9; *trans*-2b, 61332-81-8; *cis*-4, 61332-79-4; *trans*-4, 61332-80-7; trimethyloxonium hexafluorophosphate, 12116-05-1.

References and Notes

(1) Cis and trans designations are in accordance with *Chemical Abstracts* usage by which, for example, the cis isomer has the senior groups (as defined by the sequence rule) on the same side of the reference plane of the ring: cf. *Chem. Abstr.*, **76**, 85 I (1972); *J. Chem. Inf. Comput. Sci.*, **15**, 67 (1975).
(2) K. L. Marsi, *J. Org. Chem.*, **40**, 1779 (1975).
(3) (a) K. L. Marsi, J. L. Jasperse, F. M. Llort, and D. B. Kanne, *J. Org. Chem.*, **42**, 1306 (1977). (b) The pseudo-first-order rate constants for *cis*- and *trans*-**4** for the inversion component of benzyl cleavage at phosphorus are, respectively, 0.96×10^{-3} and 1.16×10^{-3} s^{-1} at 80.0 °C in 1.28 N NaOH (50% aqueous ethanol) (ref 3a).
(4) Personal communication from K. D. Berlin and D. van der Helm.
(5) R. Luckenbach, *Z. Naturforsch. B*, **31**, 1127 (1976); R. Luckenbach, *Phosphorus*, **3**, 117 (1973), and references contained therein.
(6) K. L. Marsi and R. T. Clark, *J. Am. Chem. Soc.*, **92**, 3791 (1970); K. L. Marsi, *J. Org. Chem.*, **40**, 1779 (1975); ref 3a.
(7) Stereochemical relationships among 4-*tert*-butylphosphorinane derivatives mentioned in this paper were established previously (see ref 3a).

Atomic Oxygen. 8. Reactions of Methylenecycloalkanes with Oxygen (^3P) Atoms

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The reactions of atomic oxygen with unsaturated organic compounds have demonstrated that the primary reactive intermediates can undergo extensive rearrangement before forming isolable oxygenated products. The examination of the product mixture allows one to determine two important factors of the reaction: the orientation of the oxygen atom addition to the molecule and the relative migratory aptitudes of substituents on the molecule's unsaturated site. The reactions of methylenecycloalkanes with O(^3P) illustrate the effects of ring size and strain on the former of these two factors.

In this study, conditions for the gas-phase production and reaction of atomic oxygen were derived from the pioneering work of Cvetanovic and co-workers.[2] Ground-state (^3P) oxygen atoms were produced by the mercury photosensitized decomposition of nitrous oxide.[3] The reaction apparatus and conditions have been described previously.[4] The total pressure before photolysis was 0.9 atm, and the reaction temperature was 25–30 °C.

The products of the reactions of methylenecycloalkanes (**1**) with atomic oxygen consisted of spiro epoxides (**2**), cycloalkanecarboxaldehydes (**3**), cycloalkanones (**4**), and alken-2-ones (**5**). Product yields are listed in Table I. A probable mechanism for the formation of these products is shown in Scheme I.

Several features of this mechanism are of interest. Previous research has shown that triplet oxygen atoms add to olefins to produce carbon–oxygen 1,3-biradicals. In the case of an unsymmetrical olefin, the orientation of addition parallels that obtained when a monoradical adds to the olefin. The direction of addition is controlled by radical stability. In the reactions of methylenecycloalkanes, the orientation of addition is approximately indicated by the ratio of aldehydic product **3** to ketonic products **4** and **5**. These ratios in the series of methylenecyclobutane (2.9), methylenecyclopentane (4.6), and methylenecyclohexane (21) demonstrate that increasing the ring size increases the stability of the cycloalkyl radical site (intermediate **6**) relative to the stability of the methylene radical (intermediate **7**).[5]

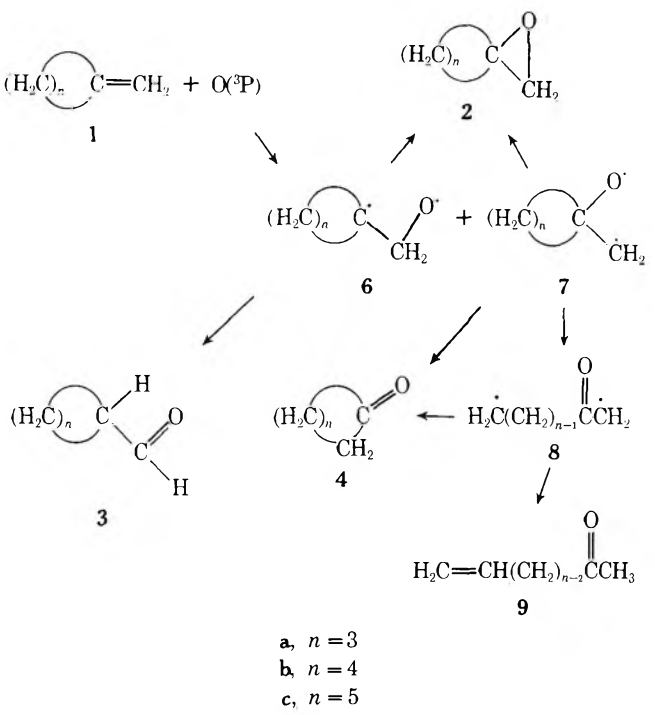
Another aspect of the proposed mechanism is the ring opening of 1,3-biradical **7** to yield the 1,ω-biradical **8**. It has been noted in previous atomic oxygen studies[6,7] that the rearrangement of alkyl radicals is partially accomplished by detachment of the migrating radical from the remainder of the molecule. In acyclic olefins, these detached alkyl radicals can be scavenged by added molecular oxygen. The formation of biradical **8** is analogous to this process.

Table I. Product Yields[a] from Reactions of O(^3P) with Methylenecycloalkanes

Reactant	Product yield, % 2	3	4	5
1a (n = 3)	35	29	7.1	2.9
1b (n = 4)	57	19	2.6	1.5
1c (n = 5)	56	26	0.81	0.40

[a] Product yields are based on the measured amounts of nitrogen produced by the mercury photosensitized decomposition of nitrous oxide. Reproducibility among reactions was ±10% of the stated yields.

Scheme I



a, $n = 3$
b, $n = 4$
c, $n = 5$

Relative rate constants for the reactions of the methylenecycloalkanes were also determined. These rates (relative to 2-methylpropene as 1.00) were: methylenecyclobutane, 1.05; methylenecyclopentane, 1.81; and methylenecyclohexane, 0.99. The same reactivity pattern has been observed for the addition of dichlorocarbene to these olefins,[8] but the origin of the enhanced reactivity of methylenecyclopentane is not clear.

Experimental Section

Reaction Technique. Procedures for the reaction of atomic oxygen with organic substrates have been described previously.[4] The olefins used were obtained from Chemical Samples Co. and were determined to be of >99% purity. Analyses of unreacted olefins recovered after photolysis showed that the reactant was not isomerized under the reaction and workup conditions used. The reaction of methylenecyclopropane with O(^3P) was attempted several times, but this substrate polymerized rapidly under the reaction conditions.

Relative rate constants of the methylenecycloalkanes vs. cyclopentene were determined by the method of Cvetanovic[2] and converted to the usual standard, 2-methylpropene, using the figure $k_{\text{cyclopentene}}/k_{\text{2-methylpropene}} = 1.19$. Reaction temperature during these studies was controlled at 24 ± 2 °C.

Product Analysis. Products of the reaction of **1a** were analyzed by VPC on a dinonyl phthalate column at 99 °C. Product mixtures from **1b** and **1c** were analyzed on an XE-60 column at 132 and 155 °C, respectively.

Authentic samples of all products were available for comparative VPC retention times and, where possible, comparative NMR, IR, and

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mass spectra. The cycloalkanones **4**, cyclohexanecarboxaldehyde (**3c**), and 5-hexene-2-one (**5b**) were obtained commercially. 4-Penten-2-one (**5a**) was available as a major impurity in 3-penten-2-one obtained from the Aldrich Chemical Co. Authentic samples of cyclobutanecarboxaldehyde (**3a**) and cyclopentanecarboxaldehyde (**3b**) were obtained from the reactions of cyclopentene and cyclohexene with oxygen atoms. Spiro epoxides **2** were prepared by reaction of the olefins with *m*-chloroperbenzoic acid. 6-Hepten-2-one (**5c**) was made by the acetoacetic ester synthesis.[9]

Trace amounts of 2-methylenetetrahydrofuran and 2-methylenetetrahydropyran were detected from the reactions of **1a** and **1b**, respectively. These enol ethers were independently synthesized by dehydrohalogenation reactions.[10]

Acknowledgments. The author gratefully acknowledges the support of this research by The Robert A. Welch Foundation. Some of the syntheses described were performed by Mr. Martin Grissom and Ms. Johna Leddy.

Registry No.—**1a**, 1120-56-5; **1b**, 1528-30-9; **1c**, 1192-37-6; **2a**, 157-48-2; **2b**, 185-60-4; **2c**, 185-70-6; **3a**, 2987-17-9; **3b**, 872-53-7; **3c**, 2043-61-0; **4a**, 120-92-3; **4b**, 108-94-1; **4c**, 502-42-1; **5a**, 13891-87-7; **5b**, 109-49-9; **5c**, 21889-88-3.

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Position of Nucleophilic Attack on Propargylic ↔ Allenylic Cations. An Ab Initio Molecular Orbital Calculation

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In an earlier communication,[1] we reported on the mechanism of addition of HCl to 1,2,3-pentatriene in ethanol–water (95% v/v). The first and rate-determining step is a proton transfer to the terminal carbon atom. In the second step, a chloride ion is attached to the intermediate cation to give 20% allenylic chloride (1,2 adduct) and 80% propargylic chloride (1,4 adduct). In sulfolane–CH_2Cl_2 (80:20 v/v), this ratio is 50:50.

$$CH_3—C^4H{=}C^3{=}C^2{=}C^1H_2 + H^+ \xrightarrow{\text{slow}} [CH_3—C_\alpha{}^4H\cdots C^3\cdots C_\beta{}^2—C^1H_3]^+$$

$$[CH_3—C_\alpha{}^4H\cdots C^3\cdots C_\beta{}^2—C^1H_3]^+ + Cl^- \rightarrow CH_3CH{=}C{=}CClCH_3 + CH_3CHClC{\equiv}CCH_3$$

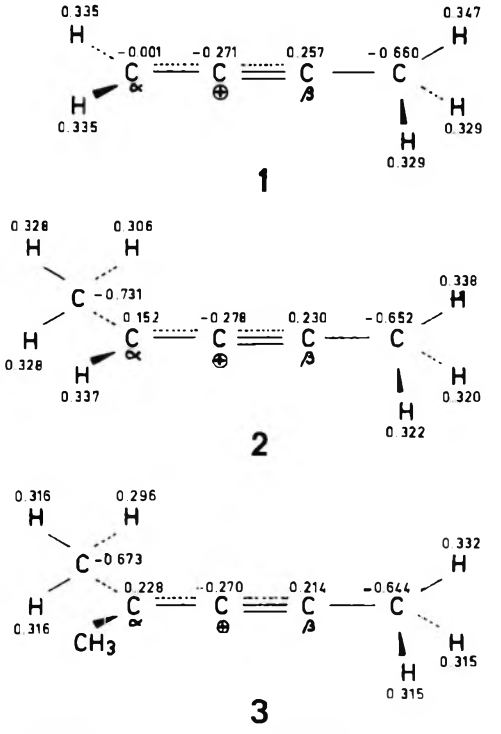

Figure 1. Net atomic charges from ab initio wave functions.

Similar intermediate carbocations are generated by S_N1 solvolysis of allenylic or propargylic halides or tosylates in aqueous solvents.[2-8] In these solvolysis reactions attack on the cation by solvent occurs exclusively at C_α to give propargylic products, unless attack at C_α is sterically hindered. The high preference for attack at C_α rather than at C_β is not expected on the basis of ^1H[9] and ^{13}C NMR[10] measurements on the relevant cations. These measurements suggest that the positive charge is present not exclusively on the propargylic position but, to a certain extent, also on the allenylic position.

In order to better understand the behavior of these cations as well as the possible influence of methyl substituents, we calculated ab initio charge distributions and molecular electrostatic potentials for cations **1–3**. A (C 6s,3p/H 3s) basis set of Gaussian-type functions contracted to a split-valence [3s,2p/2s] set was adopted.[11] Geometries of the cations were taken from ref 12–14. Gross atomic populations were calculated from the wave functions by means of Mulliken's population analysis.[15]

$$\underset{\mathbf{1}}{[C_\alpha{}^4H_2\cdots C^3\cdots C_\beta{}^2—C^1H_3]^+}$$

$$\underset{\mathbf{2}}{[CH_3—C_\alpha{}^4H\cdots C^3\cdots C_\beta{}^2—C^1H_3]^+}$$

$$\underset{\mathbf{3}}{[(CH_3)_2C_\alpha{}^4\cdots C^3\cdots C_\beta{}^2—C^1H_3]^+}$$

The corresponding net atomic charges (in units of proton charge) are given in Figure 1. It appears that cations **1** and **2** have a higher positive charge on C_β than on C_α. However, the atomic charges on C_β and C_α are not the only determining factors for nucleophilic attack. One should also include the charge distributed over the hydrogen atoms. Therefore, we have calculated the total charge on each side of the central carbon atom C^3. (The charge on C^3 is approximately equal for the three cations.) The results are given in Table I, where q_{prop} is the total charge on the atoms to the left of C^3 and q_{all} is the total charge on the right-hand side (cf. Figure 1).

In all cations, $q_{prop} > q_{all}$, i.e. most of the positive charge is associated with the propargylic center. Moreover, the ratio

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Table I. Sum of the Net Atomic Charges on Each Side of the Central Carbon Atom (in Units of Proton Charge)[a]

Cation	Registry no.	q_{prop}[a]	q_{all}[a]	q_{prop}/q_{all}	$q_{prop} - q_{all}$
1	64235-83-2	0.669	0.602	1.1	0.067
2	64235-82-1	0.720	0.558	1.3	0.162
3	53474-96-7	0.738	0.532	1.4	0.206

[a] Abbreviations prop and all refer to the left- and right-hand sides in Figure 1, respectively.

Table II. Potentials at Positions A, B, C, and D

	Potential, au				$\alpha - \beta$ difference, kcal mol^{-1}	
	C_α attack		C_β attack			
Cation	A	B	C	D	A − C	B − D
1	0.187	0.186	0.180	0.175	4.4	6.9
2	0.183	0.183	0.168	0.164	9.4	11.9
3	0.180	0.180	0.160	0.156	12.5	15.0

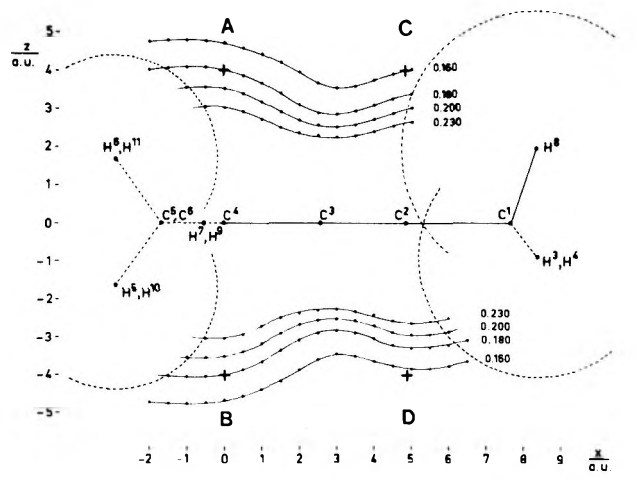

Figure 2. Contour lines of equal potential in the xz plane of cation 3.

q_{prop}/q_{all} increases when going from cation 1 to 3. It is worth noting that Olah[10] concluded from his ^{13}C NMR data on cation 3 the same ratio of 1.4. Thus, the ^{13}C NMR chemical shifts better fit the charges calculated for groups than for separate carbon atoms. This is in line with results by Fliszár,[16] who concluded that for alkanes the ^{13}C NMR shifts and calculated net charges only correlate well if part of the charge on the hydrogens is added to the carbon charge. From the increase in q_{prop}/q_{all} from cation 1 → 3, we conclude that methyl substitution at the propargylic position increases the preference for nucleophilic attack at that position.

The consideration of atomic or group charges tells us little about the difference in activation energy between attack at C_α and C_β. Ideally we should calculate the interaction energy in the R^+Cl^- system as a function of its geometry, e.g., by the ab initio SCF method. However, in view of the size of our systems, such a complete calculation was out of the question. Instead, we calculated the electrostatic potential V around the cation R^+.[17]

A first-order approximation of the energy of a chloride ion in the field of a cation can be obtained by multiplying V by the charge of Cl^-, i.e., $-e$. Since we are dealing with cations, the electrostatic potential is positive everywhere. Chloride will preferentially attack the centers with the higher positive potential. The potential field was calculated from the cation ab initio wave functions for two perpendicular planes through C^1–C^4. In the main molecular plane the potentials are appreciably smaller than in the one perpendicular to it. Therefore, we only consider the potential field in the latter plane. Contours of equal potential in this plane around cation 3 are shown in Figure 2. The potential becomes progressively higher as we approach the atomic centers. However, as soon as the charge clouds of Cl^- and the cation begin to overlap significantly, exchange forces will prevent a further approach of Cl^- toward the cation. We estimate that for this reason a region with a radius of 1.90 Å[18] around the hydrogens is not accessible (see circles in Figure 2) and likewise a region with a radius of ~1.80 Å around the carbons (based upon the C–Cl bond length) is not accessible also. The potentials are shown only outside these excluded regions. Inspection of Figure 2 shows that the potential is much higher at a given distance from C^4 or C^2 than from C^3, in agreement with the fact that C^4 and C^2 are the more positively charged carbons. In order to estimate the preference for attack at C_α[4] as compared to attack at C_β[2], we consider the value of the potential at a distance of 4.0 au (2.12 Å) above and below C^4 and C^2 (points A, B, C, and D in Figure 2; Table II). We expect that 4.0 au is about the equilibrium distance to which Cl^- can approach an undisturbed cation. The results predict the preferred attack at C_α, i.e., formation of a propargylic product. The preference increases when going from cation 1 to 3, just as expected from the group charges.

To our knowledge, so far the electrostatic potential method has not been applied to studies of nucleophilic attack on cations. Therefore, it seems necessary to provide some justification for its use under these circumstances. Notably, one ignores exchange repulsion between the charge clouds of R^+ and Cl^-, as well as polarization and charge-transfer effects. We have therefore performed an SCF ab initio calculation on the system (cation 1 + Cl^-), with Cl^- at the A and the C position. The final SCF eigenvectors of R^+ (1) and Cl^- were used as starting vectors in the SCF calculation on R^+Cl^- (R^+ = 1). In this way, the energy in the first SCF iteration yields a first-order interaction energy. The results are shown in Table III. They show that the true first-order interaction energy (coulomb + exchange energy) is less than the potential energy (−eV), which means that at a distance of 4.0 au from the carbon atom Cl^- already experiences repulsive exchange forces. At position A, the exchange energy term (0.115 hartree) is lower than at position C (0.152 hartree). Hence, the more positive propargylic center will be approached more easily than the allenylic center. Moreover, the difference between the SCF and the first-order interaction energy, i.e., the polarization and charge-transfer effects, is more favorable for chloride attack near A than near C (Table III).

We conclude that the trend in the values of the potential energy (−eV) is enhanced in the more refined SCF calculation. Thus, although in the potential energy method the energy difference between positions A and C is much too small, this method does qualitatively give useful information.

Table III. SCF Ab Initio Calculation on the (Cl^- + Cation 1) System, with Cl^- at Position A or C

	Energy, hartree		A −C difference, kcal mol^{-1}
	Position A	Position C	
Potential energy (−eV)	−0.187	−0.180	− 4.4
Coulomb + exchange energy[a]	−0.072	−0.028	−27.6
Exchange energy[b]	0.115	0.152	
SCF interaction energy[c]	−0.230	−0.169	−38.3
Polarization and charge-transfer effects[d]	−0.158	−0.141	

[a] First-order interaction energy defined as E (first iteration) $- E_{cation} - E_{Cl^-}$, with $E_{cation\ 1} = -153.606\ 838$ hartrees and $E_{Cl^-} = -458.922\ 869$ hartrees.[19] [b] Difference between (coulomb + exchange energy) and potential energy. [c] Defined as $E_{R+Cl^-}{}^{SCF} - E_{cation} - E_{Cl^-}$. In addition to the first-order energy, this includes polarization and charge-transfer effects. [d] Difference between SCF interaction energy and (coulomb + exchange energy).

We are left with the question of why in sulfolane our HCl addition occurs in equal amounts at the α and β positions, instead of predominantly at C_α. To answer this question we first remark that our calculations are "gas phase calculations." For solutions their predictive value is restricted at best to weakly solvating solvents. Furthermore, the predictive value of electrostatic arguments such as we use is restricted to reactions with an early transition state.

To a certain extent both conditions are met in our chloride ion addition reaction in 95% aqueous ethanol. Water and alcohol are relatively hard solvents.[20] These hard solvents have only a minor solvating effect on our cations.[21] An early transition state is plausible because the chloride addition is a fast step, subsequent to the slow proton transfer.

Sulfolane will have an appreciably stronger solvating effect on the cation,[22] and our quantum chemical predictions are less applicable. For example, the propargylic position (C_α) could be the more strongly solvated position and therefore more screened for attack by chloride; the ratio of propargylic to allenylic attack will be lower than predicted. Moreover, the chloride attack might be slower in sulfolane than in aqueous alcohol and correspondingly the transition state somewhat more product-like. Probably, the energies of our propargylic and allenylic products are approximately equal. For example, from calculations on $H_2C{=}C{=}CHCl$ and $HC{\equiv}C{-}CH_2Cl$,[23] we find an energy difference of only 0.2 kcal/mol, the former molecule in fact being the slightly more stable one. Thus, if the transition state is more product-like, the product ratio will shift to 1:1.

Finally, we return to the literature data on solvolysis reactions of allenylic and propargylic halides and tosylates. These reactions are of the S_N1 type; their slow step can be considered to be the reverse of our Cl^--addition step. Since, as we just mentioned, the halides have approximately equal energies, our theoretical predictions are in line with a more rapid solvolysis of propargylic than of allenylic halides. As for Cl^- addition, the condition is that the solvent must have a low solvating power for cations. All these solvolysis reactions were performed in relatively hard aqueous solutions, and indeed all follow the predicted behavior of a faster rate for the propargylic compared with the allenylic isomer.[6] In the second step of these solvolysis reactions, a solvent molecule attacks either the α or the β position. Our calculations predict preferred attack at the α position, and indeed, experimentally, propargylic products are preferentially formed, except when attack at C_α is sterically highly hindered. Actually, in these systems, the ratio of propargylic to allenylic products is even higher than in our pentatriene system because of the presence of different substituents and the use of more aqueous solvents.

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(23) $E_{(tot)\ HC{\equiv}CCH_2Cl} = -573.849\ 70$ hartrees and $E_{(tot)\ H_2C{=}C{=}CHCl} = -573.849\ 99$ hartrees.

The Spiropentyl to 3-Methylenecyclobutyl Cation Rearrangement Avoids CH^+–Trimethylenemethane or the 1-Bicyclo[1.1.1]pentyl Cation

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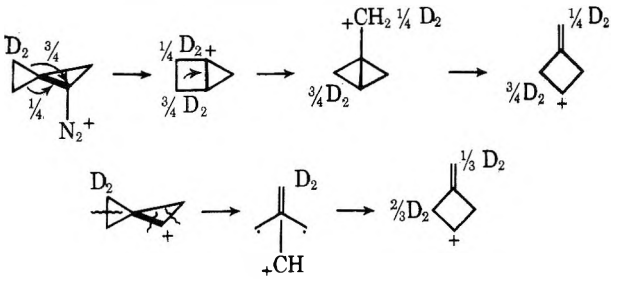
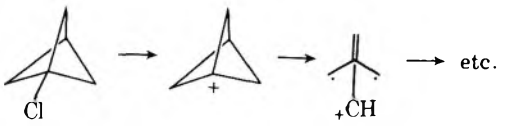
In view of successful efforts to characterize CH^+ complexes of $4n$ cyclic π systems and homologues,[1] the reported deuterium distribution in the 3-methylenecyclobutanol product from deamination of *anti*-4,4-dideuteriospiropentylamine[2] occasioned speculation in our laboratory that CH^+–trimethylenemethane (CH^+–TMM) might be involved. Applequist



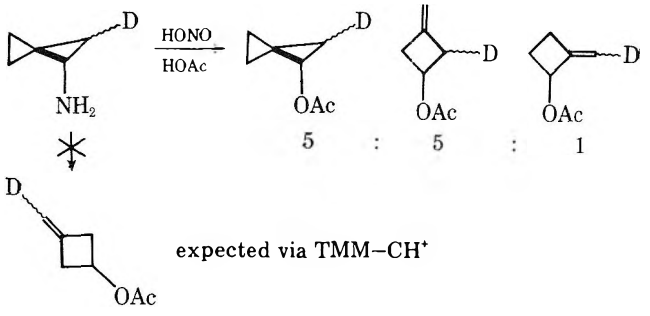
suggested that preferential migration of the anti carbon was involved to give sequentially the 1-bicyclo[2.1.0]pentyl cation, the 1-bicyclo[1.1.0]butylcarbinyl cation, and the 3-methylenecyclobutyl cation, but this was prior to Hoffmann's prediction of stabilization of CH^+–$4n$ π systems.[3] Moreover, Wiberg's[4] observations that 1-bicyclo[1.1.1]pentyl chloride has enormous solvolytic reactivity to 3-methylenecyclobutyl product might also be interpreted in terms of high stability of CH^+–TMM, although relief of ring strain was suggested as



the important factor as well as the possibility of cross-ring interaction with the opposite bridgehead.

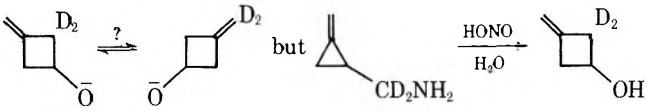
Results and Discussion

In order to distinguish between the Applequist suggestion and the more interesting CH^+–TMM complex, 2-deuteriospiropentylamine was prepared and deaminated in acetic acid. Three products were obtained; these were spiropentyl acetate, 3-methylcyclobutyl acetate, and 2-methylcyclobutyl acetate in ratio 5:5:1. The latter two products (as alcohols) were observed by Applequist in the aqueous deamination; presumably, spiropentanol does not survive the aqueous conditions. The ^2H NMR of the VPC purified reaction mixture revealed the presence of 2-deuteriospiropentyl acetate, 2-deuterio-3-methylenecyclobutyl acetate, and 2-deuteriomethylenecyclobutyl acetate in a 5:5:1 ratio with little, if any, 3-deuteriomethylenecyclobutyl acetate being formed. Thus, substantial incursion of CH^+–TMM (or the 1-bicyclo[1.1.1]pentyl cation) as an intermediate is ruled out, verifying the Applequist proposal of unsymmetrical involvement of C_4 and C_5 in the spiropentylamine deamination.



In view of the large number of isomers that have been sources of the 3-methylenecyclobutyl cation, we here summarize these pathways (Scheme I) indicating those that are ruled out by labeling studies or product distributions. Classical structures are drawn where no experimental distinction between classical or nonclassical behavior has been made.

Concern that Applequist's label distribution could be due to a reversible 1,3-sigmatropic shift in the conjugate base of 3-methylenecyclobutanol, a reaction which may be quite facile by comparison with Evans' Cope rearrangements,[6] does not appear to be the case since Kato isolated unscrambled 2,2-dideuterio-3-methylenecyclobutanol from the deamination of α,α-dideuterio-α-methylenecyclopropylcarbinylamine[5] using workup conditions comparable in acidity to those utilized by Applequist.



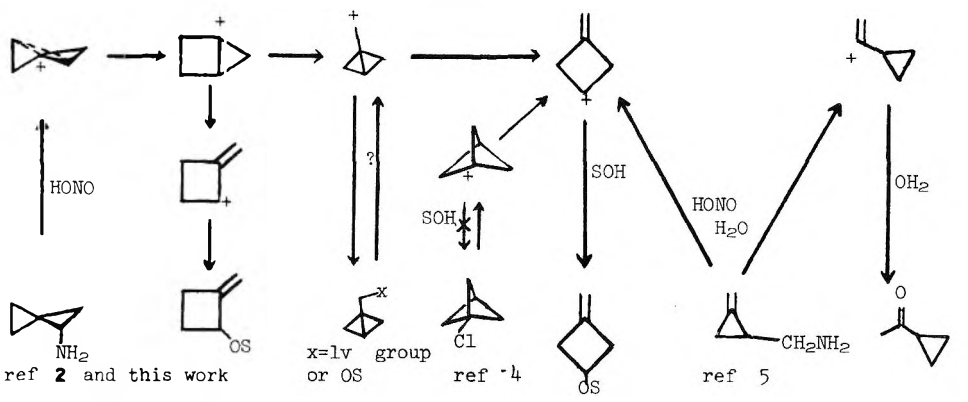
Finally, the isolation of spiropentyl acetate in the spiropentylamine deamination represents one of the few examples of nucleophilic trapping of a cyclopropyl cation which is electronically stabilized but not sterically prevented from ring opening. In the foremost example the 1-cyclopropylcyclopropyl cation is generated by solvolysis[7] or rearrangement;[8] the spiropentyl cation as studied here is generated by acidic deamination.

Experimental Section[10]

2-Deuteriospiropentaneearboxylic acid was prepared from methyl *cis*-β-deuterioacrylate and cyclopropyldiphenylsulfonium fluoroborate by Trost's method.[11] Methyl *cis*-β-deuterioacrylate was prepared by Hill's procedure[12] from methyl 3-deuteriopropiolate, which was prepared from decarboxylation of acetylenedicarboxylic acid monopotassium salt in deuterium oxide, containing 88% of one deuterium as determined by ^1H NMR: ^1H NMR of acid, δ 0.96 (s, 4 H), 1.3 (dd, 1 H, J = 4, 8 Hz), 1.5 (t, 1 H, J = 4 Hz), 1.89 (dd, 1 H, J = 4, 8 Hz), 10 (br s, 1 H). The 2-deuterio material showed a diminution in both upfield single proton resonances.

2-Deuteriospiropentylamine Hydrochloride. 2-Deuteriospiropentanecarboxylic acid azide was prepared by Weinstock's procedure.[13] Thus, rearrangement of 2-deuteriospiropentanecarboxylic acid azide to the isocyanate was effected by heating it in tetrahydrofuran to 110 °C in a sealed tube. After 3 h at that temperature, the tube was cooled and opened, and its contents poured into 20% hydrochloric acid. After stirring under nitrogen, the organic solvent was removed under aspirator vacuum. The acidic aqueous solution was then washed with ether, made basic with aqueous potassium hydroxide, and extracted with pentane. The pentane solution was dried over magnesium sulfate; then gaseous hydrogen chloride was passed over the dry pentane solution, and a white cloud formed immediately. Removal of pentane in vacuo gave 2-deuteriospiropentylamine hydrochloride as a white powder (45% yield from the acid). Spiropentylamine and its acid chloride prepared by this method have the following NMR characteristics: spiropentylamine hydrochloride (in D_2O), δ (relative to H_2O) −1.91 (dd, 1 H, J = 6, 3 Hz), −3.46 (t, 1 H, J = 6 Hz), −3.64 (dd, 1 H, J = 6, 3 Hz), −3.82 (s, 4 H); spiropentylamine (in CCl_4), δ (relative to Me_4Si) 0.55 (t, 1 H, J = 4 Hz), 0.73 (d,

Scheme I



4 H, J = 7 Hz), 0.91 (dd, 1 H, J = 4, 6 Hz), 1.1 (br s, 2 H), 2.41 (dd, 1 H, J = 4, 6 Hz).

Deamination of 2-Deuteriospiropentylamine Hydrochloride. 2-Deuteriospiropentylamine hydrochloride (0.3 g, 5.2 mmol) was dissolved in 10 mL of glacial acetic acid and solid sodium nitrite (0.36 g, 5.2 mmol) was added in small portions over a 3-h period. After standing overnight, an additional 0.36 g of sodium nitrite was added over a 6-h period. The reaction mixture was allowed to stand 2 h after addition of sodium nitrite was complete; then 45 mL of a 10% sodium hydroxide solution was added cautiously. The still acidic reaction mixture was extracted four times with a total of 75 mL of pentane. The combined organic extracts were washed with a 10% sodium bicarbonate solution until the washings were basic. The solution was then washed once with saturated brine and dried over magnesium sulfate. Pentane was removed through a Vigreux column till approximately 1 mL of solution was left. The residue was analyzed by an SE-30 column, revealing a single peak which was collected: ^{2}H NMR (in $CDCl_3$) δ (relative to Me_4Si) 1.25 (two peaks of equal intensity, 5 D), 3.05 (two peaks of equal intensity, 5 D), 5.10 (two peaks of equal intensity, 1 D). In a separate run, spiropentylamine hydrochloride was deaminated in glacial acetic acid. The ^{1}H NMR spectrum [δ (CCl_4) 0.75 (s), 1.0 (m), 1.13 (t), 1.95 (3 s), 2.2~2.5 (br m), 2.75 (br m), 2.95 (br m), 4.1 (dd), 4.82 (p), 4.90 (m), 5.35 (m)] of the single peak on the SE-30 column indicated three acetates. On a 200 °C DBTCP capillary column a 5:5:1 mixture of three compounds was observed. On a UCON preparative column two peaks in a ~1:1 ratio were observed and collected. One peak was spiropentyl acetate; δ 0.79 (m, 3 H), 1.0 (m, 2 H), 1.14 (t, 1 H, J = 6 Hz), 1.96 (s, 3 H), 4.1 (d of d, 1 H, J = 6, 2 Hz).

The second peak was a mixture of 2- and 3-methylenecyclobutyl acetate in a 1:5 ratio: ^{1}H NMR of mixture, δ 1.97 (s, 3 H), 2.0 (s, 0.6 H), 2.40 (v br m, 0.8 H), 2.75 (br m, 2 H), 2.95 (br m, 2H), 4.80 (p, 2 H, J = Hz), 4.9 (m, 1.4 H), 5.35 (m, 0.2 H).

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for partial support of this work.

Registry No.—2-Deuteriospiropentanecarboxylic acid, 64345-60-4; 2-deuteriospiropentanecarboxylic acid azide, 64345-61-5; 2-deuteriospiropentane isocyanate, 64345-62-6; 2-deuteriospiropentylamine hydrochloride, 64345-63-7; 2-deuteriospiropentylamine, 64345-64-8; 2-deuteriospiropentyl acetate, 64345-65-9; 2-deuteriomethylenecyclobutyl acetate, 64345-66-0; 2-deuterio-3-methylenecyclobutyl acetate, 64345-67-1.

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(10) ^{1}H NMR spectra were determined on a Varian HR-220 MHz spectrometer operated in the CW mode; ^{2}H NMR spectra were determined on the same spectrometer operated in the FT mode at 33.77 MHz—a 0.2-ppm downfield shift of deuterium resonances relative to proton resonances were observed. ^{2}H NMR line widths were on the order of 0.06 ppm. Gas chromatography was performed on Varian aerograph A-90 P and 1220-2 series chromatographs using the following columns: $\frac{3}{8}$ in. × 20 ft SE-30; $\frac{1}{4}$ in. × 20 ft UCON 50-HB-2000; and a 200 in. × 0.01 in. i.d. di-*n*-butyl tetrachlorophthalate (DBTCP) capillary column.
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Mass Spectrometry of Pyrimidine Anhydronucleosides

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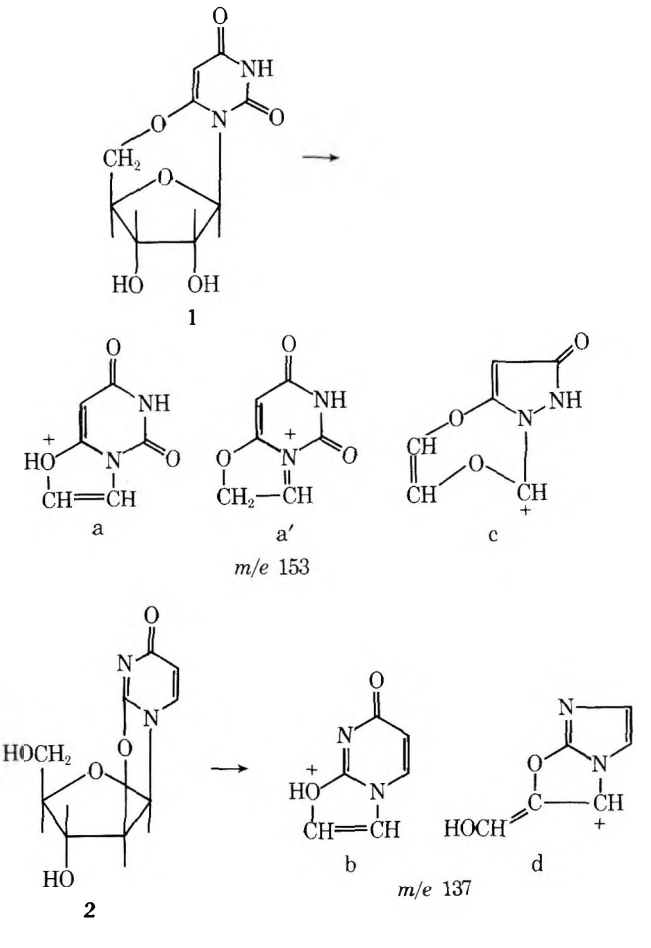
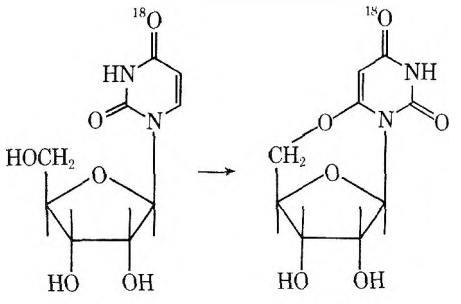
Anhydronucleosides often play an important role in the synthesis of nucleosides,[2,3] and their mass spectra have been shown to be useful for structural characterization (e.g., ref 4–10). The fragmentation reactions of anhydronucleosides are somewhat different from those of conventional nucleosides[11,12] in that conformational rigidity prevents base–sugar hydroxyl interactions that usually generate the primary reaction paths[13] and because of increased complexity of the system due to the anhydro linkage. In the mass spectra of O^6,5′-anhydropyrimidine nucleosides, a decomposition sequence has been proposed in which CO is first eliminated from the molecular ion and in which additional fragmentation of the base proceeds during subsequent reaction steps.[5] The latter rationale contrasts with the general behavior of normal nucleosides in which the heterocyclic base remains intact in initial reaction steps and decomposes only at the stage at which the free base has been generated. However, because initial reaction steps involve loss of neutral species which contain C, H and O but not N, the interpretation of both low- and high-resolution mass spectra is ambiguous, and fragmentation could proceed from either the base or sugar moieties.

The leading examples which clearly demonstrate the principle involved are the intermediate fragment ions *m/e* 153 ($C_6H_5N_2O_3$) from O^6,5′-anhydrouridine (**1**) and *m/e* 137 ($C_6H_5N_2O_2$) from O^2,2′-anhydrouridine (**2**). Originally de-



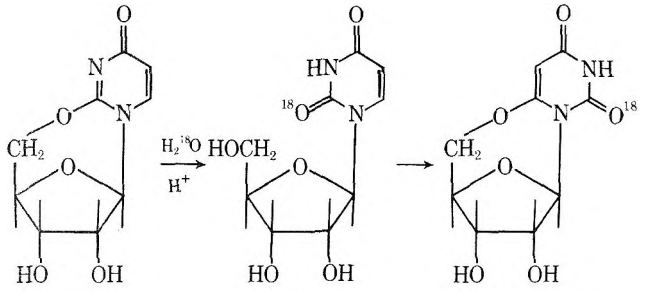
picted as structures a and b,[6] a subsequent and detailed interpretation of the mass spectra led to assignments c and d in which the elements of CO were expelled from the pyrimidine ring.[8] The ion of *m/e* 153 was represented as one step of the sequence *m/e* 242 (M) → 196 → 154 → 153 → 110, in which contraction of the pyrimidine ring was postulated as the first step.

To settle this issue using **1** as a model the ^{18}O-labeled analogue **3** was prepared by cyclization[5,6] of uridine-O^4-^{18}O (**4**).[14]



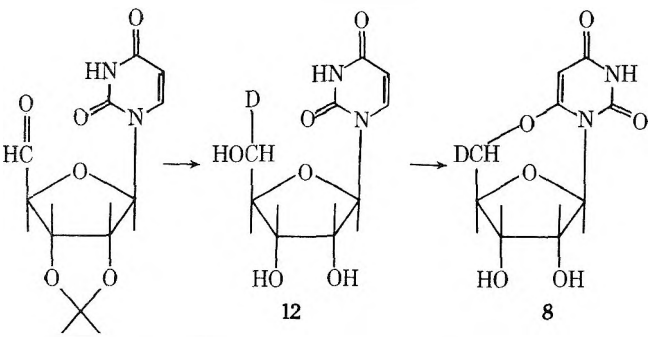
4 **3**

In order to exclude the additional possibility that *m/e* 153 had lost CO from C-2 rather than from C-4, **5** was obtained by opening of **6**[15] in the presence of $H_2{}^{18}O$ and then cyclized to give the O^2-labeled compound **7**. Precursors of ion *m/e* 153 in

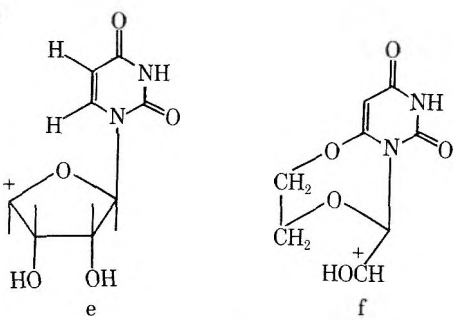


6 **5** **7**

the mass spectrum of **1** were found to be *m/e* 213 (M − CHO), 195, and 154 through detection of metastable ion species by scanning the accelerating voltage with fixed electric sector voltage and fixed magnetic field. Therefore, the monodeuterio model **8** was prepared[16-18] from **9** to distinguish between the assignments previously made as e[6] and f.[8]



9 **12** **8**



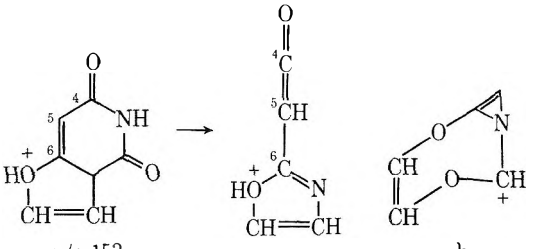
e f

m/e 213

Results and Discussion

Mass spectra of the ^{18}O-labeled compounds **3** and **7** showed essentially complete (~95%) retention of the base labels in all major ions in the upper mass region of the mass spectrum,[8] including *m/e* 153, 154, 195, 196, and 213. Structure a (or its tautomer a′) is thus supported and c is excluded. Analogous results were obtained for the *m/e* 137 fragment ion derived from **2**-O^4-^{18}O.[19] Therefore, structure b is supported and d is excluded, ruling against fragmentation of the pyrimidine ring as a common structural feature. Deuterium labeling at C-5′ (**8**) resulted in a quantitative shift of *m/e* 213, militating against structure e. Ion f or some tautomer is therefore preferred if the original assumption[8] that CHO is expelled from C-3′ rather than C-2′ is correct. The original preference[8] for f over e was expressed on the basis that e should in principle give rise to abundant ions of the base + H (*m/e* 112) and base + 2H (*m/e* 113) type,[20] which were not observed. Although our isotopic-labeling experiment excludes structure e, the earlier reasoning[8] is not necessarily valid. Ions of the base + H type appear to originate mechanistically from precursors in which the charge resides in the base,[13] which is not the case in structure e. Base + 2H ion species are derived principally from base + CH_2O and base + C_2H_4O precursors,[13] which are not significant in the mass spectrum of **1**.

The prominent fragment ion of mass 110 (70% rel int), shown by a metastable transition to be derived from *m/e* 153, was found to contain O^4 and H-5′ but lack O^2. Taking into account the structure of ion a, *m/e* 110 is judged to be formed



m/e 153 g h

m/e 110

by retro-Diels–Alder expulsion of HNCO[21] (ion g), excluding structure h[22] proposed earlier.[8] The O^2-linked anhydronucleoside **2** lacks the required cyclohexene-type structure[23] and so *m/e* 110 is absent.

These results further underscore the complexity of electron impact induced reactions of anhydronucleosides, which evidently involve extensive restructuring of the sugar skeleton. However, in spite of a presently incomplete understanding of the reactions involved, mass spectrometry provides a useful means for characterization of anhydronucleoside structure, with the principal exception that O-2′- and O-3′-linked isomers cannot generally be distinguished.[4,6]

Experimental Section

Thin-layer chromatography was performed using Quanta/Gram Q1F plates (Quantum Industries, Fairfield, N.J.) and preparative thin-layer chromatography utilized SIlicAR 7GF plates of 1000- or 2000-μm thickness (Analtech, Inc., Newark, Del.). Plates were developed in ethyl acetate/1-propanol/water (4:1:2; v/v/v; upper phase). Oxygen-18 enriched H_2O (99%) was purchased from Koch Industries (Cambridge, Mass.) and Norsk-Hydro Sales (New York, N.Y.). Sodium borodeuteride (99%) was purchased from Merck Isotopes (St. Louis, Mo.). Mass spectra were acquired using an LKB-9000S mass spectrometer operating at a 70-eV ionizing energy and an ion source temperature of 270 °C. Metastable ion measurements[24] were made using a CEC 21-110B mass spectrometer.

Samples were checked for purity and extent of ^{18}O incorporation by conversion to the trimethylsilyl derivatives and subjecting the samples to gas chromatography–mass spectrometry [3-ft OV-17 (1%) programmed from 180 °C at 4°/min]. Chromatograms from all samples exhibited a single peak. Underivatized samples were examined

for purity by TLC and mass spectrometry (samples introduced by direct probe). Mass spectra of ^{18}O- and deuterium-labeled compounds whose preparations are described below were identical with the exception of isotopic mass shifts to those from the unlabeled materials; peaks due to impurities or starting materials were absent.

Uridine-O^2-^{18}O (5). A solution of O^2,5′-anhydrouridine (**6**)[15] (180 mg) in $H_2{}^{18}O$ (99%) (250 μL) and concentrated HCl (25 μL) was heated at 90 °C for 1.5 h. The reaction mixture was cooled and applied to three 20 × 20 cm preparative TLC plates (2000 μm). The band corresponding to uridine was scraped from the plate and eluted with MeOH until no more UV-absorbing fractions were eluted. The MeOH was evaporated in vacuo. The residue was crystallized from aqueous EtOH (99%) to give 80 mg (40%) of **5**. Mass spectral analysis showed 90% incorporation of ^{18}O (correction for dilution of the $H_2{}^{18}O$ by $H_2{}^{16}O$ of the HCl showed quantitative incorporation of ^{18}O).

5-Iodouridine-O^2-^{18}O (10). A solution of dioxane (9 mL) and 0.5 N HNO_3 (1 mL) containing I_2 (160 mg) and **5** (80 mg) was refluxed for 3 h.[25] The reaction mixture was cooled and applied to a 20 × 20 cm preparative TLC plate. The plate was developed and scraped, and the band corresponding to **10** was eluted with MeOH. After evaporation of the MeOH, the residue was crystallized from EtOH to give 60 mg (50%) of **10**.

O^6,5′-Anhydrouridine-O^2-^{18}O (7). A solution of **10** (60 mg) in dry Me_2SO (10 mL) was added rapidly to a solution of potassium *tert*-butoxide in dry *tert*-butyl alcohol (10 mL) under nitrogen.[5,6] The solution was stirred for 24 h at 70 °C and excess potassium *tert*-butoxide was destroyed with water. The reaction mixture was applied to water-washed Dowex-50 (H^+) (3 mL) and washed with water until no more UV-absorbing fractions were eluted. The eluate was taken to dryness in vacuo and the residue crystallized from EtOH to give 18 mg (46%) of **7**.

5-Iodouridine-O^4-^{18}O (11). Prepared like **10** above except that uridine-O^4-^{18}O (90% ^{18}O)[14] (80 mg) was used as starting material, yield 60 mg (50%).

O^6,5′-Anhydrouridine-O^4-^{18}O (3). Prepared like **7** above using **11** (60 mg) as starting material, yield 20 mg (51%).

Uridine-5′-*d* (12). A solution of 2′,3′-*O*-isopropylideneuridine-5′-aldehyde (**9**)[16] (1.6 g) in EtOH (50 mL) and sodium borodeuteride (99%) was stirred at room temperature for 1 h. The solvent was evaporated in vacuo and the residue extracted with hot acetone (3 × 25 mL). The residue, after evaporation of the acetone under reduced pressure, was covered with aqueous trifluoroacetic acid (10 mL) and stirred at room temperature for 10 min.[18] Trifluoroacetic acid was removed under reduced pressure and the oil residue was triturated with ether until an off-white solid was obtained. After decantation of the ether, the solid was crystallized from EtOH to give 750 mg (54%) of **12** from **9**. Mass spectral analysis showed 95% incorporation of deuterium at the 5′ position.

5-Iodouridine-5′-*d* (13). Prepared like **10** above except **12** (100 mg) was used as starting material, yield 70 mg (51%).

O^6-5′-Anhydrouridine-5′-*d* (8). Prepared like **7** above except **13** (78 mg) was the starting material, yield 24 mg (47%).

Acknowledgments. The authors are indebted to the National Institutes of Health for support of this work (CA 18024, GM 13901). K.H.S. was recipient of an National Institutes of Health Postdoctoral Fellowship (CA 02466).

Registry No.—**3,** 64235-90-1; **5,** 64235-89-8; **6,** 22329-20-0; **7,** 64252-84-2; **8,** 64235-87-6; **9,** 27999-65-1; **10,** 64235-86-5; **11,** 64235-85-4; **12,** 64235-88-7; **13,** 64235-84-3.

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Enhanced Nucleophilic Reactivity (α Effect) in the Reaction of Peroxobenzoate Anions with *p*-Nitrophenyl Acetate[1]

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Progress in the experimental study of enhanced nucleophilic reactivity (α effect) and the theoretical interpretation of the phenomenon has recently been reviewed by Hudson.[2] Although peroxo anions are recognized as α nucleophiles,[3] few species of this type have been studied,[4,5] probably as a result of the difficulties in preparing the materials, and no systematic investigation of structure–nucleophilic reactivity relationships has been reported. The present work forms part of a study of oxidations by peroxo acids in aqueous solution, relating particularly to hydroperoxidase enzyme systems,[6] in which nucleophilic attack by the peroxo anion may be an important component of the oxidation pathway. We report studies of the nucleophilic reactivity of the peroxobenzoate anion and nine substituted peroxobenzoate anions toward *p*-nitrophenyl acetate, a choice of substrate which permits comparison with a wide range of data in the literature.[4,7]

Experimental Section

Kinetic measurements were made using procedures described in the literature[4] (pseudo-first-order conditions; initial [peroxo acid]/[*p*-nitrophenyl acetate] was >10:1; pH 10 ($NaHCO_3/Na_2CO_3$ buffer); ionic strength 0.1 mol L^{-1} ($NaNO_3$); 25 ± 0.2 °C), recording the release of the *p*-nitrophenolate ion at 402 nm. Peroxobenzoic acid and *m*-chloroperoxobenzoic acid were recrystallized (3:1 v/v, petroleum ether/diethyl ether) to give materials of purity >99%. Other peroxobenzoic acids were ~85% pure, the only significant impurity being the respective parent carboxylic acid. The pK_a values (Table I) were determined by potentiometric titration[8] (25 °C, ionic strength approximately constant at 0.1 mol L^{-1} ($NaNO_3$)). Solutions were checked cerimetrically to ensure that no hydrogen peroxide was present. Calculated second-order rate constants (Table I) were corrected for the "blank rate" in buffer solution alone. EDTA (5×10^{-4} mol L^{-1}) was added in a number of experiments but had no influence on the rate.

Results and Discussion

The nucleophilic reactivity of the meta- and para-substituted peroxobenzoate anions varies systematically with basicity, giving a Brønsted slope of 0.38 (Figure 1, a). The data for *o*-chloroperoxobenzoate falls on the line described by the meta- and para-substituted analogues, whereas *o*-nitro- and

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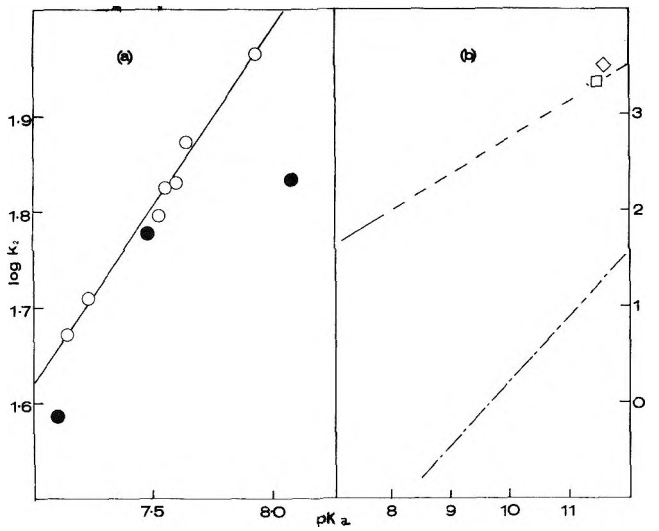

Figure 1. Brønsted-type correlations of log k_2 vs. pK_a for the reaction of oxygen nucleophiles with *p*-nitrophenyl acetate: (a) ○, meta- and para-substituted peroxobenzoic acids, ●, ortho-substituted peroxobenzoic acids; (b) – – –, data described in this work; – · –, data of ref 6 for phenoxides and alkoxides; ◇, HOO^- (ref 3); □, CH_3OO^- (ref 3).

Table I. Nucleophilic Reactivities of Peroxobenzoate Anions (PBA) toward *p*-Nitrophenyl Acetate[a]

Anion	Registry no.	pK_a[b]	k_2,[c] L mol^{-1} s^{-1}
p-OMe-PBA	64235-66-1	7.93	92.4
PBA	35683-46-6	7.64	74.7
p-Cl-PBA	64235-65-0	7.60	67.9
p-SO_3^--PBA	64235-73-0	7.56	67.1
m-Cl-PBA	64235-64-9	7.53	62.6
m-NO_2-PBA	64235-63-8	7.23	51.5
p-NO_2-PBA	64235-62-7	7.14	47.1
o-CO_2^--PBA	7770-90-3	8.08	68.3
o-Cl-PBA	64235-61-6	7.48	60.0
o-NO_2-PBA	64235-60-5	7.10	38.7

[a] Registry no.: *p*-nitrophenyl acetate, 830-03-5. [b] Measured at ionic strength 0.1 mol L^{-1} (sodium nitrate as added electrolyte), 25 °C. [c] At 25 °C, ionic strength 0.1 mol L^{-1}, pH 10 ($NaHCO_3$/Na_2CO_3 buffers).

o-carboxyperoxobenzoate, which may exhibit steric effects and pK_a values influenced by intramolecular H bonding, show experimental values below the line. Comparison of the pK_a values of the meta- and para-substituted peroxobenzoic acids with those of their parent benzoic acids gives a Hammett ρ value of 0.67.

The Brønsted correlation may be extrapolated to comprehend the activities of hydroperoxide and methyl hydroperoxide anions (Figure 1, b). Jencks and Gilchrist[7] have shown that, when data for "normal" oxygen anion nucleophiles over a wide range of basicity are considered, the Brønsted plots are nonlinear, the slope varying from 1.0 for nucleophiles which are less basic than the leaving group to a limiting value of about 0.3 for nucleophiles of high basicity. They have classified the reactions into two limiting types on the basis of this behavior. In these terms, the sensitivity to basicity of peroxo anion nucleophiles approaches limiting type I behavior, although normal nucleophiles show a much greater sensitivity in this range of basicity.

A variety of bases for quantitation of the α effect have been employed. In most recent experimental and theoretical work,[2] the comparison is made between an α nucleophile and a normal nucleophile of similar basicity (phenoxides and alkoxides in the case of oxygen anion nucleophiles). As shown in Figure 1 (b), this basis of comparison yields α effects of 10^2–10^3, increasing with decreasing nucleophile basicity in accord with the general decrease in the α effect with increasing pK_a of oxime nucleophiles in alkylation, acylation, and phosphorylation, as noted by Hudson.[2]

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The Chemistry of Benzyl Hydroperoxide

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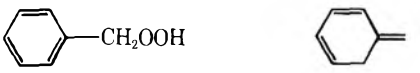
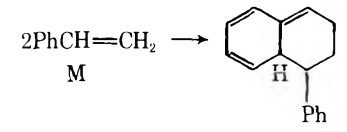
Although benzyl hydroperoxide (BHP) was synthesized a number of years ago,[1] very little data on its stability in solution have been reported.[2] Therefore, we report here the results of a study of BHP, including its rate of decomposition in an inert solvent and in styrene, the rate of polymerization of styrene initiated by benzyl hydroperoxide, and the chain-transfer constant of BHP in styrene.



BHP MCH

Our interest in BHP derives from a study underway in our laboratory of the chemistry of 5-methylene-1,3-cyclohexadiene (MCH). We are studying MCH as a model for the Diels–Alder dimer of styrene, AH, a molecule that is postulated[3] to be responsible for the initiation of the polymerization of styrene by a molecule-assisted homolysis[4] of a C–H bond (eq 1–3).[3b] We have studied the initiation of polymerization



(1)

$$AH + M \longrightarrow A\cdot + HM\cdot \quad (2)$$

$$A\cdot(HM\cdot) + M \longrightarrow M_n\cdot \quad (3)$$

of styrene by MCH,[5] and, since benzyl hydroperoxide is a potential impurity in MCH, we found it necessary to measure the dependence of the rate of polymerization of styrene on BHP as well.

We have observed that BHP is formed by air oxidation of MCH at room temperature in $CHCl_3$ solvent. Although we have not studied this process in detail, the mechanism may proceed with an initiation reaction involving MCH and oxygen

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Table I. Modes of Decomposition of Benzyl Hydroperoxide in 8.35 M Styrene at 60 °C

$[PhCH_2OOH] \times 10^3$	$k_d \times 10^5$,[c] s^{-1}	$R_i \times 10^9$,[a] M/s	Fraction consumed: By initiation	By chain transfer[b]	By other reactions
7.83	0.9	5.0	0.04	0.03	0.93
3.76	1.4	2.7	0.03	0.01	0.96
2.50	1.8	2.0	0.02	0.01	0.97

[a] Calculated from Figure 1 and eq 1. [b] Rate of transfer equals $C[PhCH_2OOH]R_p/[M]$. [c] The reaction is assumed to be first order in BHP. The correlation coefficients of the three runs listed here for plots of log [BHP] vs. time are 0.96, 0.99, and 0.99. Correlation coefficients of these data plotted for second-order kinetics in BHP are 0.97, 0.99, and 0.98. See discussion in the text.

(eq 4), followed by a chain sequence (eq 5 and 6).[6]

$$MCH + O_2 \longrightarrow PhCH_2\cdot + HO_2\cdot \quad (4)$$

$$PhCH_2\cdot + O_2 \longrightarrow PhCH_2OO\cdot \quad (5)$$

$$PhCH_2OO\cdot + MCH \longrightarrow \underset{BHP}{PhCH_2OOH} + PhCH_2\cdot \quad (6)$$

A number of reports on other hydroperoxides demonstrate that hydroperoxides undergo a decomposition in olefins like styrene at a rate that is greatly accelerated over that observed in "inert" solvents such as alkanes.[7] The rate of polymerization of monomers like styrene also is greater than would be predicted from the rate of decomposition of hydroperoxides measured in nonolefin solvents. Several proposals that rationalize these accelerated rates have been published.[7b-d,8]

We observed that the rate of decomposition of an approximately 0.02 M solution of BHP in octane is slow at 100 °C. The apparent first-order rate constant is 5.4×10^{-7} s^{-1}, corresponding to a half-life of 15 days. The rates of decomposition of hydroperoxides are often reported to be of a kinetic order in hydroperoxide greater than unity.[7] However, first-order kinetic plots of the logarithm of the BHP concentration vs. time for our data have correlation coefficients greater than 0.99, whereas second-order plots show slight but noticeable curvature. Thus, our data do not require the postulation of a decomposition that is more complex than first order for BHP in octane.

As expected, the rate of decomposition of BHP in styrene is accelerated over that observed in octane. The data could be plotted with virtually equal precision in plots that are either first or second order in BHP.[9] (Data in styrene were less precise than in octane because the polystyrene precipitates during the iodometric titration.) From analogy with our results in octane, we have assumed that the decomposition of BHP in styrene is first order in BHP, and Table I shows the rate constants calculated in this way at 60 °C. The rate constant of approximately 1×10^{-5} s^{-1} at 60 °C is approximately 20 times faster than the rate in octane at 100 °C.

Benzyl hydroperoxide initiates the polymerization of styrene. The rate of polymerization, R_p, due to an initiator I is given by eq 7,[8,10]

$$R_p = \frac{k_p[M]R_i^{0.5}}{(2k_t)^{0.5}} = \frac{k_p[M](k_d f[I])^{0.5}}{k_t^{0.5}} \quad (7)$$

where k_d is the rate constant for decomposition of I and f is the efficiency of the decomposition in producing free radicals. Figure 1 shows a plot of the rate of polymerization vs. the square root of the BHP concentration, and it can be seen that eq 7 is obeyed. If the value of $2k_t/k_p^2$ is taken as 1722 at 60 °C,[11] then the value of R_i for BHP is calculated to be 5.1×10^{-9} M s^{-1} for 8×10^{-3} M BHP. The value of $k_d f$, therefore, is 6.4×10^{-7} s^{-1} at 60 °C.

In styrene, BHP decomposes partly by an induced process in which polystyryl radicals attack the peroxide (eq 8).

$$M_n\cdot + PhCH_2OOH \rightarrow M_nH + PhCH_2OO\cdot \quad (8)$$

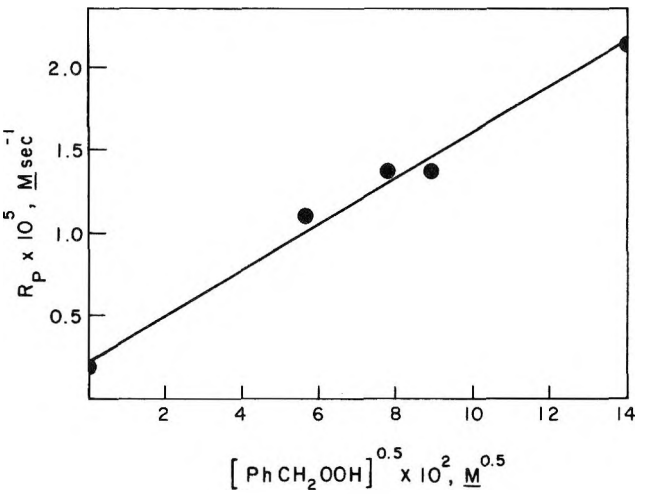

Figure 1. A plot of the rate of polymerization vs. the square root of the concentration of benzyl hydroperoxide at 60 °C.

The rate constant for this process can be obtained from the chain-transfer constant, $C = k_{tr}/k_p$. Using standard techniques,[12] we have determined the transfer constant of BHP to be 0.15 at 60 °C in styrene, a value that is consistent with values reported for other hydroperoxides.[13] Despite the large transfer constant, only a small fraction of the BHP decomposes by chain transfer (see Table I).

By comparing the total rate of decomposition of BHP in styrene (determined by iodometric titration) with values of R_i, the efficiency of initiation can be determined; our data give f, the efficiency, as 0.04. Thus only about 4% of BHP disappears in styrene to give free radicals that initiate polymerization. The majority of the BHP decomposes by other than radical pathways or by cage processes that do not produce free radicals.[7] Table I summarizes the importance of various modes of decomposition observed for BHP in styrene.

Finally, some comment seems appropriate concerning our observation of the rapid oxidation of 5-methylene-1,3-cyclohexadiene (MCH) to benzyl hydroperoxide. We have not optimized the conditions for this oxidation, but it is dependent both on the solvent, being much faster in chloroform than in octane or benzene, and on the method of preparation (and presumably the impurities) in MCH.[14] It is clear that the oxygenation reaction occurs with MCH and not toluene, since attempts to prepare BHP by autoxidation of toluene have failed.[15] The secondary hydrogens in MCH are very labile,[4] and it seems reasonable that reaction 4 would be fast for MCH if it occurs at all.[6,16]

Experimental Section

Solvents. Heptane and octane were first washed with a mixture of concentrated H_2SO_4 and HNO_3, dried, distilled, and passed through a silica gel column. Styrene was commercial material which was purified by first washing with 10% NaOH to remove inhibitor, fractionating under reduced pressure, and then refractionating and fil-

tering through alumina just before use: bp 46–47 °C (15 mmHg).

Benzyl hydroperoxide (BHP) was prepared in low yield by the method of Walling and Buckler[1] and purified by column chromatography (silica gel, CH_2Cl_2) and vacuum transfer to give material 96% pure by iodometric titration.[17] The NMR spectrum in $CDCl_3$ is δ 4.83 (s, 2 H, CH_2), 7.28 (m, 5 H, phenyl), 8.6 (br s, variable with temperature, 1 H, OOH).[18] The BHP prepared in this way is identical in all respects with the product of oxidation of 5-methylene-1,3-cyclohexadiene.

Samples were prepared in 10-mL drying ampules fitted with "O" ring seals for attachment to a vacuum line. The ampules were cleaned by soaking in concentrated HNO_3, washing thoroughly with water, and drying at 110 °C. The appropriate amount of hydroperoxide was dissolved in solvent and samples were pipetted into the reaction vessels. The ampules were degassed by at least three freeze-thaw cycles and then sealed at 5×10^{-5} mmHg.

Decomposition in octane was carried out by immersion of ampules containing 1-mL samples in a 100.2 °C oil bath. Concentration of hydroperoxide was followed through 80% reaction by titration[17] of samples removed at regular intervals.

Decomposition in styrene was carried out as above on 5-mL samples through 40% reaction at 60.0 °C. Due to the increase in viscosity of the styrene solutions and probably the trapping of hydroperoxide in the polymer (which precipitates during analysis), the precision is less than in octane.

Polymerization rates at 60.0 °C were determined gravimetrically by precipitation of the polymer in cold methanol. The styrene solution (5 mL) was first diluted with a small amount of toluene (2–3 mL) and then very slowly pipetted into 400 mL of reagent-grade methanol at 10 °C. The precipitated polymer was filtered on a sintered glass funnel and brought to constant weight under vacuum. Rates were determined for the first 5% conversion of monomer.

Chain-transfer constant of benzyl hydroperoxide was determined by standard methods[12] from the intrinsic viscosity of polymer solutions in benzene. Concentrations of hydroperoxide from 9×10^{-4} to 8×10^{-3} M were used.

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Registry No.—BHP, 3071-34-9; octane, 111-65-9; styrene, 100-42-5.

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Direct α-Lithiation of Phenoxyacetic Acid and Electrophilic Substitution

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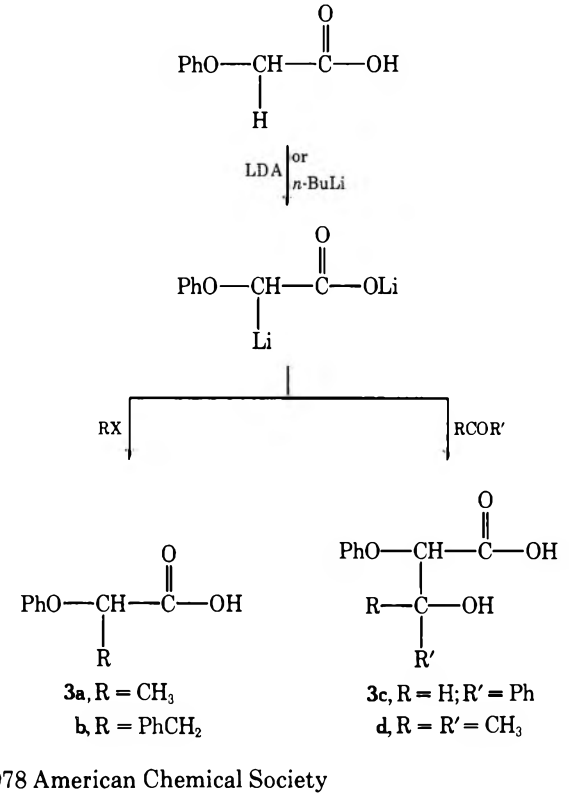
The destabilization exerted by juxtaposed oxygen atoms on carbanionic centers is well recognized.[2] This effect is most dramatically accentuated in the side-chain metalation of thioanisole vs. ring metalation of anisole by *n*-butyllithium.[3] A powerful synthetic utilization has been the Corey–Seebach reagent,[4] prepared by direct metalation of 1,3-dithiane with *n*-butyllithium, conditions which fail to produce the corresponding 2-carbanion from 1,3-dioxane.[2a] However, allylic ethers were recently[5] converted efficiently into allyloxy carbanions with *sec*-butyllithium, and α-alkoxynitrile carbanions[6] have been used as synthons, showing that the destabilizing influence of the α-oxygen atom can be moderated by conjugation. In fact the enolate ion of 2-carbomethoxy-1,3-dioxolane was formed only fivefold slower than that of the carbocyclic analogue, i.e., 2-carbomethoxycyclopentane, in the methoxide-catalyzed deuterium exchange.[7]

These facts suggested that it should be possible to prepare stable solutions of the hitherto unknown enolate **2** by metalation of phenoxyacetic acid with strong bases such as *n*-butyllithium or lithium diisopropylamide (LDA).[8] The potential usefulness of such a α-lithiocarboxylate **2** as synthon encouraged us to explore the direct lithiation of phenoxyacetic acid (**1**). Presently we report our successful generation of this enolate and its reaction with electrophiles.

Treatment of phenoxyacetic acid (**1**) in THF with stoichiometric amounts (2 mol) of *n*-BuLi at −78 °C generated



3a, R = CH_3
b, R = $PhCH_2$
3c, R = H; R' = Ph
d, R = R' = CH_3

a clear yellow solution. Deuteration of the reaction mixture with excess D_2O and NMR analysis of the reisolated acid **1** confirmed that the enolate **2** was formed in ca. 80% yield. Some carbonyl addition had also taken place. Since excess *n*-BuLi had to be avoided in view of the troublesome carbonyl addition, we decided to use LDA as base catalyst. At −78 °C in THF and 100% excess LDA the phenoxyacetic acid (**1**) was converted in over 90% yield to the α-lithiocarboxylate **2** as yellow solution, confirmed by NMR analysis of the deuterated reaction mixture.

The reaction of the phenoxy enolate **2** with common electrophiles proceeded smoothly. Discoloration of the characteristic yellow color of the α-lithiocarboxylate **2** took place immediately on addition of the electrophile. Thus, the enolate **2** afforded 2-phenoxypropionic acid (**3a**) with methyl iodide, 2-phenoxy-3-phenylpropionic acid (**3b**) with benzyl bromide, and the diastereomeric 3-hydroxy-2-phenoxy-3-phenylpropionic acids (**3c**) with benzaldehyde in good yields. These condensation products were identified on the basis of literature reported physical constants and NMR and IR spectral data. With acetone as electrophile the enolate **2** gave the unknown 3-hydroxy-3-methyl-2-phenoxybutyric acid (**3d**) in ca. 80% yield, mp 62 °C (from hexane–benzene, as hydrate) and 77 °C (sublimed, as free acid). The structure of **3d** is based on the correct elemental analysis and IR and NMR spectral data.

We are now extending this direct lithiation method to alkoxy-, diaryloxy-, and dialkoxyacetic acids and are planning to utilize these novel enolates as synthons.

Experimental Section

Microanalyses were performed by Galbraith Laboratories Inc., Knoxville, Tenn. Melting points are uncorrected. NMR spectra were run on an Hitachi Perkin-Elmer R-24B instrument and IR spectra on a Perkin-Elmer 237B Infracord. Solvents and reagents were purified and starting materials were prepared and purified according to standard, published procedures.

General Procedure. A dry, 50-mL, two-necked, round-bottom flask, provided with magnetic spinbar, rubber septum, and three-way stopcock, was attached to a nitrogen manifold and flushed with dry nitrogen for at least 5 min while flame-drying. While under a positive nitrogen gas pressure (ca. 50 mm, regulated with a mercury bubbler), the reaction vessel was charged by means of a syringe with 1.62 g (16 mmol) of diisopropylamine (freshly distilled from calcium hydride) and 20 mL of anhydrous THF (freshly distilled from benzophenone ketyl radical). By means of a dry ice–methanol bath the reaction flask was cooled to −78 °C and while stirring vigorously 16 mmol of *n*-butyllithium in *n*-hexane (standardized by acidimetry) was added by means of a syringe. After complete addition (ca. 5 min) the cooling bath was removed and the reaction mixture was allowed to reach room temperature (ca. 30 °C) while stirring. After ca. 10 min the contents were cooled again to −78 °C and by means of a syringe 608 mg (4 mmol) of phenoxyacetic acid in 5 mL of anhydrous THF was added while magnetically stirring. The yellow solution was stirred at −78 °C for 15 min and subsequently ca. 8 mmol (200% excess) of the electrophile was added and allowed to stir at −78 °C for 15–60 min until complete disappearance of the yellow color.

The reaction mixture was poured onto ca. three to five times crushed ice and extracted with 2 × 20 mL of ether and the aqueous layer acidified with 10% hydrochloric acid until pH ca. 3. The product was extracted with 5 × 20 mL of ether, the combined extracts were dried over anhydrous $MgSO_4$, and after rotoevaporation, first at ca. 30 °C (25 mmHg) and finally at ca. 30 °C (1 mmHg), the residue was purified by recrystallization. The individual cases are detailed below. Yields have not been optimized.

2-Phenoxypropionic acid (3a) was prepared in 70% yield by the above procedure, mp 112–114 °C from water (lit.[9] mp 115–116 °C), by adding 1.15 g (8 mmol) of methyl iodide at −78 °C and stirring for 30 min.

2-Phenoxy-3-phenylpropionic acid (3b) was prepared in 50% yield by the above procedure, mp 82 °C from methanol/water (1:2) (lit.[10] mp 81 °C), by adding 1.37 g (8 mmol) of benzyl bromide at −78 °C and stirring for 60 min.

3-Hydroxy-2-phenoxy-3-phenylpropionic acid (3c) was prepared in 50% yield by the above procedure, mp 116–117 °C from hexane/benzene (1:1) (lit.[11] mp 93–94 °C), by adding 0.85 g (8 mmol) of benzaldehyde at −78 °C and stirring for 15 min.

3-Hydroxy-3-methyl-2-phenoxybutyric acid (3d) was prepared in 80% yield by the above procedure, mp 62 °C as hydrate (needles from benzene/hexane) and 77 °C after sublimation, by adding 0.93 g (16 mmol) of acetone at −78 °C and stirring for 15 min. The spectral data are: IR ($CHCl_3$) 3500–2500 (OH and CO_2H) and 1740 cm^{-1} (C=O); ^1H NMR (60 MHz) δ ($CDCl_3$, Me_4Si) 1.45 (6 H, s, CH_3), 4.40 (2 H, s, OH and CO_2H), 4.45 (1H, s, O–C–H), and 6.7–7.4 (5 H, m, C_6H_5); mass spectrum (70 eV) *m/e* (rel) 210 (11.0), 152 (99.6), and 107 (100). Anal. Calcd for $C_{11}H_{14}O_4H_2O$: C, 57.89; H, 7.07. Found: C, 57.75; H, 7.15.

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Registry No.—**3a**, 940-31-8; **3b**, 64682-83-3; **3c**, 64682-84-4; **3d**, 64682-85-5; phenoxyacetic acid, 122-59-8; LDA, 4111-54-0; *n*-butyllithium, 109-72-8; methyl iodide, 74-88-4; benzyl bromide, 100-39-0; benzaldehyde, 100-52-7; acetone, 67-64-1.

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Pyrolysis of *N*-*p*-Toluenesulfonylsulfilimines[1]

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Sulfilimines (**1**) have received considerable attention in the past several years with respect to their synthesis[2] as well as their chemistry.[3] Of particular interest to us have been studies relating to the pyrolysis of sulfilimines. Both Swern[4] and Oae[5] have noted that pyrolysis of sulfilimines in which one of the sulfur substituents contains a β hydrogen (e.g., **2**)

1 **2**

results in a facile elimination yielding an alkene and a sulfenamide. More recently the pyrolysis of *N*-toluenesulfonylsulfilimines in which no β hydrogens are present has been reported.[6] Various solvents were used, and the products obtained depended markedly on the nature of the solvent. We have found[1] that in the absence of solvent the pyrolysis of *N*-toluenesulfonylsulfilimines yields a significantly different mixture of products, and we wish to report those results.

Results and Discussion

The pyrolytic decomposition of *S*,*S*-dimethyl-*N*-*p*-tosylsulfilimine **3** in the absence of solvent at 300 °C yielded the

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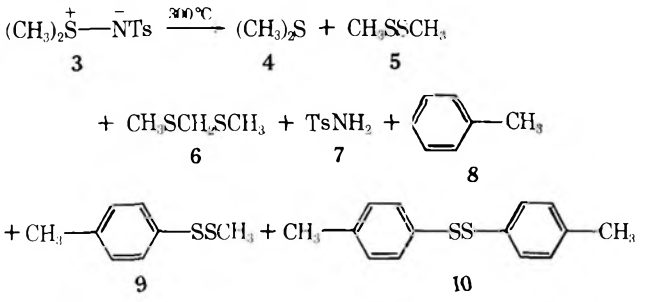
Table I. Pyrolysis of *S,S*-Dimethyl-*N*-tosylsulfilimine (3)[a]

Compd	Registry no.	Yield, mmol	yield (rel),[b] mol	% yield[c]
4	75-18-3	0.339	0.109	11
5	624-92-0	0.288	0.092	18
6	1618-26-4	0.578	0.185	37
7	70-55-3	0.877	0.281	28
8	10888-3	0.500	0.160	16
9	57266-34-9	0.15	0.048	10
10	103-19-5	0.264	0.085	17

[a] Yields are given for pyrolysis of 3.12 mmol of 3 at 300 °C for 1 h. [b] Assuming number of moles of 3 = 1.00. [c] Calculated based on available sulfur and tolyl groups.

Scheme I



products shown in Scheme I. The yields, as noted in Table I, account for 71% of the "*S*-methyls" and 66% of the "tolyl" groups present in the starting sulfilimine. In order to determine if products **8**, **9**, or **10** were arising from thermal decomposition of initially formed toluenesulfonamide (**7**), pyrolysis of this substance was carried out. The only product which could be identified was toluene; disulfides **9** and **10** were not found to be present.

In marked contrast to the complexity of the pyrolysis of **3**, decomposition of *S,S*-diphenyl-*N*-*p*-tosylsulfilimine **11** under identical conditions yielded only diphenyl sulfide, toluenesulfonamide, and a trace of toluene. The low yield of toluenesulfonamide is presumably accounted for by the tarry residue also formed in the pyrolysis which, when totalled with the products isolated, raises the material recovery to over 90%.

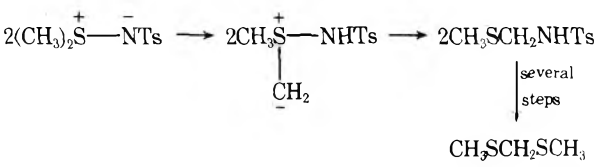
$$\underset{\mathbf{11}}{(C_6H_5)_2S^+-N^-Ts} \xrightarrow{300\ ^\circ C} \underset{(90\%)}{(C_6H_5)_2S} + \underset{(32\%)}{TsNH_2} + \underset{(\text{trace})}{C_6H_5CH_3}$$

The complexity of the pyrolysis of **3** precludes writing a simple mechanism for the process, and in the absence of any direct experimental evidence, mechanistic details must remain speculative. Certain points are worthy of note, however. The relative simplicity of the pyrolysis of **11** suggests that the α hydrogens of **3** play a significant role in the decomposition process. The pyrolysis of the *N*-acetylsulfilimine **12** was found[4] to give, as the major product, the sulfide **6**. It was suggested that abstraction of an α hydrogen followed by a Pummerer type rearrangement would lead to the observed product. Such a process might be proposed for the formation of **6** as the major product in the pyrolysis of **3**, as outlined in Scheme II.

$$\underset{\mathbf{12}}{(CH_3)_2S^+-N^-COCH_3} \xrightarrow{\Delta} \underset{\mathbf{6}}{CH_3SCH_2SCH_3} + \text{other products}$$

One other mechanistic point worthy of mention involves the possible intermediacy of a nitrene (or nitrene-like) species in the decomposition process. Several authors[2c,d,7] have suggested initial formation of nitrenes in sulfilimine pyrolyses, although these species have not been trapped, as they have been in studies of sulfilimine photolysis.[3d] In our work, the formation of dimethyl sulfide might be viewed as arising from heterolytic cleavage of the S-N bond, simultaneously generating a tosylnitrene (or nitrene-like) species. Tolyl radical formation (presumably necessary for formation of toluene and disulfides **9** and **10**) could then be the result of decomposition of this species. As we have no direct experimental evidence bearing on this point, however, we can only speculate as to the intermediacy of a nitrene in our system.

Scheme II



Experimental Section

IR spectra were obtained as $CHCl_3$ or CCl_4 solutions using a Perkin-Elmer Model 137 infracord spectrophotometer. NMR spectra were obtained with a Perkin-Elmer Model R-20 or R-24 spectrometer using $CDCl_3$ as solvent and Me_4Si as internal standard. Mass spectra were obtained on a Hitachi Perkin-Elmer Model RMU-6E spectrometer.[8] Melting points were obtained with a Thomas-Hoover apparatus and are uncorrected. VPC analyses were carried out on a Varian Model 920 chromatograph fitted with a 15 ft., 10% SE-30 on Chromosorb W column.

S,S-Dimethyl-N-p-toluenesulfonylsulfilimine (3). Following the procedure of Mann and Pope,[9] a solution of chloramine-T (10.0 g, 0.035 mol) in 100 mL of water was chilled in ice and shaken with 2.5 g (3.0 mL, 0.040 mol) of dimethyl sulfide. The white solid which formed was filtered, washed with cold water, and allowed to air dry. Recrystallization with benzene yielded 5.00 g (53%) of the pure product as white needles, mp 157–158 °C (lit.[10] mp 157–158 °C).

Pyrolysis of 3. Crystalline sulfilimine (0.72 g, 3.12 mmol in a typical run), contained in either a Pyrex or a procelain boat, was placed in a 25 mm o.d. Vycor tube horizontally mounted and connected to a cold trap. The system was flushed with N_2 and then heated to 300 °C for 1 h with a tube furnace (Lindberg "Hevi-Duty"). Throughout the heating period a flow of ca. 30 mL/min of N_2 was maintained. Volatile products were collected by cooling the trap to −196 °C. After warming to room temperature the products in the trap were dissolved in a small amount of benzene, and this solution used for VPC analysis. The products were identified as follows: Dimethyl sulfide (**4**) (21.0 mg, 0.339 mmol[11]) identified by IR comparison with a known sample. Dimethyl disulfide (**5**) (27.1 mg, 0.288 mmol): IR (CCl_4) 1420, 1300, 955 cm^{-1} (identical with the IR of an authentic sample[12]); NMR δ 2.38(s); mass spectrum *m/e* 94 (M^+, $C_2H_6S_2$), 79. Bis(thiomethoxy)methane (**6**) (62.4 mg, 0.578 mmol): IR (CCl_4) 1430, 1200, 985 cm^{-1}; NMR δ 2.15 (s, 6 H, CH_3S), 3.58 (s, 2 H, SCH_2S); mass spectrum *m/e* 108 (M^+, $C_3H_8S_2$), 93, 61 ($M - CH_3S$). Toluene (**8**) (46.0 mg, 0.500 mmol) was identified by comparison with a known sample. Methyl *p*-tolyl disulfide (**9**) (ca. 25 mg, 0.15 mmol): NMR δ 2.30 (s, 3 H), 2.38 (s, 3 H), 7.2 (A B quartet, 4 H, p-tolyl); mass spectrum *m/e* 170 (M^+, $C_8H_{10}S_2$), 155, 123 ($M - SCH_3$), 91 ($C_7H_7^+$). Di-*p*-tolyl disulfide (**10**) (65 mg, 0.264 mmol): IR ($CHCl_3$) 1480, 1030 cm^{-1}; NMR δ 2.24 (s, 6 H, CH_3Ar), 7.15 (A B quartet, 8 H, *p*-tolyl); mass spectrum *m/e* 246 (M^+, $C_{14}H_{14}S_2$), 123 ($M - C_7H_7S$), 91 ($C_7H_7^+$). The inlet tube to the pyrolysis trap was washed with methanol and yielded, after evaporation, 150 mg (0.877 mmol) of a white solid, identified as *p*-toluenesulfonamide (**7**) by spectral comparison with an authentic sample.

S,S-Diphenyl-N-p-toluenesulfonylsulfilimine (11). Using a procedure[13] somewhat modified from the one described above, a solution of 4.18 g (14.9 mmol) of chloramine-T in 50 mL of 50% ethanol–water was stirred at room temperature with 1.84 g (9.92 mmol) of diphenyl sulfide. After heating on a steam bath for 0.5 h the mixture was allowed to stand at room temperature overnight. Reheating the mixture on a steam bath, addition of water until cloudiness was noted, and cooling yielded the crude product as a white solid. After suction filtration and recrystallization from benzene–hexane, 2.68 g (7.54 mmol, 76%) of product was obtained as white needles, mp 110–111 °C (lit.[14] mp 108–110 °C).

Pyrolysis of 11. Using the apparatus described above for the pyrolysis of **3**, the pyrolytic decomposition of **11** (0.770 g, 2.16 mmol) was

carried out at 300 °C for 2 h. The reaction products were identified by spectral and VPC comparison with authentic samples as diphenyl sulfide (0.361 g, 1.94 mmol), *p*-toluenesulfonamide (0.117 g, 0.684 mmol), and toluene (3.2 mg, 0.035 mmol).[11] A nonvolatile black residue (0.218 g) was also recovered from the pyrolysis tube.

An attempt to pyrolyze **11** at 250 °C resulted in only a trace amount of decomposition and the recovery of 98% starting sulfilimine.

Pyrolysis of *p*-Toluenesulfonamide (7). Under conditions identical to those described above, **7** (0.605 g, 3.54 mmol) was pyrolyzed at 300 °C for 1 h. VPC analysis showed toluene (22.8 mg, 0.248 mmol, 7%) as the only product present. Considerable black char was noted in the pyrolysis boat.

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Registry No.—**3,** 13150-75-9; **11,** 13150-76-0; chloramine-T, 127-65-1; diphenyl sulfide, 139-66-2.

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Migration of Acyl Groups in Acetyl–Alkoxycarbonyl Mixed Diacyl Derivatives of o-Aminophenol

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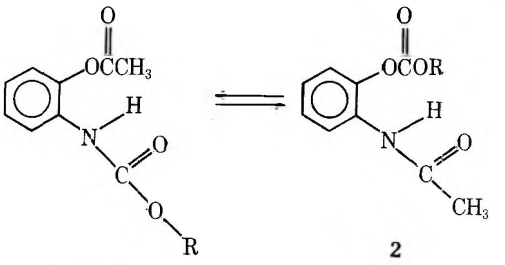
In an earlier article it was shown that the migration results obtained with several typical acyl groups were generally consistent with the hypothesis that the more stable isomer was that one with the poorer electron releasing group attached to nitrogen.[1] As discussed in some detail by Amundsen and Ambrosio, all reported work with acylalkoxycarbonyl mixed diacyls has resulted in isolation of only the isomer in which the alkoxycarbonyl group is attached to nitrogen.[2] Since these results are not consistent with the usually assumed order of the relative electron releasing powers of alkyl and alkoxy groups, it is felt desirable to investigate the synthesis and isomerization behavior of representative acetyl–alkoxycarbonyl systems. The present work presents results obtained with the acetyl–benzyloxycarbonyl and the acetyl–*n*-butoxycarbonyl systems **1–2.** System **1a** and **2a** was studied earlier



1 **2**

a, R = $PhCH_2$
b, R = *n*-Bu

by Amundsen and Ambrosio who were unable to prepare **2a** and found only the urethane on saponification of **1a.** System **1b** and **2b** had not been studied prior to this work and it was chosen since it represents a more clear-cut comparison of the relative electron-donating powers of an alkyl and an alkoxy functional group.

The diacyl derivatives were prepared by *O*-acylation of the *N*-alkoxycarbonyl and *N*-acyl compounds. Isomerization of purified samples of **1a** and **2a** in absolute alcohol was complete in 2 h at 26 °C and resulted in the formation of an equilibrium mixture containing 96.5% of 1a. Isomerization of **1b** and **2b** was very much slower than for **1a** and **2a** but after 380 h an equilibrium mixture was obtained containing 94.5% **1b.**

In pyridine solution, isomerization was much slower for both pairs of isomers. However, the same equilibrium composition was reached for **1a** and **2a** in about 24 h standing in pyridine at 25 °C. With **1b** and **2b, 1b** contained only 2% isomerized product after 382 h of standing time, while **2b** contained 54% of the isomerized product.

Saponification of either **1a** or **2a** gave a mixture containing 32, 50, and 18% of benzyl o-hydroxycarbanilate, benzoxazolone, and *o*-hydroxyacetanilide, respectively. Converting the benzoxazolone weight to benzyl o-hydroxycarbanilate from which it was derived[3] showed that saponification must have initially produced 83% benzyl *o*-hydroxycarbanilate. Since both isomers gave the same composition of saponification products, it seems clear that isomerization in the alkaline solution was rapid relative to saponification. It also seems clear that **2a** saponified faster than **1a** since it may be calculated that equal rates of saponification of the equilibrium mixture would yield a mixture of monoacyls containing 97.8% of benzyl o-hydroxycarbanilate.

Saponification of **1b** and **2b** produced only 4% of benzoxazolone in contrast to the 50% obtained with **1a** and **2a.** Correcting for this by-product as before, isomer **1b** yielded 93% *n*-butyl o-hydroxycarbanilate while isomer **2b** gave only 84% of this monoacyl. Thus, while isomerization in this system is much faster than saponification, there appears to be less difference in these rates than was the case for the **1a–2a** system. Had the saponification rates of **1b** and **2b** been equal and equilibrium attained instantly, it may be calculated that the saponification mixture would have contained 96.9% *n*-butyl o-hydroxycarbanilate. The most likely explanation of these results is that **2b** saponifies more rapidly than **1b** and that some saponification of **2b** occurs before it has had time to completely isomerize to the equilibrium mixture.

Experimental Section

Melting points are uncorrected and were taken on a Fisher digital melting point analyzer. Infrared spectra were recorded from potassium bromide disks on a Perkin-Elmer Model 21 spectrophotometer. Ultraviolet spectra were recorded using a Bausch and Lomb Model 600 UV–visible spectrophotometer.

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Table I. Diacyl Derivatives of o-Aminophenol [a]

No.		Registry No.	Mp, °C	UV_{max} [b] λ, nm	UV_{max} [b] ($\epsilon \times 10^{-3}$)	IR, μm Ester	IR, μm Amide
1a	Benzyl o-acetoxycarbanilate	5211-52-9	93–5	233	20.0	5.78	5.78
2a	o-Acetamidophenylbenzyl carbonate	64682-86-6	88–90	239	11.9	5.73	5.90
1b	n-Butyl o-acetoxycarbanilate	64682-87-7	Oil	238	18.4	5.75[c]	5.75[c]
2b	o-Acetamidophenyl-n-butyl carbonate	64682-88-8	55–7	233	16.0	5.66	5.98

[a] Satisfactory analytical data (average ±0.2% for C, H) were reported for all new compounds listed in this table. [b] n-Hexane solutions. [c] Small but definite absorption at 5.62 μm.

Table II. Approximate Retention Time and Response Data for Acyl Derivatives of o-Aminophenol with Chloroform Developing Solvent [a]

Compd name	Registry no.	R_t, min	Peak ht, mm/μg
Benzyl o-acetoxycarbanilate (**1a**)		1.25	31
n-Butyl o-acetoxycarbanilate (**1b**)		1.28	24
Benzyl o-hydroxycarbanilate	64682-89-9	1.70	29
n-Butyl o-hydroxycarbanilate	64682-90-2	1.72	28
o-Acetamidophenylbenzyl carbonate (**2a**)		2.25	86
o-Acetamidophenyl-n-butyl carbonate (**2b**		2.28	105
Benzoxazolone	59-49-4	3.80	14
o-Hydroxyacetanilide	614-80-2	7.80	25

[a] Burdick and Jackson "distilled in glass" solvent containing about 1% ethanol stabilizer was modified by the addition of 0.2% by volume acetic acid. The solvent flow rate was 3 mL/min with a back pressure of about 2500 psig.

The chromatographic analyses were performed using a Waters ALC-GPC 202 liquid chromatograph equipped with a differential ultraviolet detector (254 nm) and a 30 cm × 4 mm (i.d.) μ-Porasil column. The developing solvent was chloroform (ethanol stabilized) to which 0.2% (v/v) acetic acid was added. Standard solutions were prepared in chloroform and no evidence of isomerization of the mixed diacyls in this solvent was observed after several weeks standing.

A. Preparation of Monoacyl Derivatives. Benzyl and n-butyl o-hydroxycarbanilate were prepared by the method of Groenvik.[4] The melting points of these compounds were in agreement with literature values and each gave only a single peak when analyzed by HPLC. The o-hydroxyacetanilide was obtained from Aldrich Chemical Co.

B. Preparation of Mixed Diacyl Derivatives. Benzyl o-Acetoxycarbanilate (1a). This mixed diacyl was prepared by the reaction of acetyl chloride with benzyl o-hydroxycarbanilate in acetic acid solution. In a typical preparation, 0.5 g of benzyl o-hydroxycarbanilate was dissolved in 25 mL of acetic acid and 0.5 mL (theory = 0.15 mL) of acetyl chloride was added over a period of 3 h with continuous stirring. HPLC analysis of an aliquot showed that 30% conversion had been obtained. An additional 0.5 mL of acetyl chloride was added and the mixture was stirred overnight. Analysis showed that 99% conversion had occurred. The solution was poured over 250 mL of cracked ice with stirring. The white precipitate formed weighed 0.63 g (54% theory) and melted at 93–4 °C. Recrystallization from 30% benzene in cyclohexane yielded 0.30 g of hard granular crystals melting at 93.5–94.5 °C. HPLC analysis showed the presence of 1% unreacted benzyl o-hydroxycarbanilate and 1.5% **2a**.

***o*-Acetamidophenylbenzyl Carbonate (2a).** The desired product was synthesized by treating 1 g of o-hydroxyacetanilide dissolved in 56 mL of 10% pyridine in acetone with 3 mL of benzyl chloroformate (theory = 0.94 mL) dissolved in 10 mL of acetone. The benzylchloroformate was added dropwise to the stirred o-hydroxacetanilide solution over a period of 30 min, and the resulting mixture was poured into 25 mL of 10% aqueous HCl. Most of the acetone was removed by evaporation in a hood overnight and the aqueous suspension was extracted with chloroform. The chloroform extract was filtered and evaporated to obtain 2.20 g of a gummy solid. This was triturated with 15 mL of cyclohexane to remove some oily material. The extracted crystals weighed 1.55 g and HPLC analysis showed them to contain 9% benzoxazolone and 9% unreacted o-hydroxyacetanilide. Three recrystallizations from 10% chloroform in cyclohexane yielded 0.5 g of light feathery crystals melting at 88–90 °C. Very remarkably, a 50/50 mixture of **1a** and **2a** showed practically no depression in mp, the mixture melting from 88–92 °C! HPLC analysis showed the presence of 1.5% **1a**, 1.5% o-hydroxyacetanilide, and 1.0% benzyl o-hydroxycarbanilate in the purified **2a** crystals.

***n*-Butyl *o*-Acetoxycarbanilate (1b).** This product was prepared by treating 2 g of n-butyl o-hydroxycarbanilate dissolved in 60 mL of 4% pyridine in ethyl ether solution with 1.7 mL of acetyl chloride (theory = 0.68 mL). The acetyl chloride was added dropwise over about 1 h and the reaction mixture was stirred overnight. The ether solution was extracted three times with 30-mL portions of 1.6 N HCl to remove pyridine and pyridine hydrochloride and then with two 30-mL portions of water to remove the residual acid. Evaporation of the ether left 1.5 g of a slightly yellowish oil which resisted all attempts to cause it to crystallize from various solvent mixtures. HPLC analysis showed the oil to contain about 8% of n-butyl o-hydroxycarbanilate as the only detectable impurity. This impurity was reduced to 3% by dissolving the oil in hot hexane and cooling slowly so that the more insoluble n-butyl o-hydroxycarbanilate precipitated selectively. Evaporation of the hexane solution left 0.5 g of clear oil melting at about −30 °C.

***o*-Acetamidophenyl-*n*-butyl Carbonate (2b).** This compound was prepared by slurrying 1.5 g of o-hydroxyacetanilide with 50 mL of ethyl ether and 3.4 mL of n-butyl chloroformate (theory = 0.94 mL). A solution of 4 mL of pyridine in 30 mL of ether was added with constant stirring over a period of 1 h. The reaction mixture was stirred for 3 h and extracted with three 50-mL portions of 3 N HCl to remove pyridine and pyridine hydrochloride and with two 50-mL portions of water to remove the acid. Evaporation of the ether yielded about 5 mL of a viscous yellow oil. The oil was dissolved in 70 mL of boiling hexane, carbon treated, and allowed to cool slowly to −10 °C. After several days of standing long white needles were obtained which melted at 55–7 °C. HPLC analysis showed only trace amounts of **1b** to be present. However, on standing at room temperature this material slowly reverted to an oil which was principally isomer **1b**. For example, two batches of this isomer stored at room temperature for 44 and 47 days after recrystallization were found to contain 83 and 87%, respectively, of **1b**.

C. Isomerization of Mixed Diacyls. For isomerization rate studies of **1a** and **2a** relatively concentrated solutions (1–2%) were prepared in absolute ethanol and aliquots diluted tenfold with $CHCl_3$ at appropriate time intervals. In this way, the isomerization was quenched so that replicate analyses could be made if required, and the solution concentrations were adjusted to the proper range for HPLC analysis. The rate of isomerization of **1b** and **2b** was very slow so that it was found more convenient to evaporate aliquots of approximately 0.4% solutions and reconstitute these with $CHCl_3$ just prior to analysis. In all cases, solutions were made up accurately so that material balance calculations could be made on the basis of the analytical results. The standard deviation of these balances was estimated to be ±5% of the amount present.

D. Saponification of Mixed Diacycls. Isomers **1a** and **2a** were saponified by stirring 0.10 g at room temperature in 10 mL of 1.0% NaOH. The dense granular crystals of **1a** dissolved very slowly even with continuous stirring and powdering of the larger granules. Complete solution required about 1 h. In marked contrast, **2a** dissolved completely in about 5 min. Both mixtures were stirred an additional 20 min after a clear solution of **1a** was obtained, the solutions were acidified, and the white powdery precipitate which formed was filtered. The material recovered in this way was found to be nearly pure benzyl o-hydroxycarbanilate as was previously reported for the saponification of **1a** by Amundsen and Ambrosio. Since, however, only 14% of the theoretical quantity expected (assuming 100% conversion to this monoacyl) was recovered, the aqueous filtrates were extracted with $CHCl_3$ and the extract was analyzed by HPLC. Benzoxazolone

and *o*-hydroxyacetanilide in about a 3:1 ratio were found in this extract, along with a small amount of additional benzyl o-hydroxycarbanilate. Conversion of the benzoxazolone weight to benzyl o-hydroxycarbanilate from which it was formed gave average material balances of 75%.

Isomers **1b** and **2b** were saponified by stirring 0.20-g samples with 10 mL of 2% NaOH. Solution was complete in about 15 min and the reaction mixtures were stirred for an additional 2 h before being acidified. The acid mixtures were evaporated to dryness, the residues were extracted with 15 mL of $CHCl_3$, and these extracts were filtered and diluted to 25 mL for HPLC analysis. The material balances in these saponifications averaged 65%.

Registry No.—Acetyl chloride, 75-36-5; benzyl chloroformate, 501-53-1; butyl chloroformate, 592-34-7.

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Styrene Bromination: Evidence for a Bridged Rate-Determining Transition State

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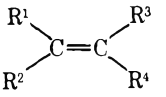
The mechanism of the bromination of styrene and its derivatives has been the subject of debate.[1] An open carbonium-ion-like rate-determining transition state has been proposed on the basis of stereochemical evidence[2] and the magnitude of the negative ρ values[3] for bromination of ring substituted styrenes. A bridged rate-determining transition state has been proposed, based upon the observation that the initial enthalpy difference between pairs of cis,trans isomeric alkenes was increased at the bromination transition state.[4]

One way of resolving this problem is to compare the structure-reactivity profiles of bromination with two model reactions: one involving a bridged, the other an open-ion-like rate-determining transition state. The following reactions have been chosen as models. Protonation of alkenes in acid-catalyzed hydrations has been established to proceed by an open ion through the entire range of reactivity.[1,5] The addition of arenesulfenyl halides to alkenes is a reaction which proceeds through a bridged rate-determining transition state for the entire range of reactivity.[1] The purpose of this note is to make such a comparison of the bromination, hydration, and addition of 4-chlorobenzenesulfenyl chloride to the following compounds. The rate data are collected in Table I.

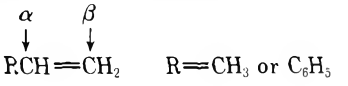
Table II. Ratios $k(\alpha\text{-}CH_3)/k(H)$ and $k(\beta\text{-}CH_3)/k(H)$

Compd	Br_2 in HOAc	Br_2 in CH_3OH	ArSCl in TCE	Hydration
2-Phenylpropene (2)/styrene (1)	60.7		4.27	1070
cis-1-Phenylpropene (3)/styrene (1)	0.80		0.69	
trans-1-Phenylpropene (4)/styrene (1)	1.10		1.91	0.34
Methylpropene (6)/propene (5)		89	2.7	7500
cis-2-Butene (7)/propene (5)		43	6.5	1.68
trans-2-Butene (8)/propene		28	2.1	0.71



	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
1	C_6H_5	H	H	H	5	CH_3	H	H	H
2	C_6H_5	CH_3	H	H	6	CH_3	CH_3	H	H
3	C_6H_5	H	CH_3	H	7	CH_3	H	CH_3	H
4	C_6H_5	H	H	CH_3	8	CH_3	H	H	CH_3

The effect of substituting a methyl group for a hydrogen on the rate of addition is used as the mechanistic probe. For purpose of comparison, the positions of the methyl groups which replace the olefinic hydrogens in styrene and propene can be designated α and β as follows:



The effect of substituting the olefinic hydrogens on styrene and propene by methyl groups on the rates of addition is different for the two limiting mechanisms. By expressing the rates as the ratios $k(\alpha\text{-}CH_3)/k(H)$ and $k(\beta\text{-}CH_3)/k(H)$, this fact is clearly demonstrated as shown in Table II.

Several points are evident from the data in Table II. As expected, substituting a methyl group in the α position has the greatest effect on hydration where an open ion is formed. The $k(\alpha\text{-}CH_3)/k(H)$ ratio for the bromination of styrene is not unusually large. It is about the same as propene and much smaller than that for hydration.

The small variation in the ratio $k(\alpha\text{-}CH_3)/k(H)$ and $k(\beta\text{-}CH_3)/k(H)$ for additions of bromine and 4-chlorobenzenesulfenyl chloride in the propene series indicate a bridged rate-determining transition state in accordance with the accepted mechanisms of these additions.[1] The methyl substitutents affect the rates of bromination more than those of

Table I. Rates of Hydration, Bromination, and Addition of 4-Chlorobenzenesulfenyl Chloride at 25 °C

Compd	Registry no.	$k_2(Br_2)$,[a] $M^{-1}\,s^{-1}$	$k_g(Br_2)$,[b] $M^{-1}\,s^{-1}$	$k_2(ArSCl)$, $M^{-1}\,s^{-1}$	$k_2(H^-)$,[e] $M^{-1}\,s^{-1}$
Styrene (1)	100-42-5	11.2		62.0[c]	0.326×10^{-6}
2-Phenylpropene (2)	98-83-9	680		265[c]	0.967×10^{-4}
cis-1-Phenylpropene (3)	766-90-5	8.89		43.0[c]	
trans-1-Phenylpropene (4)	873-66-5	12.3		118[c]	1.12×10^{-7}
Propene (5)	115-07-1		30.7	205[d]	0.495×10^{-7}
Methylpropene (6)	115-11-7		2730	550[d]	0.371×10^{-3}
cis-2-Butene (7)	590-18-1		1310	1340[d]	8.32×10^{-8}
trans-2-Butene (8)	624-646		847	434[d]	3.51×10^{-8}

[a] In acetic acid solvent, ref 6. [b] In methanol containing 0.2 M NaBr, ref 7. [c] In 1,1,2,2-tetrachloroethane, ref 8. [d] In 1,1,2,2-tetrachloroethane, ref 9. [e] The second-order rates of hydration were obtained by dividing the observed rates extrapolated to $H_0 = 0$ by the acidity function h_0 for that acidity, ref 10.

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Table III. Ratios $k(\alpha\text{-}CH_3)/k(t\text{-}\beta\text{-}CH_3)$

Parent compd	$k(\alpha\text{-}CH_3)/k(t\text{-}\beta\text{-}CH_3)$		
	ArSCl	Br_2	Hydration
Styrene	2.24	55	3147
Propene	1.26	3.2	10563

addition of 4-chlorobenzenesulfenyl chloride. This indicates that more charge is developed on the ring carbons in the bridged rate-determining transition state in the addition of bromine than arenesulfenyl chlorides. This is consistent with the greater ability of sulfur to support a positive charge.

By comparing the effect of methyl groups in the α and β positions, in terms of the ratios $k(\alpha\text{-}CH_3)/k(t\text{-}\beta\text{-}CH_3)$, we can obtain an estimate of the symmetry of the rate-determining transition state. These data are presented in Table III. To eliminate any problems due to steric hindrance, the values of the trans-β isomers are used. The difference between addition of 4-chlorobenzenesulfenyl chloride and hydration is striking. For a bridged rate-determining transition state the ratio is small (1.3–2.2) while for an open-ion-like transition state the ratio is large (10^3–10^4).

Bromination in the propene series closely resembles the addition of 4-chlorobenzenesulfenyl chloride. Clearly the rate-determining transition state for these additions is quite symmetrical. The $k(\alpha\text{-}CH_3)/k(t\text{-}\beta\text{-}CH_3)$ ratio for the bromination in the styrene series more closely resembles that of the addition of 4-chlorobenzenesulfenyl chloride than hydration. Consequently, the data are best explained by proposing a weakly bridged rate-determining transition state. Thus the structures range from strongly bridged for arenesulfenyl chloride to weakly bridged for bromination to an open one for hydration.

These data indicate that the formation of nonstereospecific products in the bromination of styrene and its derivatives is due to the intervention of open ions *after* the rate-determining step.

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References and Notes

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Reductive Alkylation of Phenazine. Electrochemical Preparation of 5,10-Dihydro-5,10-dimethyl and 5,10-Dihydro-5,10-diethyl Derivatives

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In conjunction with research on the chemical behavior of certain cation radical species and as part of a more general study of reductive alkylation initiated electrochemically, a method has been developed for the facile synthesis of 5,10-dialkyl-5,10-dihydrophenazine derivatives in high yield.

Previous methods for the synthesis of *N,N'*-dialkyldihydrophenazines consisted of chemical reduction of phenazine followed by treatment with the appropriate alkylating agent. For example, Gilman and Dietrich[1] prepared the dimethyl derivative in 1,2-dimethoxyethane (DME) by reduction of phenazine with potassium metal, followed by addition of methyl iodide. Only 62% yield was reported. In a more elaborate preparation, Mikhailov and Blokhina[2] synthesized the diethyl derivative by first isolating the disodium salt of reduced phenazine after treatment with sodium metal in DME for 30–35 h. The salt was then reacted with either ethyl chloride or ethyl iodide for an additional 40 h, resulting in only 40–44% yield.

More recently, reactions of this type have been carried out electrochemically.[3,4] This technique offers the advantage of a selective reduction potential such that the parent compound can be reduced at a potential where the alkylating agent is not. Thus both reagents can be present in solution simultaneously. The alkylating agent reacts with reduced parent compound as it is generated at the cathode eliminating the need for stepwise addition of reagents or isolation of reactive intermediates.

Results and Discussion

A cyclic voltammogram of phenazine in acetonitrile shows two reduction waves, a reversible one-electron reduction at −1.60 V (vs. Ag|0.1 M Ag^+), and a second irreversible one-electron transfer at −2.41 V. The radical anion species is very stable showing completely reversible behavior at scan rates as slow as 20 mV/s. Also, controlled potential coulometry at the first reduction wave yields an n_{app} value of 1.0 (where n_{app} is the number of equivalents of electrons added per mole of substrate). The second wave exhibits irreversible behavior at scan rates as fast as 50 V/s indicating the presence of a fast following chemical reaction which is most likely protonation by solvent or trace impurities to produce the 5,10-dihydro derivative.[4]

In the presence of a fourfold excess of dimethyl sulfate, which is itself electroinactive, the first reduction wave of phenazine exhibits irreversible behavior at slow scan rates indicating a reaction between the phenazine anion radical and the added alkylating agent. Also, two new oxidation waves appear at −0.18 and +0.52 V on scan reversal. When the cyclic scan is allowed to include both reduction waves these same two oxidation waves appear in greater magnitude showing that the reaction of dimethyl sulfate with either the radical anion or dianion of phenazine yields the same product.

With diethyl sulfate as an alkylating agent, no change is observed in the first reduction wave indicating that the reaction between the phenazine radical anion and diethyl sulfate is very slow. With inclusion of the second reduction wave in the cyclic scan two new oxidation waves appear at −0.28 and +0.48 V and a third, smaller wave at −0.46 V, showing a rapid reaction does occur with the phenazine dianion.

Ethyl bromide is electrochemically reducible at a more negative potential than either reduction process exhibited by phenazine. Its effect on the phenazine reduction however is similar to that observed on addition of diethyl sulfate: slow reaction with the radical anion, and rapid reaction with the dianion species. The anodic portion of the scan includes the new oxidation waves at −0.28 and +0.48 V, the latter obscured by the oxidation of Br^-, a reaction by-product. A wave at +0.78 V corresponding to the oxidation of Br_3^- is also observed.

Controlled potential coulometry at the first reduction wave of phenazine yields an n_{app} of 2.0 when any of the three alkylating agents is added in excess to the solution. Since an n_{app} value of 1.0 is observed in the absence of alkylating agent, the alkylating agents must react with the phenazine radical anion

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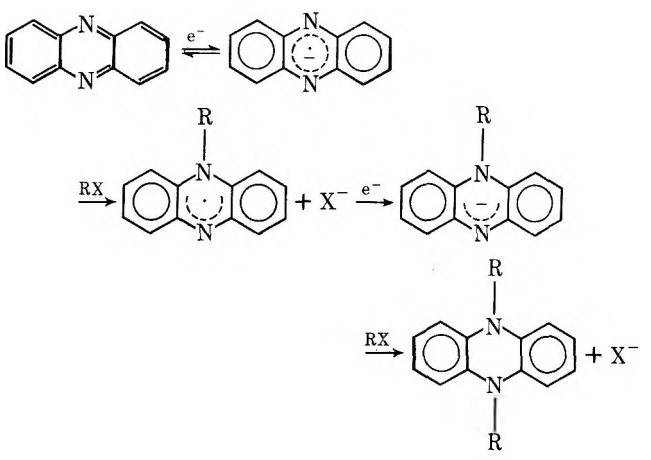
to produce an intermediate species which is further reducible at the applied potential. Also, a minimum of 2 equiv of alkylating agent is required for complete reaction. The following mechanism is suggested:



where R = CH_3 or C_2H_5 and X = Br, $[SO_4CH_3]$, or $[SO_4C_2H_5]$

Qualitatively, dimethyl sulfate is the fastest reacting alkylating agent as evidenced by the fact that the deep purple color indicative of the radical anion never develops in solution during electrolysis. Diethyl sulfate is somewhat slower reacting with build-up of the radical anion during electrolysis, although for both alkylating agents the total electrolysis time is approximately 30 min. Ethyl bromide is the slowest alkylating agent requiring over 90 min for complete reaction under similar conditions. The inconvenience of longer reaction time is offset by the wider range of phenazine derivatives available from alkyl halides than from alkyl sulfates.

On completion of the electrolysis with dimethyl sulfate or diethyl sulfate two reversible one-electron oxidation waves are observed whose wave heights are the same as the height of the reduction waves of neutral phenazine. In addition, controlled potential electrolysis at the first oxidation wave of either product yields an n_{app} of 1.0 and a deep green solution of the cation radical. Both results indicate a 100% yield of the dialkylated product, which is a substantial improvement over existing procedures. The only loss occurs during product work-up where the light green color of the crystals suggests contamination by the salt of air-oxidized dialkyl derivatives.

The electrochemically initiated reductive alkylation reaction provides a convenient route to the synthesis of 5,10-dihydro-5,10-dialkylphenazines and shows substantial improvement on both time and product yields of existing procedures.

Experimental Section

The electrochemical cell is similar to one described previously.[6] The total cell volume is approximately 140 mL with 70 mL in the working compartment. A platinum wire sealed in soft glass and ground to a flat disk was used as a working electrode for cyclic voltammetry. Controlled potential coulometry was carried out on a large surface area platinum gauze electrode. All potential measurements are vs. a $Ag|Ag^+$ (0.10 M) reference electrode.

Acetonitrile (Eastman, 0.05% H_2O), solvent for all electrochemical experiments, was vacuum distilled over P_2O_5 and stored over dried molecular sieves. Tetraethylammonium perchlorate (TEAP) (Southwestern Analytical Chemicals, Inc., Polarographic grade), supporting electrolyte for all experiments, was ground to fine powder and stored under vacuum. Phenazine (Aldrich, Technical grade) was purified by vacuum sublimation. Dimethyl sulfate (Aldrich, Gold Label) was used as received. Diethyl sulfate (Eastman, Practical grade) was vacuum distilled. Ethyl bromide (J. T. Baker, Reagent grade) was used as received. Electrochemical experiments were performed with a PAR Model 170 electrochemistry system using positive feedback to compensate for solution resistance.

A General Procedure for Electrochemical Generation of 5,10-Dihydro-5,10-dialkylphenazine. Phenazine (0.288 g) was added to the working compartment of the cell containing 70 mL of AN/0.3 M TEAP for a total concentration of 0.023 M in phenazine. The solution was degassed for 10 min with N_2 prior to addition of the alkylating agent and a steady flow of N_2 was maintained over the solution throughout all electrochemical manipulations. Sufficient alkylating agent was added to give a total concentration of 0.092 M and the solution was electrolyzed at −1.90 V until the current had decayed to 0.1% of its initial value signaling 99.9% completion of the reaction. Following the reduction, the solvent was removed on a rotary-evaporator and the solid residue was partitioned with 1:1 degassed benzene/water. The benzene fraction was evaporated and the solid was filtered using degassed methanol for transfer and washing. Both dimethyl- and diethylphenazine were recrystallized from ethanol/methanol mixtures.

5,10-Dihydro-5,10-dimethylphenazine from Dimethyl Sulfate. Dimethyl sulfate (16 mL, 6.4 mmol) was added directly to the working compartment of the cell containing 1.6 mmol of phenazine in 0.3M TEAP/AN. The solution was electrolyzed at −1.90 V and gave an n_{app} of 2.0 with a total electrolysis time of 30 min. The solution was then oxidized at the first product oxidation wave yielding an n_{app} = 1.0 and producing a deep green solution whose spectra matched that reported for the cation radical of 5,10-dihydro-5,10-dimethylphenazine in AN[7] (λ_{max} 720, 650, 600, 455, 447, 435, 320). The sample was reduced back to the neutral compound, isolated from the solution, and recrystallized. Colorless crystals (0.30 g) were collected: 91% yield; mp 153 °C (lit.[1] mp 153–155 °C).

5,10-Dihydro-5,10-diethylphenazine from Diethyl Sulfate. Diethyl sulfate (0.84 mL, 6.4 mmol) was added to 1.6 mmol of phenazine in 0.30 M TEAP/AN and electrolyzed at −1.90 V, n_{app} = 2.0, time of electrolysis was 30 min. Product collected: 0.349 g of silvery light green crystals; 91% yield; mp 129 °C (lit.[2] mp 130–131 °C).

5,10-Dihydro-5,10-diethylphenazine from Ethyl Bromide. Ethyl bromide (0.48 mL, 6.4 mmol) was added to 1.6 mmol of phenazine in 0.30 M TEAP/AN and electrolyzed at −1.90 V, n_{app} = 2.0, time of electrolysis was 96 min. Product collected: 0.35 g of silvery light green crystals; mp 129 °C.

Registry No.—5,10-Dihydro-5,10-dimethylphenazine, 15546-75-5; dimethyl sulfate, 77-78-1; phenazine, 92-82-0; 5,10-dihydro-5,10-dimethylphenazine radical cation, 56545-30-3; 5,10-dihydro-5,10-diethylphenazine, 62248-00-4; diethyl sulfate, 64-67-5; ethyl bromide, 74-96-4.

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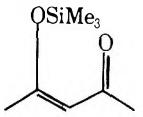
Communications

Dimethyldicyanosilane: A Reagent for Concurrent Silylation and Cyanosilylation of β-Diketones[1]

Summary: Six-membered rings (5-cyano-2,6-dioxa-1-silacyclohex-3-enes) are obtained by the reaction of β-diketones with dimethyldicyanosilane, in which concurrent silylation and cyanosilylation of the two carbonyl groups of β-diketones occur.

Sir: Recently cyanosilylation by trimethylcyanosilane has been developed as a useful method for the protection of carbonyl groups.[2] In connection with our study on the reactions of enol ethers, synthesis of cyanosilylated derivatives (such as **2**) of monosilylated β-diketones (such as **1**) were required.[3] Attempts to mask the carbonyl group of monosilylated β-diketone **1** with trimethylcyanosilane with the aid of heat or some catalyst such as zinc iodide[2] were unsuccessful. These reactions always afforded significant amounts of isomeric product **3** in addition to desired **2**.[4]



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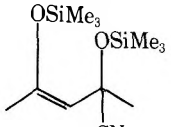
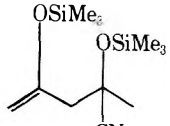


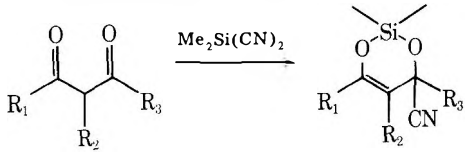
2 (*E* + *Z*)



3

To overcome this problem, the use of a bifunctional organosilicon reagent occurred to us, and we have now developed a method for the preparation of analogues of **2** in an efficient and selective manner from β-diketones.

We wish to report that dimethyldicyanosilane [$Me_2Si(CN)_2$][5] readily reacts with β-diketones to give high yields of six-membered ring products **4**. The compounds **4** were the desired ones in which enol and carbonyl portions of β-diketones were concurrently silylated and cyanosilylated without generation of side products analogous to **3**.



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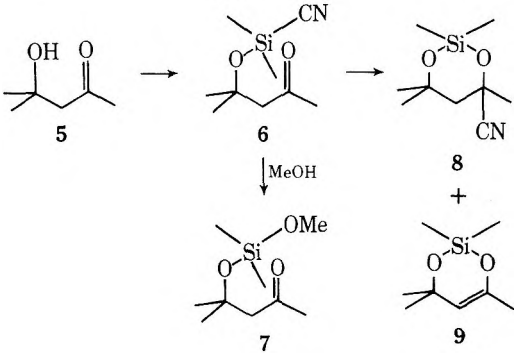
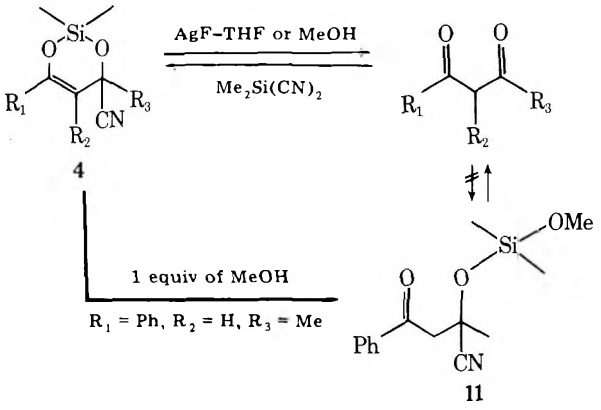
The reaction takes place exothermically with the evolution of hydrogen cyanide at room temperature to give **4**. In a representative procedure dimethyldicyanosilane (12 mmol) is dissolved in dichloromethane (3 mL) and the solution is cooled to −40 °C. The β-diketone (10 mmol) is slowly added to the solution by a hypodermic syringe, and the mixture is allowed to warm to room temperature over 1 h. After removal of hydrogen cyanide and the solvent, purification is effected by distillation or recrystallization. The products obtained are very hygroscopic and should be manipulated under an atmosphere of dry nitrogen. The results are summarized in Table I.

Except for the case of one difficultly enolized β-diketone[6] (entry 2 in Table I), the reaction proceeded immediately without any catalysts. The orientation of enolization in β-diketones is reflected in the structure of the products. In the case of β-diketones in which the orientation of enolization is distinctly determined by conjugation, a single regioisomer was obtained (see entry 5 and also entries 7 and 8 in Table I). It is noteworthy that the present reaction involves the silylation

Scheme I

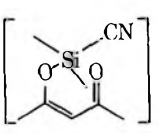


Scheme II



to give the *Z* form product selectively, despite the fact that the other methods for silylation of β-diketones give a mixture of *E* and *Z* isomers.[7]

The reaction of dimethyldicyanosilane with diacetone alcohol (**5**) in Scheme I follows a path that may be consistent with that followed by the reaction described in this study. The major products of this reaction were **8** and **9**.[8] The NMR spectrum of the reaction mixture after 1 h showed the predominant formation of cyanoalkoxysilane **6**, which seemed to be stable at low temperature (−30 °C) and could be intercepted to afford dialkoxysilane **7** in 76% yield upon treatment with methanol.[9] By analogy, the reaction of dimethyldicyanosilane with β-diketones may start with the silylation of the enolic portion to give **10** followed by intramolecular cyanosi-



10

lylation. However, we were unable to intercept the initial product **10** corresponding to **6**. This suggests that the intramolecular cyanosilylation must be very fast in the case of **10**.[10,11]

The six-membered ring products are moisture sensitive and can be easily converted to parent β-diketones on treatment with methanol or silver fluoride in THF (Scheme II).[12] Interestingly, the reaction of the cyclic product of benzoyl acetone with 1 equiv of methanol gave **11** in 76% yield. This result implies that methanolysis proceeds stepwise (the enol silyl

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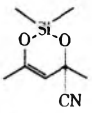
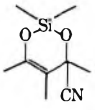
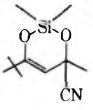
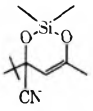
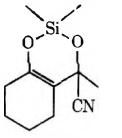
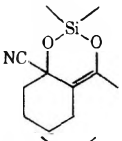
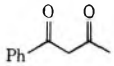
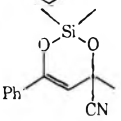
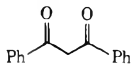
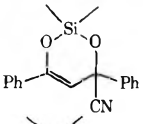
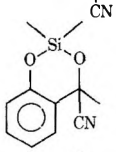
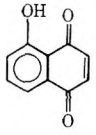
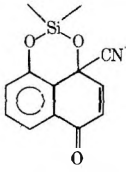
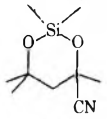
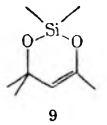
Table I. Concurrent Silylation and Cyanosilylation of β-Diketones and Related Compounds

Entry	β-Diketone	Products[a]	% yield[b]	Bp, °C (mp, °C)	IR, cm^{-1}	NMR (CCl_4), δ[c]
1			91	87-90 (20 mm)	1668	0.26 (s, 3 H) 0.41 (s, 3 H) 1.58 (s, 3 H) 1.79 (s, 3 H) 4.52 (s, 1 H)
2[d]			81	101-103 (26 mm)	1663	0.24 (s, 3 H) 0.35 (s, 3 H) 1.66 (s, 3 H) 1.70 (s, 3 H) 1.85 (s, 3 H)
3			86 (38:62)[e]	108-110 (23 mm)	1663	0.22 (s, 3 H) 0.38 (s, 3 H) 1.06 (s, 9 H) 1.60 (s, 3 H) 4.59 (s, 1 H)
						0.22 (s, 3 H) 0.38 (s, 3 H) 1.01 (s, 9 H) 1.84 (s, 3 H) 4.55 (s, 1 H)
4			98 (68:32)[e]	109-111 (7 mm)	1663	0.25 (s, 3 H) 0.37 (s, 3 H) 1.62 (s, 3 H) 140-2.50 (c, 8 H)
						0.25 (s, 3 H) 0.38 (s, 3 H) 1.80 (s, 3 H) 1.40-2.50 (c, 8 H)
5			97	101-104 (0.3 mm)	1643	0.36 (s, 3 H) 0.51 (s, 3 H) 1.73 (s, 3 H) 5.30 (s, 1 H) 7.20-7.58 (m, 5 H)
6			95	(68.5-70.0)	1640	0.40 (s, 3 H) 0.59 (s, 3 H) 5.53 (s, 1 H) 7.18-7.80 (m, 10 H)
7[f]			85	77-78 (0.35 mm)	1610	0.32 (s, 3 H) 0.43 (s, 3 H) 1.89 (s, 3 H) 6.70-7.37 (m, 4 H)
8[f]			62	(132-134)	1637 1680	0.24 (s, 3 H) 0.66 (s, 3 H) 0.68 (d-d, 2 H) 7.09-7.40 (m, 3 H)
9[f,g]		 8	7	63-64 (8 mm)		0.14 (s, 3 H) 0.26 (s, 3 H) 1.28 (s, 3 H) 1.59 (s, 3 H) 1.61 (s, 3 H) 1.99 (s, 1 H) 2.03 (s, 1 H)
		 9	41	56-58 (38 mm)	1665	0.17 (s, 6 H) 1.23 (s, 6 H) 1.68 (s, 3 H) 4.37 (s, 1 H)

[a] All products except 8 gave satisfactory analytical data. [b] Isolated yields. [c] The assignment of structures is based on the fact that a methyl group on an sp^3 carbon atom generally resonates at higher field than that on an sp^2 carbon, for example, $(CH_3)_2C(CN)OSiMe_3$ δ 1.54 (CCl_4) and $CH_2{=}C(CH_3)OSiMe_3$ δ 1.67 (CCl_4). [d] Catalytic amount of zinc iodide was used. [e] Determined by NMR. [f] 2 equiv of dimethyldicyanosilane were used. [g] With 1 equiv of dimethyldicyanosilane, $(RO)_2SiMe_2$ (ROH = diacetone alcohol) was also formed: NMR (CCl_4) δ 0.12 (s, 6 H), 1.34 (s, 12 H), 2.11 (s, 6 H), 2.52 (s, 4 H).

ether moiety was methanolized in the first stage). This partially methanolyzed product 11 has the structure of a monocyanosilylated β-diketone which appears to be otherwise inaccessible, since the reaction of trimethylcyanosilane with β-diketones does not give monocyanosilylated products.[13]

It should be noted that the present transformation may be useful for the protection of β-dicarbonyl or β-hydroxycarbonyl moieties. In addition, the results for juglone (entry 8) provide

a new method of differentiation of one carbonyl group from the other.

Various synthetic applications of the product **4** may be envisaged.[14]

References and Notes

(1) Synthesis via Silyl Alkenyl Ethers. Part 14. Part 13: I. Ryu, S. Murai, and N. Sonoda, *Tetrahedron Lett.*, 4611 (1977).

(2) D. A. Evans and J. M. Hoffman, *J. Am. Chem Soc.*, **98**, 1983 (1976); D. A. Evans, J. M. Hoffman, and L. K. Truesdale, *ibid.*, *95*, 5822 (1973); D. A. Evans, L. K. Truesdale, and G. L. Carroll, *J. Chem. Soc., Chem. Commun.*, 55 (1973).

(3) Cyanosilylated derivatives of monosilylated β-diketones should have electron rich C=C double bonds to allow interesting reactions with various electrophiles.

(4) **3**: IR (neat) 1640 cm^{-1}; NMR (CCl_4) δ 0.23 (s, 18 H), 1.55 (s, 3 H), 2.18–2.56 (d-d, 2 H), 4.08 (s, 2 H); MS *m/e* 271 (M^+).

(5) J. J. McBride, Jr., and H. C. Beachell, *J. Am. Chem. Soc.*, **74**, 5247 (1952); J. Hundeck, *Z. Anorg. Allg. Chem.*, **345**, 23 (1966). Also commercially available from Petrarch Systems, U.S.A. Recently we developed an improved procedure for dimethyldicyanosilane from dimethyldichlorosilane and silver cyanide: I. Ryu, S. Murai, T. Horiike, A. Shinonaga, and N. Sonoda, *Synthesis*, in press.

(6) For enolization of β-diketones, see: S. Forsen and M. Nilsson in "The Chemistry of the Carbonyl Group", Vol 2, J. Zabicky, Ed., Interscience, London, 1970, Chapter 3; H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972. pp 157–240.

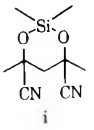
(7) S. Torkelson and C. Ainworth, *Synthesis*, 722 (1976), and references cited therein.

(8) It is not clear whether **9** was formed from dehydrocyanation of **8** or directly from **6**.

(9) **6**: NMR (CH_2Cl_2) δ 0.33 (s, 6 H), 1.34 (s, 6 H), 2.06 (s, 3 H), 2.56 (s, 2 H). **7**: IR 1720 cm^{-1}; NMR (CCl_4) δ 0.07 (s, 6 H), 1.33 (s, 6 H), 2.09 (s, 3 H), 2.48 (s, 2 H), 3.39 (s, 3 H); MS *m/e* 189 (P − 15).

(10) Well accepted 1,6 interaction of silicon and oxygen may be responsible for this: see T. J. Pinnavaia and J. A. McClarin, *J. Am. Chem. Soc.*, **96**, 3012 (1974), and references cited therein.

(11) The possibility that the initial formation of doubly cyanosilylated product i followed by dehydrocyanation might afford **4** is not precluded at the present stage.



(12) For example, the parent β-diketone of 5-cyano-1,1,3,5-tetramethyl-2,6-dioxa-1-silacyclohex-3-ene was regenerated on treatment with methanol (2 mL for 4 mmol of **4**) in 85% (room temperature, 20 h).

(13) The reaction of trimethylcyanosilane with 1 equiv of acetylacetone gave the enol silyl ether 1 (*E* + *Z*) in a high yield.

(14) Attempts of cyclopropanation of the product **4**, which may promise the one carbon homologation of β-diketones, are now in progress.

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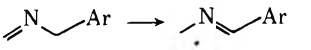
Imine Prototropy: Synthetic Consequences in the Generation of Metalloenamines

Summary: *N*-allylic imines and α,β-unsaturated imines undergo facile prototropic isomerization to *N*-alkenylimines which, upon reaction with *tert*-butyllithium, are converted into metalloenamines; the overall process allows for the regiocontrolled, sterically unimpeded generation of these organometallic intermediates.

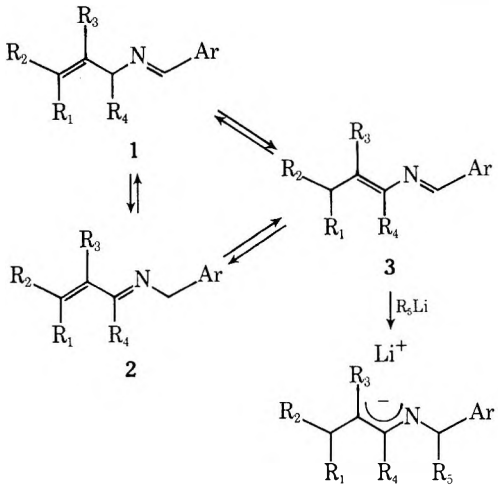
Sir: Initial reports from the laboratories of Stork[1a] and Wittig[1b] on the utility of metalloenamines in controlled alkylation and directed aldol processes, respectively, have fostered in subsequent years a rapid expansion of methodology[2] and synthetic strategies[3] based on these intermediates. Notwithstanding this record, the preparation of metalloenamines is confined presently to imine deprotonation with strong base, a procedure which is only useful for metalation (and hence bond formation) at the less-substituted α site of an unsymmetrically substituted ketimine.[4] Moreover, the efficiency of imine metalation with various bases is found to decrease with increasing substitution at the deprotonation site.[1b] We recently reported on methods which circumvent these limitations by the regiospecific, reductive generation of metalloenamines from α,β-unsaturated imines.[5] A further solution to the above noted problems is described herein.

Two studies bear on the genesis of the present method. In 1929, Ingold and associates[6] reported that *N*-benzylimines undergo prototropic isomerization with base to provide a thermodynamic mixture of imine isomers (eq 1). More re-



(1)

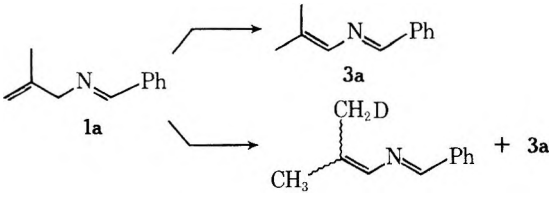
cently, it has been proposed[7] (albeit not demonstrated) that the enzyme inactivation produced by suicide enzyme substrates, such as propargylamine, involves a similar prototropic isomerization of an active site bound *N*-propargylimine. By analogy with these studies and the results of our previous work, we reasoned that the readily available *N*-allylic imines (**1**) of arylaldehydes would be sufficiently activated for base-catalyzed rearrangement to *N*-alkenylimines (**3**) (eq 2). Nu-



(2)

cleophilic addition to these intermediates would then be expected to provide the corresponding metalloenamines in a regiospecific, sterically unimpeded manner.

In order to explore this rationale the proclivity of imine **1a** to prototropic isomerization was initially examined. Addition of this imine to a solution of potassium *tert*-butoxide (*t*-BuOK) in tetrahydrofuran (THF) was accompanied by an instantaneous reaction which upon workup provided alkenylimine **3a**[8] in essentially quantitative yield. The facility



of this transformation at ambient temperature precluded an accurate determination of its half-life; however, at −78 °C a value of ~60 min was obtained. When the isomerization was conducted at 5 °C with 0.33 mol equiv of *t*-BuOK in the presence of 7.6 mol equiv of *t*-BuOD, the reaction was complete within 10 s and provided on workup d_1 and d_0 alkenylimines[9] in a ratio (1:2, respectively, as determined by NMR and mass spectroscopy) which is consistent with competing inter-

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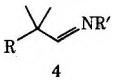
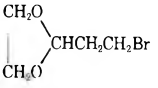
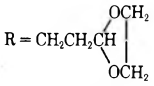
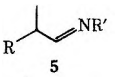
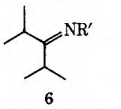
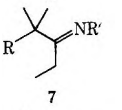
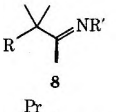
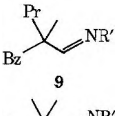
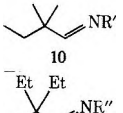
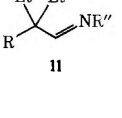
Table I

Entry	Starting material: Ar	R_1	R_2	R_3	R_4		Equilibrium composition, %: 1	2	3
1	Ph	H	H	Me	H	(1a)			>95
2	Ph	H	H	H	H	(1b)			>95
3	Ph	H	H	H	*i*-Pr	(1c)		>95	
4	Ph	H	H	Me	Et	(1d)			>95
5	Ph	H	H	Me	Me	(1e)			>95
6	Ph	H	Me	H	H	(1f)		*a*	
7	Ph	H	$-(CH_2)_4-$		H	(1g)		>95	
8	Ph	H	Et	Me	H	(2h)			>95
9	Ph	H	Me	Me	H	(2i)			>95
10	Ph	H	Me	H	H	(2f)		*a*	
11	Ph	H	*i*-Pr	H	H	(2j)		>95	
12	Ph	H	Me	Et	H	(2k)		>95	
13	PhOMe-*p*	H	Me	Et	H	(2l)			>95

[a] Isomerization of this substrate to **3f** was accompanied by polymerization.

Table II

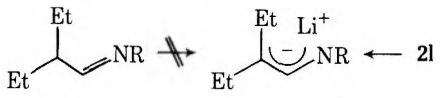
Entry	Starting material	Electrophile	Product[a]		% isolated yield
1	1a	MeI	 **4**	R = Me	93
2		BzBr		R = Bz	86
3		*n*-BuI		R = *n*-Bu	95
4		CH_2CHCH_2Br		R = CH_2CHCH_2	83
5		*i*-PrI		R = *i*-Pr	94
6					60
7		PhCOCl		R = PhCO	81
8		Me_3SiCl		R = Me_3Si	82
9		H_2O		R = H	81
10	1b	MeI	 **5**	R = Me	58
11		CH_2CHCH_2Br		R = CH_2CHCH_2	65
12		$CH_2C(Br)CH_2Br$		R = $CH_2C(Br)CH_2$	48
13	1c	MeI	 **6**		55
14	1d	MeI	 **7**	R = Me	90
15		H_2O		R = H	83
16	1e	MeI	 **8**		93
17	2h	BzBr	 **9**		86
18	2i	MeI	 **10**		87
19	2l	EtI	 **11**	R = Et	80
20		BzBr		R = Bz	83

[a] R′ = $-CH[C(CH_3)_3]Ph$; R″ = $-CH[C(CH_3)_3]$PhOMe-*p*.

and intramolecular isomerization processes.[6] Exchange of all nonaromatic hydrogens for deuterium was achieved upon prolonged exposure (>100 h) of imine **1a** to *t*-BuOK/*t*-BuOD. Other bases such as potassium isopropoxide and potassium ethoxide were also found to catalyze the rearrangement, while potassium hydroxide and potassium methoxide were only effective when used in combination with 18-crown-6 ether.

The effect of substitution in the allylic moiety on the above rearrangement is exemplified by the entries in Table I. In general, the isomer (**1**, **2**, or **3**) with the more highly substituted double bond is favored at equilibrium.[10] Whereas appropriately substituted unsaturated imines (**2**) can also be used in the preparation of alkenylimines (**3**) (entries 8 and 9), the equilibrium position is again dependent on substitution on the allylic or unsaturated imine moieties (entries 10–12). However, this limitation may be circumvented by substitution on the aromatic ring. The effectiveness of this modification is exemplified with 2-ethylbut-2-enal: the corresponding *N*-benzylimine **2k** is recovered unchanged under basic equilibrating conditions, whereas under the same conditions the *N*-(*p*-methoxybenzyl)imine **2l** provides the desired *N*-alkenylimine **3l** (>95%).

Transformation of the *N*-alkenylimine into the corresponding metalloenamine is readily performed by reaction of the former with *tert*-butyllithium. The efficiency of this process, as determined by trapping of the metalloenamine with various electrophiles, is illustrated by the entries in Table II. Several features of this tabulation are noteworthy. First, the overall yields are moderate to excellent, even in cases, such as entry 5, where the conjunction of a sterically encumbered nucleophile and electrophile is required in the alkylation step. Secondly, the process is regiocontrolled: imines **1c** and **1d** are converted into imines **6** (>99.5% VPC isomeric purity) and **7** (R = Me, >99.5% VPC isomeric purity), respectively, without evidence of crossover (i.e., metalloenamine equilibration). Similarly, imine **1e** regiospecifically provides the alkylated imine 8 (>99.5% VPC isomeric purity). By contrast, the metalloenamine generated in this process (**1e** → 8) cannot be prepared from the corresponding methyl ketimine using conventional deprotonation, since such methodology is restricted to metalation "on the methyl group only".[4] Finally, the process is not subject to the steric constraints encountered in imine deprotonation. For example, Wittig[1b] reported that imine **12** (R = c-C_6H_{11}) was not deprotonated by lithium di-

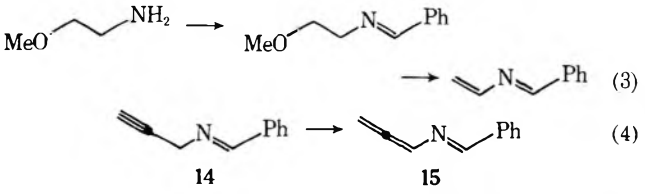


12 13

isopropylamide (2 h), tritylsodium, or tritylpotassium (for periods exceeding 4 weeks). Using the present method, the related metalloenamine **13** (R = CH(*t*-Bu)PhOMe-*p*) was efficiently generated from **2l** and converted to **11** (R = Bz) in an overall yield of 83% (isolated).

The *N*-allylic imines used in the present study were formed in >91% yield through condensation of the allylic amine[11] with benzaldehyde and converted to the corresponding metalloenamines using commercially available reagents. The following procedure is representative. Imine **1a** (16.5 mmol, ~1 M THF) was added to a solution of *t*-BuOK (3.4 mmol) in THF (42 mL). The resulting solution was stirred at ambient temperature (10 min), cooled to −78 °C, and transferred via cannula to a well-stirred solution (−78 °C) of *t*-BuLi (25 mmol) in pentane (14.8 mL). After 15 min, *n*-butyl iodide (33.5 mmol) was added. The resulting solution was stirred for 1 h at −78 °C, 1 h at ambient temperature, and treated with an equivalent volume of water. The mixture was extracted with methylene chloride and the combined organic phase was dried (Na_2SO_4) and concentrated. Distillation of the crude oil provided imine **4** (R = Bu, bp 119–129 °C (0.2 mm), 95%).[12] The alkylated imines are readily converted into the carbonyl derivatives by hydrolysis with 2 N hydrochloric acid or by distillative hydrolysis using aqueous oxalic acid.

In addition to the transformations of allylic imines and unsaturated imines into alkylated imines (and thence ketones and aldehydes) noted above, several further consequences of this chemistry are noteworthy. For example, the allylic imine isomerization involves a transient species which is functionally equivalent to a homoenolate. Thus, the method can be used to prepare β-deuteriocarbonyl derivatives (vide supra).[13] Furthermore, the imine functionality can be used to facilitate elimination reactions (eq 3) and, as such, this strategy can be employed as an alternative method for the preparation of al-



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kenylimines.[14] Finally, in vitro analogy for suicide enzyme inhibition has been demonstrated in the conversion of propargylimine **14** into the novel allenylimine **15** (eq 4). Further studies are in progress.

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(8) The alkenylimines and alkylated imines prepared in this study gave IR and NMR data completely in accord with the assigned structures. The latter compounds were additionally characterized by conversion to the known carbonyl compounds, which were further characterized by transformation to previously reported derivatives.

(9) The *E* and *Z* isomers of the d_1 alkenylimine were formed in approximately equal amounts.

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(15) National Science Foundation Predoctoral Fellow, 1975–1977.

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Total Synthesis of (±)-Sarracenin

Summary: The synthesis of the iridoid monoterpene sarracenin is described.

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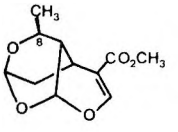
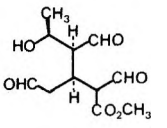
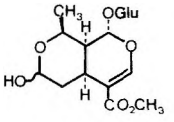
Sir: In 1976, Miles[1] reported the isolation and single-crystal x-ray structural determination of the monoterpene sarracenin (**1**), obtained from the roots and leaves of the insectivorous golden trumpet (*sarracenin flavia*) growing in the Okefenokee swamp. The structural similarity between sarracenin and other secoiridoid terpenes [e.g., morroniside (**2**)][2] is evident from inspection of the trialdehyde **1a** resulting from "unzipping" the novel bisacetal–enol ether system present in sarracenin.



1



1a



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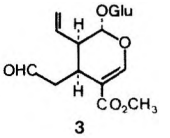
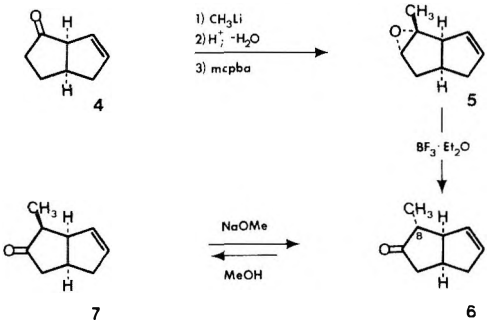


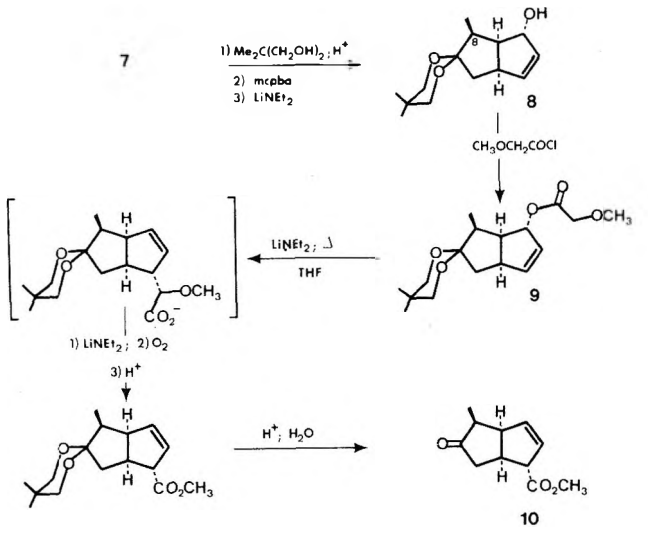
3

The biosynthetic pathway leading from mevalonic acid through the cyclopentanoid monoterpenes to the indole alkaloids has been traced as far as secologanin (**3**).[3] Miles has postulated that sarracenin may play an important role in this sequence by supplementing or possibly supplanting the route through secologanin. This hypothesis is intriguing in that sarracenin displays the same absolute configuration at C-8 (absent in secologanin) that is present in many of the indole alkaloids (e.g., reserpinine and ajmalicine). We thus undertook the total synthesis of sarracenin in order to set the stage for the preparation of radiochemically double-labeled material that could be used for feeding–incorporation studies.

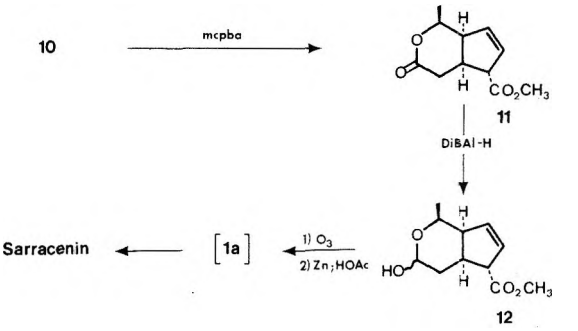
Scheme I



Scheme II



Scheme III



We planned our synthetic strategy around the concept of sequentially cleaving both rings of an appropriately constituted bicyclo[3.3.0]octyl skeleton, ultimately forming the trialdehyde **1a** (as some cyclic, hemiacetal form).[4] The sequence outlined in Scheme I was used to refunctionalize the left-hand ring of the readily available bicyclic ketone **4** in preparation for eventual oxidative cleavage.[5] The methyl ketone **6** obtained from the rearrangement of epoxide **5** had predominantly the incorrect relative stereochemistry at C-8; however, equilibration with base gave a 1.3:1 exo/endo mixture from which the desired endo-isomer **7** was easily separated using a Waters Prep 500 System liquid chromatograph.

The regioselective introduction of the allylic carbomethoxy group was accomplished as outlined in Scheme II.[6] Regiospecific formation of the allylic alcohol **8** was accomplished, after protection of the carbonyl group as the ketal,[7] via a dialkylamide initiated rearrangement of the epoxide.[8] The new carbon–carbon bond was then established by an ester enolate Claisen rearrangement of the α-methoxyacetate **9**. Oxidation of the resulting carboxylate as the dianion using molecular oxygen followed by decarboxylation–dehydration removed the superfluous carbon and produced the desired carbomethoxy group. The entire sequence from ketone **7** to ketone **10** was carried out with an overall yield of 25%.

Baeyer–Villiger oxidation of ketone **10** with *m*-chloroperbenzoic acid in methylene chloride in the presence of heterogeneous bicarbonate[9] proceeded cleanly and afforded the lactone **11** essentially uncontaminated by epoxides (Scheme III).[10] Partial and selective reduction of the lactone carbonyl, accomplished with diisobutylaluminum hydride, afforded the crude lactol **12** as mixture of anomers in 72% yield. Without purification, **12** was subjected to ozonolytic cleavage followed by reduction with zinc in acetic acid. Dehydrative cyclization of the penultimate intermediate **1a** was accomplished simply by warming the acetic acid solution resulting from reduction of the ozonide. After chromatographic purification, racemic sarracenin was obtained in 15% yield with mp 107–108 °C (mp 127–128 °C dec for the (−)-enantiomer) and with infrared, ^{1}H and ^{13}C nuclear magnetic resonance, and mass spectral data identical with authentic material.[11,12] We are proceeding now with the preparation of optically active sarracenin as well as radiochemically labeled material.

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(8) Proton NMR, infrared, and high-resolution mass spectral data consistent with the proposed structures of all new compounds except **1a** were obtained.
(9) Dr. P. S. Stotter, University of Texas at San Antonio, has found that comparatively slow Baeyer–Villiger oxidations are accelerated by the presence of bicarbonate (private communication). In the present case, the rate is approximately doubled.
(10) Under identical conditions, the ketoolefin **7** underwent epoxidation to the exclusion of lactone formation.
(11) We are grateful to Professor Miles for an authentic sample and copies of the original spectra of sarracenin.
(12) In a separate series of experiments, the *exo*-methyl ketone **6** was converted to 8-episarracenin and in neither series was there a loss of stereochemical integrity at C-8.

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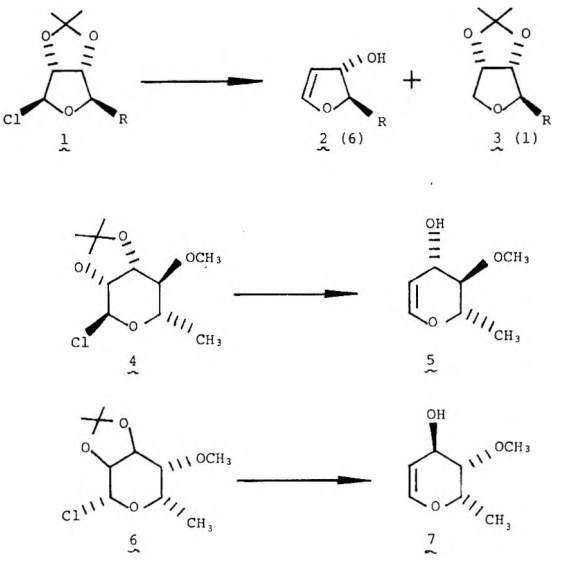
An Efficient Method for the Preparation of Furanoid and Pyranoid Glycals[1]

Summary: The reduction of furanosyl and pyranosyl halides with lithium–ammonia provides an efficient high yielding synthesis of furanoid and pyranoid glycals.

Sir: In connection with a synthetic program underway in these laboratories on the total synthesis of ionophores, it became necessary to prepare both furanoid and pyranoid glycals. While the total synthesis project is not yet complete, a recent report by Eitelman and Jordaan[2] on a similar, but not as efficient and general, method for the formation of furanoid glycals prompts us to report our results on this phase of the work now.

Glycals in general tend to undergo acid-catalyzed allylic rearrangement,[3] particularly as their C-3 hydroxyl derivatives. This tendency is most pronounced in the furanoid system where the C-3 carbon–oxygen bond of either epimer is more nearly coplanar with the π cloud of the enol ether double bond. In order to avoid this undesirable result, the C-3 oxygen substituent must be a poor leaving group[4] and the reaction conditions should be basic rather than acidic. For furanoid glycal formation, particularly, these considerations preclude the use of the classical Fischer–Zach method[5] for pyranoid glycal generation by zinc–acetic acid reduction of acetylated pyranosyl halides. The well-known fragmentation of β-alkoxyethyl halides on treatment with metals in inert solvents suggests a solution to this problem and the prospect for a general glycal formation procedure.

To test this possibility 2,3-*O*-isopropylidene-β-D-erythrofuranosyl chloride [**1**, R = H; mp 60–61.5 °C; $[\alpha]^{24}_D$ −167° ($HCCl_3$, *c* 0.8)] was prepared from D-erythronolactone in 79% overall yield by acetonide formation [CH_3COCH_3, $(CH_3)_2C(OCH_3)_2$, *p*-TSA] and partial reduction (DIBAL, Et_2O, −78 °C) to 2,3-*O*-isopropylidene-D-erythrose [mp 30–32.5 °C, $[\alpha]^{24}_D$ −79.3° ($HCCl_3$, c 0.925)] and then chloride formation



[CCl_4, THF, $(C_6H_5)_3P$]. Reduction of this furanosyl chloride **1** (R = H) with lithium in liquid ammonia (4 equiv of Li, NH_3, 2 h; 6 equiv of NH_4Cl; evaporate NH_3; extract Et_2O) resulted in a 60% yield of a 6:1 (NMR) mixture [evaporative distillation 60–70 °C (35 mmHg)] of the glycal **2** (R = H) and the tetrahydrofuran **3** (R = H) from hydride displacement without fragmentation. This mixture was not separated due to the lability of the glycal, and for most preparative purposes the presence of the tetrahydrofuran component is not deleterious.

Turning to the more functionalized pentose series D-ribonic acid δ-lactone was converted to its acetonide [CH_3COCH_3, $(CH_3)_2C(OCH_3)_2$, *p*-TSA, 12 h, room temperature], O-methylated at C-5 (Ag_2O, CH_3I, CH_3CN, 18 h, 50 °C), and then reduced (DIBAL, Et_2O, 1 h, −78 °C) to the blocked sugar [bp 82.5 °C (0.03 mmHg); $[\alpha]^{26}_D$ −18.75° ($HCCl_3$, c 1.68)] in 90% overall yield. Chloride formation (CCl_4, THF, $(C_6H_5)_3P$; 90%) resulted in the furanosyl chloride **1** [R = CH_2OCH_3; evaporative distillation 60–70 °C (0.03 mmHg); $[\alpha]^{27}_D$ −71° ($HCCl_3$, c = 1.80)] which on reduction with lithium in ammonia as above afforded a 75% yield of a 6:1 (NMR) mixture [evaporative distillation 80–90 °C (0.2 mmHg)] of the glycal **2** (R = CH_2OCH_3) and the corresponding tetrahydrofuran derivative[7] **3** (R = CH_2OCH_3). An analytical sample of the glycal **2** [R = CH_2OCH_3; $[\alpha]^{22}_D$ +318° ($HCCl_3$, *c* 0.83)] was obtained with significant material loss (70% recovery) by chromatography on silica gel or Florisil, and the mass spectrum of this monomeric glycal showed only methyl furfuryl ether (*m/e* calcd 112.053, found 112.052). Despite the lability of this furanoid glycal that results in poor recovery after purification, pure glycal is available by this procedure and in most instances the mixture itself may be used directly in subsequent synthetic transformations. These results contrast with those of Eitelman and Jordaan[2] who obtained similar furanoid glycals in no more than 11% yield together with significant amounts of dimeric products as a result of coupling when furanosyl bromides were reduced with sodium or potassium in dry tetrahydrofuran.

Application of this reduction procedure to the pyranose series was even more rewarding. By a similar series of blocking reactions starting with methyl α-L-rhamnopyranoside[8] and methyl 6-deoxy-α,β-L-gulopyranoside,[9] the pyranosyl chlorides **4** [evaporative distillation 95 °C (1.0 mmHg); $[\alpha]^{23}_D$ −114.5° ($HCCl_3$, *c* 1.56)] and **6** [evaporative distillation 65 °C (0.05 mmHg); $[\alpha]^{23}_D$ +45.3° ($HCCl_3$, c 1.23)] were prepared in 65 and 71% overall yields, respectively. Reduction of these halides with lithium in liquid ammonia as above led in 90% yields to the corresponding pyranosyl glycals **5** [mp 76–77 °C;

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$[\alpha]^{24}_D$ −0.24° ($HCCl_3$, c 1.25)] and **7** [evaporative distillation 95 °C (1.0 mmHg); $[\alpha]^{23}_D$ −121° ($HCCl_3$, c 1.43)]. In the pyran series only reductive fragmentation was observed and none of the products from direct hydride displacement was observed. While these glycals can be prepared by the Fischer–Zach method, the high yield of this process together with the generation of the glycal itself rather than the more labile ester derivative offers significant advantages. It should be noted that while the acetonide blocking group is used early in the synthetic sequence to achieve functional group selectivity, it is also a requisite of the lithium–ammonia reduction process and serves two useful roles.[10]

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(1) This work was made possible through a grant from the National Institutes of Health, Grant No. HL21367-01.
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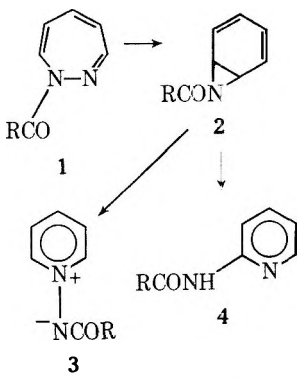
Heterocyclic Studies. 45. Thermal Isomerization of a 1,2-Diazepine to a 1,3-Diazepine

Summary: The 1,2-diazepine **5** at 110 °C gives a mixture of the 6-benzamidopyridine **6** and the 1-benzoyl-1,3-diazepine **7**.

Sir: 1-Acyl- and 1-alkoxycarbonyl-1,2-diazepines, readily available by photoisomerization of 1-iminopyridinium ylides,[1] undergo a variety of reactions on heating. 1-Benzoyl-1,2-diazepines[2] and 1-acyl-3,5,7-triaryldiazepines[3] give 1-acyliminopyridinium ylides **3**, and this path is also observed on treatment of 1-alkoxycarbonyl-1,2-diazepines **1** (R = OR′) in hot acetic acid.[4] 2-Aminopyridine derivatives **4** are formed in low yields, together with acyclic dienaminonitriles, on heating 1-alkoxycarbonyldiazepines at 150–170 °C neat or in refluxing



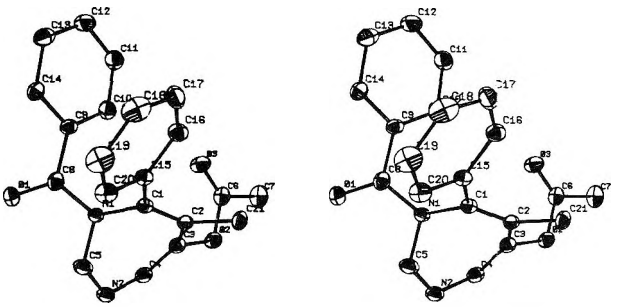
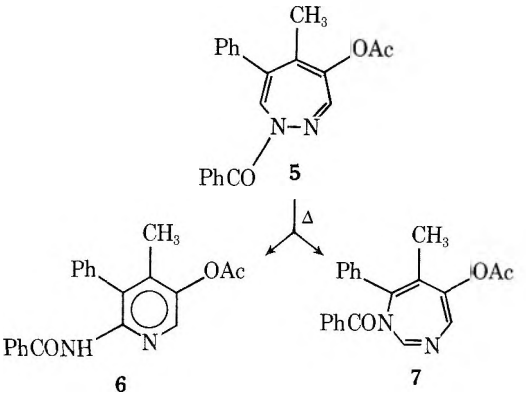


Figure 1. ORTEP stereoprojection of **7** (hydrogens omitted).

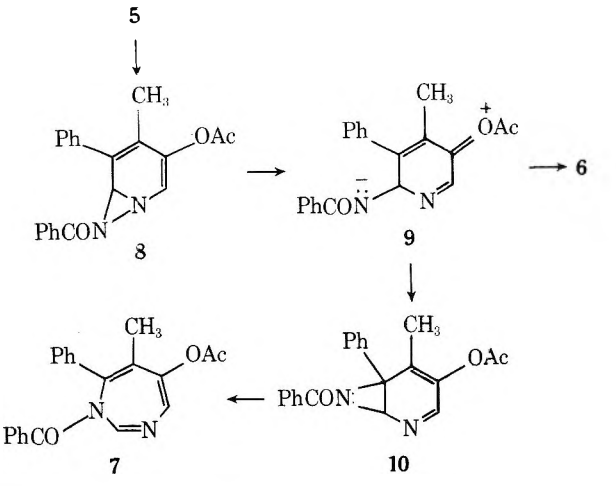
xylene.[4,5] The pyridine products from these reactions have been suggested to arise via 1,7-diazabicyclo[4.1.0]heptadiene valence isomers, but the factors that determine the product distribution are not well defined.

We have now found an additional pathway for the thermal isomerization of 1,2-diazepines. 1-Benzoyl-4-acetoxy-5-methyl-6-phenyl-1,2-diazepine (**5**), prepared by O-acetylation of the 1,5-dihydrodiazepinone,[6] undergoes a very facile thermal reaction to give the 3-acetoxy-6-benzamidopyridine **6** in 50% yield. A second product, isolated in 16% yield, is the 1-benzoyl-1,3-diazepine **7**, in which the positions of carbon and nitrogen in the seven-membered ring have been interchanged. Fully unsaturated 1,3-diazepines such as **7** are little known compounds, although the corresponding 1,3-oxazepines are well characterized.[7,8] The structure of **7** was established by x-ray crystallography.



Several other 1-acyl-4-acyloxydiazepines gave similar mixtures of products (as seen by NMR) on heating in chlorobenzene at 120 °C. In each case the 6-acylamido-3-acyloxypyridines were isolated and characterized as the major products; the minor products have not been isolated but are presumed to be the corresponding 1,3-diazepines.

Scheme I



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The pathway to the 1,3-diazepines **7** from the 1,2-diazepine **5** must involve the bicyclic valence isomers **8** and **10** (Scheme I). Analogous steps have been postulated[8,12] for the formation of 2-arylbenz[*d*]-1,3-oxazepines with the photoisomerization of 2-arylquinoline 1-oxides; however, benzo[*d*]-1,3-diazepines are not observed in the analogous reactions of quinoline-1-acylimides.[13,14] The fact that products of type **6** or **7** have not been observed in thermal reactions of other 1-benzoyldiazepines suggests that the acetoxy group of **5** is an important factor in the mechanism. A possible role is stabilization of a dipolar intermediate such as **9**, which could give rise to **6** and **10** by well precedented steps.

Experimental. A solution of **5** in toluene was kept at 110 °C for 40 min. After removal of solvent, the NMR spectrum of the solid residue indicated a mixture of two products in a 6:4 ratio. Fractional crystallization of the mixture from CH_2Cl_2–ether gave the main product (50% yield) as white crystals: mp 169–170 °C; IR ν (KBr) 3300, 1755, 1650; NMR δ ($CDCl_3$) 1.97 (s, 3), 2.38 (s, 3), 7.2–7.7 (m, 10), 7.82 (br, 1), 8.33 (s, 1); anal.[9] This compound was identified as the 6-benzamido-3-acetoxypyridine **6** by mild alkaline hydrolysis to the known 6-benzamido-3-hydroxypyridine.[10] The more soluble fractions were recrystallized several times from ether and benzene to give the 1,3-diazepine **7** as large, faceted prisms: mp 146–147 °C; IR ν (KBr) 1760, 1670, 1635; NMR δ ($CDCl_3$) 1.75 (s, 3), 2.28 (s, 3), 6.7–7.7 (m, 12); anal.[9]

Crystallography. Crystals of **7** were orthorhombic, space group *Pbca*, with $a = 25.029$ (9), $b = 10.123$ (6), and $c = 14.191$ (6) Å; $d_{calcd} = 1.28$ g cm^{-3} for $Z = 8$.

Intensity data were obtained with Mo Kα radiation with scan rate of 1°/min over a range of 1.75° plus Kα_1 − Kα_2. A total of 2345 reflections were measured, with 2093 observed. No absorption correction was made. The structure was solved by tangent refinement techniques using the ORTEP program to find a possible molecule from several *E* maps. Subsequent cycles of least-squares refinement located all nonhydrogen atoms with anisotropic temperature factors.[11] Hydrogen positions were calculated and were not refined. Further refinement led to a final $R = 0.083$ and $R_w = 0.071$ where $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R_w = [\Sigma_w(|F_o| - |F_c|)^2/\Sigma_w|F_o|^2]^{1/2}$. A final difference map encompassing the atoms of the seven-membered ring showed no electron density greater than 0.5 e/Å^3. A stereoscopic view of **7** is shown in Figure 1.

Acknowledgment. We are most grateful to Dr. Lloyd Guggenberger, E. I. du Pont de Nemours and Co., for providing the diffractometer data used in the crystallographic analysis.

Supplementary Material Available: Table of positional and thermal parameters for the structure of 7 (2 pages). Ordering information is given on any current masthead page.

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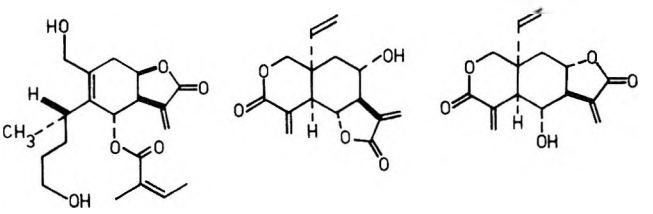
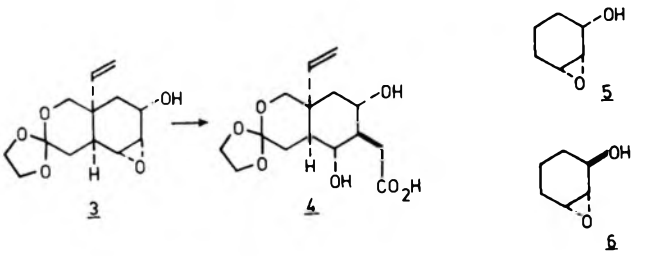
Ring-Opening Reactions of α-Oxy Epoxides with *tert*-Butyl Dilithioacetoacetate

Summary: *tert*-Butyl dilithioacetoacetate has been employed in ring-opening reactions of certain α-hydroxy epoxides and α-methoxymethyloxy epoxides. The regiochemical nature of ring opening for this dinanion is essentially the same as that previously observed for dilithioacetate. A notable exception, however, was observed with an α-methoxymethyloxy epoxide bearing a geminal dialkyl substituent at the α′ position. This substance was found to regiospecifically open to the corresponding 1,3-dioxy system.

Sir: The occurrence in nature of antitumor agents such as eriolangin (**1**) and vernolepin (**2**) which contain either cis- or trans-lactone arrays bearing an α-hydroxy group has prompted the experimental consideration of elaborating such systems by the vehicle of ring opening of α-oxygen substituted epoxides with an appropriate nucleophile. In a brilliant series of investigations, Danishefsky and co-workers succeeded in this regard with the ring opening of the α-hydroxy epoxide **3** with dilithioacetate to realize formation of the acid diol **4**, subsequently converted into both vernolepin and vernomenin.[1] In addition, these authors have also studied the dilithioacetate induced ring opening of the simple α-hydroxy epoxides **5** and **6** together with their trimethylsilyloxy analogues.[2]

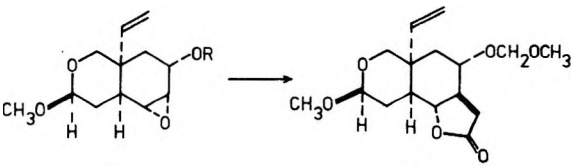


1 Eriolangin **2** Vernolepin **8** Vernomenin



3 **4** **5** **6**

Recently, we attained the same synthetic juncture in our synthesis of vernolepin which required regiospecific ring opening of the α-hydroxy epoxide **7**. We were, however, interested in using an alcohol-protected form of **7** to realize the exclusive formation of vernolepin as opposed to the concurrent construction of both vernolepin and its biologically less active isomer vernomenin (**8**). Taking cognizance of Danishefsky's results, which indicated that α-trimethylsilyloxy epoxides would either not react or would open predominantly in the undesired manner,[1,2] we nevertheless examine the feasibility of preparing vernolepin by ring opening of the α-methoxy-



7 R = H **22**
9 R = CH_2OCH_3

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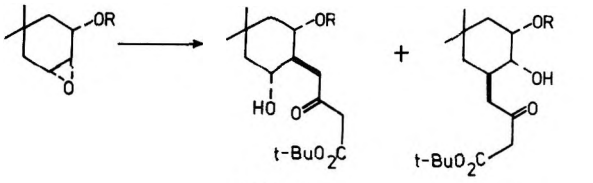
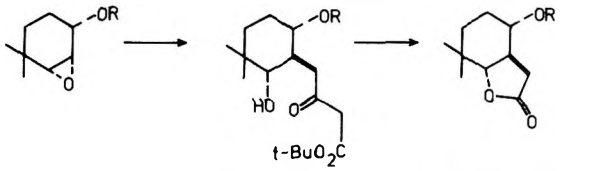
methyloxy epoxide **9**. Compound **9** was obtained from **7** by reaction of the latter with chloromethyl methyl ether.[3] Not surprisingly, reaction of **9** with dilithioacetate gave only unreacted epoxide even under forcing conditions. This result brought us to the conclusion that use of **9** in a vernolepin synthesis would require a more energetic nucleophile for epoxide ring opening. We thus set out to examine the ring opening of the model α-hydroxy epoxides **10**[4] and **11**[4] as well as their α-methoxymethyloxy analogues with tert-butyl dilithioacetoacetate.[5] Compound **10**, on reaction with 3 equiv of *tert*-butyl dilithioacetoacetate[6] for 2 h at 22 °C, gave in 90% yield a 3:1 mixture of compounds **12** and **13**, respectively.[7] The



10 R=H
14 R=CH_2OCH_3
12 R=H
15 R=CH_2CCH_3
13 R=H
16 R=CH_2OCH_3

α-methoxymethyloxy epoxide **14** gave a 1:5 mixture of compounds **15** and **16** under the same conditions.[7] These results parallel those obtained by Danishefsky.[2]

The α-hydroxy epoxide **11**, on the other hand, gave a 70% yield of the adduct **17** with no detectable regioisomeric product when treated with 5 equiv of *tert*-butyl dilithioacetoacetate for 24 h at 22 °C. Even more gratifying was the finding that the α-methoxymethyloxy epoxide **18**, on reaction



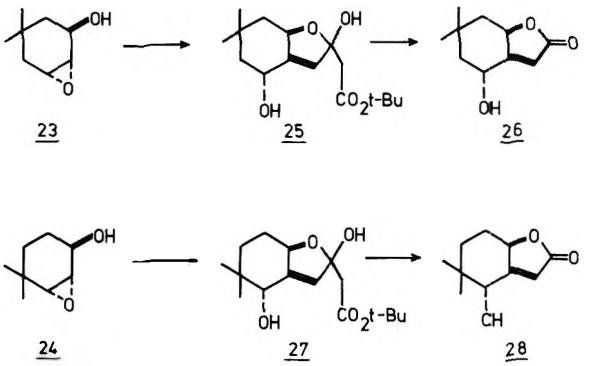
11 R=H
18 R=CH_2OCH_3
17 R=H
19 R=CH_2OCH_3
20 R=CH_2OCH_3
21 R=H

with 7 equiv of *tert*-butyl dilithioacetoacetate for 7 h at 22 °C, gave a 97% yield of the desired adduct **19**. The steric buttressing effect of the geminal dimethyl group adjacent to the epoxide clearly enhances the desired regiospecificity of this reaction and completely overwhelms the counter directive effect anticipated from the α-methoxymethyloxy moiety.

Use of *tert*-butyl dilithioacetoacetate for these ring-opening reactions introduces four carbon atoms instead of the desired two atoms; thus, it was imperative for us to develop a means of transforming products such as **19** into the desired lactonic substances. To this end, a second-order Beckmann rearrangement was applied to **19** in which the β-keto ester was treated first with isoamyl nitrite and potassium *tert*-butoxide in *tert*-butyl alcohol and second with acetic acid, sodium acetate, and acetic anhydride to afford, after chromatography and crystallization, the lactone **20** (mp 55–56 °C) in 62% yield.[8] Treatment of **20** with perchloric acid in acetonitrile gave the corresponding lactone alcohol **21** (mp 95–97 °C) in 65% yield.[9] This reaction sequence constitutes a regiospecific synthesis of an unsymmetrically substituted lactone system of this type by an epoxide ring-opening process.

Encouraged by these results, which we felt represented a reasonable model for our vernolepin intermediate, we then reacted **9** with *tert*-butyl dilithioacetoacetate. The resulting adduct subjected to the Beckmann degradation sequence gave the lactone **22** (mp 158–160.5 °C) in 65% overall yield.[10]

At this point we were curious as to the course of reaction between *tert*-butyl dilithioacetoacetate and the *trans*-α-hydroxy epoxides **23** and **24**, since successful reaction in these instances could serve as model studies for a synthesis of eriolangin (**1**). Compounds **23** and **24** were readily available using the recently developed method of Heathcock.[11] Reaction of **23** with *tert*-butyl dilithioacetoacetate (8 equiv) for 4 h at 22 °C afforded a waxy solid, spectroscopically identified as the *cis*-lactol **25** (81% yield). Treatment of **25** with 1 equiv of



23
25
26
24
27
28

potassium *tert*-butoxide in *tert*-butyl alcohol for 24 h at 50 °C gave in 55% yield the *cis*-lactone **26** (mp 64–65.5 °C). Similarly, the epoxide **24** on reaction with 8 equiv of *tert*-butyl dilithioacetoacetate at 50 °C for 3 h gave the lactol **27** in 80% yield, again as a waxy solid. Subsequent base treatment of this lactol using the same conditions as previously described gave the *cis*-lactone **28** (mp 93.5–95 °C) in 60% yield. In neither the preparation of lactone **26** nor in the preparation of lactone **28** could any other regioisomeric lactone component be detected. It thus appears that ring opening of *trans*-α-hydroxy epoxide systems with *tert*-butyl dilithioacetoacetate is more regioselective than comparable reactions carried out with dilithioacetate.

Acknowledgments. This research was supported by PHS Grant CA-18485-02. Support from the Hoffmann-LaRoche Foundation is gratefully acknowledged.

References and Notes

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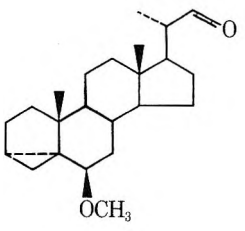
A Stereoselective Wittig Reagent and Its Application to the Synthesis of 25-Hydroxylated Vitamin D Metabolites

Summary: A method for the selective preparation of trans-homoallylic alcohols is described, and its mechanism discussed in terms of an internal Schlosser "trans-selective Wittig" reaction.

Sir: The Wittig reaction is one of the most important in synthetic organic chemistry.[1] We have made use of this condensation reaction in a number of syntheses of 25-hydroxycholesterol. For example, reaction of 3α,5α-cyclo-(20*S*)-formyl-6β-methoxypregnane (**1**) with dibromomethylenetriphenylphosphorane[2] or with dichloromethylenetris(dimethylamino)phosphorane[3] leads to the dihalovinyl compounds **2**.[4] The ylide **3** derived from isoprene condensed with the same aldehyde to give the diene **4**.[5,6] The compounds **2** and **4** were then converted to 25-hydroxycholesterol as described previously.[4,6]



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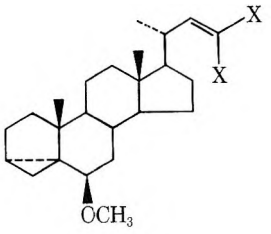

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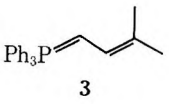

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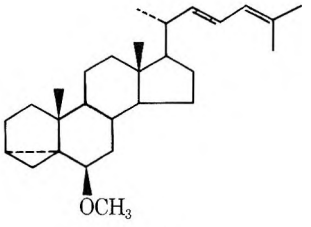

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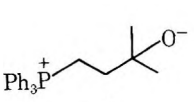
In this communication we wish to report a further preparation of 25-hydroxycholesterol through the agency of a novel stereoselective Wittig reagent.[7] Methylenetriphenylphosphorane, prepared in tetrahydrofuran from methyltriphenylphosphonium bromide and *n*-butyllithium, reacts with isobutylene oxide at 0 °C.[8] The product, which possesses either the betaine structure **5** or more likely the oxaphospholane structure **6**,[9] reacts with a further mole of *n*-butyllithium to yield the ylide **7**.[10]



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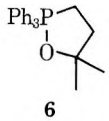

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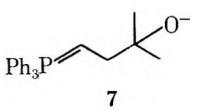
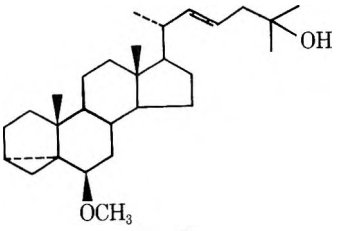


7

The aldehyde **1** reacts with this ylide to give the Δ^{22}-25-hydroxy product **8**. The manner in which the reaction is performed is important. In the first step of the preparation of the ylide **7** it is necessary to ensure that all of the methyltriphenylphosphonium bromide is converted to the methylene ylide, otherwise during the subsequent addition of *n*-butyllithium some of the methylene ylide will again be formed as a contaminant, giving rise to the methylene compound **9** as a by-product.

Similarly, if insufficient isobutylene oxide is added in the second step, the same methylene by-product will result. If too much isobutylene oxide is used and the excess is not removed, *n*-butyllithium will be consumed by the epoxide in the next stage. Finally, in the second addition of *n*-butyllithium an excess must be avoided lest the aldehyde **1** be consumed, giving rise to the alcohol **10**. In short, if the reaction is not conducted with due regard to the stoichiometry of the reagents, yields are adversely affected. In properly conducted reactions yields of isolated alcohol **8**[11] are in the range 75–86%.



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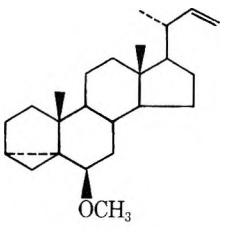

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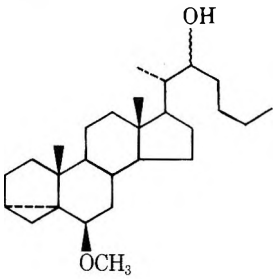
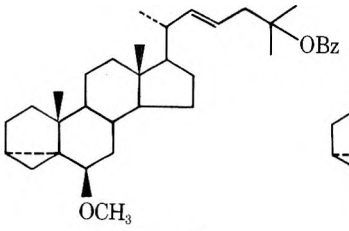


10

Two stereochemical considerations are germane to the reaction of the aldehyde **1** with the ylide **7**. The first is the retention of chirality at C-20; clearly any epimerization at this center would result in the lowering of yield of the desired product **8** having the correct natural 20*R* stereochemistry. Generally aldehydes are easily epimerized by base so at the outset of this work we were concerned about the presence of a fully developed alkoxide anion in the ylide **7**. Compounds **11**, **12**, and **13** were therefore independently prepared.[12]



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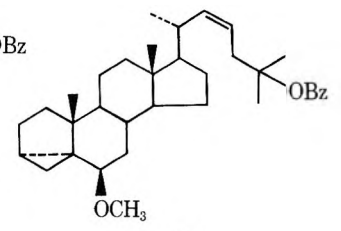

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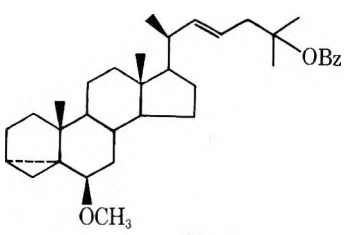

13

Comparison of the NMR spectra[13] of these compounds with that of the total crude product mixture (after benzoylation) revealed that no epimerization at C-20 had taken place. The

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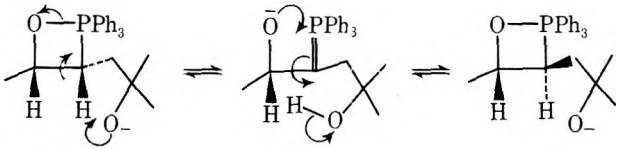
results indicate that C–C bond formation between aldehyde and ylide is faster than deprotonation at C-20, easily rationalized after the event since aldehydes are known to react rapidly even at −70 °C with ylides to give oxaphosphetane intermediates[14] (see below).

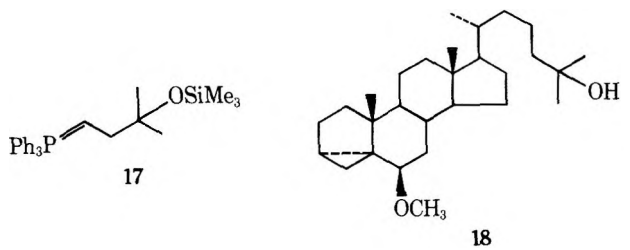
The second important, and possibly more interesting, stereochemical aspect of this reaction is the configuration of the resulting double bond. The NMR spectra of the crude product also revealed a mixture in which the $\Delta^{22}E/\Delta^{22}Z$ ratio was approximately 85:15. The isolated crystalline material is pure $\Delta^{22}E$ compound **8**, a somewhat surprising result since, normally, nonstabilized ylides are cis selective. This has been elegantly rationalized by Vedejs and Snoble[14] in terms of the first step of a Wittig reaction being a $_{\pi}2_s + {}_{\pi}2_a$ cycloaddition to give an oxaphosphetane. For maximum overlap of the relevant orbitals in such a cyclization, the π bonds must approach one another orthogonally. If this is done in the least hindered orientation, the most hindered oxaphosphetane inevitably results. Thus, the first product of our reaction would be the oxaphosphetane **14**. If this were to collapse to olefin and triphenylphosphine oxide, the $\Delta^{22}Z$ product would of course be the result. An explanation for the predominant production of $\Delta^{22}E$ in our reaction is that there exists an intrinsic Schlosser "trans-selective Wittig" mechanism.[15] Thus, the initially formed *cis*-oxaphosphetane **14**,[16] if prevented from collapsing to olefin, can enter into equilibrium with the ylide **15** through a five-center transition state as depicted. By rep-



14 **15** **16**

rotonation of C-22 from the other side this ylide **15** can then establish equilibrium with the more stable *trans*-oxaphosphetane **16**, which ultimately decomposes to give the $\Delta^{22}E$ product. Based on this postulate the aldehyde **1** and ylide **7** were mixed at low temperature (−35 to −20 °C) and kept at this temperature for a period of time (usually about 1 h) before warming and allowing the oxaphosphetanes to decompose to olefin and triphenylphosphine oxide. This did indeed lead to greater yields of the trans product than had been obtained in earlier experiments conducted in the range of 0–20 °C.

Confirmation of the need for the 25-alkoxide function in the formation of the $\Delta^{22}E$ product and support for this intramolecular mechanism were derived by allowing the ylide **7** to react with 1 mol of trimethylsilyl chloride, yielding the ylide **17**. Condensation with the aldehyde **1** gave an oily mixture of olefins in which the approximate *E*/*Z* ratio was dramatically changed to 15:85.[17]



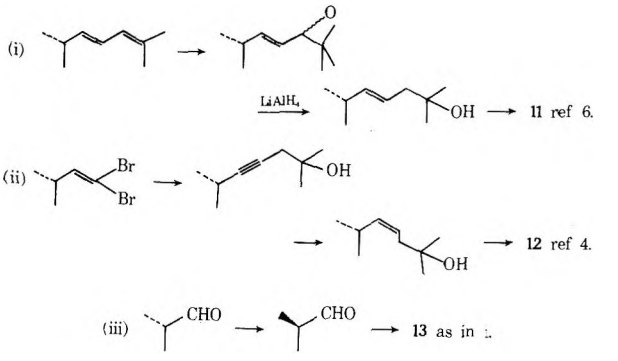
17 **18**

Hydrogenation of the olefin **8** in methylene chloride solution over a 5% platinum on carbon catalyst led essentially quantitatively to the saturated derivative **18**,[4,6,18] which is readily transformed to 25-hydroxycholesterol and thence to the vitamin D metabolites.

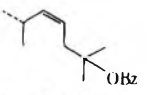
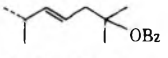
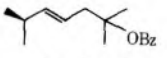
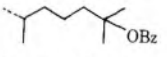
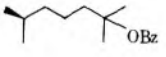
We believe that this type of ylide has possibilities of wider application in organic synthesis where a stereoselective synthesis of trans-homoallylic alcohols is desired.[19]

References and Notes

(1) For a recent review see J. Mathieu and J. Weill-Raynal, "Formation of C–C Bonds", Vol. II, Thieme-Edition Publishing Sciences Group, New York, N.Y., 1975, pp 608–639.
(2) F. Ramirez, N. B. Desai, and N. McKelvie, *J. Am. Chem. Soc.*, **84**, 1745 (1962); E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 3769 (1972).
(3) W. G. Salmond, *Tetrahedron Lett.*, 1239 (1977).
(4) W. G. Salmond, M. C. Sobala, and K. D. Maisto, *Tetrahedron Lett.*, 1237 (1977).
(5) R. F. N. Hutchins, M. J. Thompson, and J. A. Svoboda, *Steroids*, **15**, 113 (1970).
(6) W. G. Salmond and M. C. Sobala, *Tetrahedron Lett.*, 1695 (1977).
(7) A brief preliminary discussion of this material is given by W. G. Salmond in "Vitamin D, Biochemical, Chemical and Clinical Aspects Related to Calcium Metabolism", Walter deGruyter, Berlin and New York, 1977, pp 61–70.
(8) For examples of the reaction of epoxides with phosphoranes see: D. B. Denney, J. J. Vill, and M. J. Boskin, *J. Am. Chem. Soc.*, **84**, 3944 (1962); L. Horner, H. Hofmann, and V. G. Roscano, *Chem. Ber.*, **95**, 536 (1962); E. Zbiral, *Monatsh. Chem.*, **94**, 78 (1963); W. E. McEwen, A. P. Wolf, C. A. VanderWerf, A. Blade-Font and J. W. Holfe, *J. Am. Chem. Soc.*, **89**, 6685 (1967).
(9) A. R. Hands and A. J. H. Mercer, *J. Chem. Soc. C*, 1099 (1967); 2448 (1968). See also C. F. Garbers, J. S. Malherve and D. F. Schneider, *Tetrahedron Lett.*, 1421 (1972); A. Turcant and M. LeCorre, *ibid*, 1280 (1976); 789 (1977). Oxaphospholanes of this type undergo Witting reactions themselves to give approximately 50:50 mixtures of cis and trans olefins, but the conditions of the reaction are severe.
(10) The reaction of the hydroxyphosphonium salt, $Ph_3P^+CH_2CH_2CH_2OH\ Br^-$, with 2 mol of butyllithium followed by reaction with benzaldehyde is reported cryptically to yield the olefin $PhCH{=}CHCH_2CH_2OH$ in 65% yield. The report appears in S. Trippett in "Advances in Organic Chemistry", Interscience, New York, N.Y., 1960, p 83ff. The material is referenced to S. Trippett, unpublished results. No comment is made upon the stereochemistry of the reaction.
(11) Crystallized as needles from acetone/hexane: mp 133–134 °C; NMR ($CDCl_3$) δ 0.30–0.63 (m), 0.75 (s, 3 H), 1.03 (s, 3 H), 1.03 (d, J = 6 Hz, 3 H), 1.18 (s, 6 H), 2.78 (m, 1 H), 3.33 (s, 3 H), 5.38 (m, 2 H).
(12) The compounds were prepared by the following sequences:



For 20*R* aldehyde see ref 4.
(13) NMR data ($CDCl_3$)—position of peaks given in hertz downfield from Me_4Si. See also T. A. Narwid, K. E. Cooney and M. R. Uskokovic, *Helvetica*, **50**, 771 (1974); E. N. Trachtenberg, C. Byron, and M. Gut, *J. Am. Chem. Soc.*, **99**, 6145 (1977).

Compd	C-18	C-19	C-21 doublet	
	47	62	55	61
	43	61	56	61
	40	59	48.5	55
	43	62	53	58
	43	61	47	53

(14) E. Vedejs and K. A. J. Snoble, *J. Am. Chem. Soc.*, **95**, 5778 (1973).
(15) M. Schlosser and K. F. Christmann, *Angew. Chem., Int Ed. Engl.*, 126 (1966).
(16) The structures in this scheme are intended to show only relative stereochemistry at C-22 and C-23, not absolute chirality at these centers.
(17) Determined by GLC on a 15 ft 2% SE-30 column at 245 °C.

(18) J. J. Partridge, S. Faber, and M. R. Uskokovic, *Helvetica*, **51**, 764 (1974).
(19) For an alternative method of preparation of trans-homoallylic alcohols involving reaction of lithium *trans*-alkenyltrialkylaluminates with epoxides, see E. Negishi, S. Baba, and A. O. King, *J. Chem. Soc., Chem. Commun.*, 17 (1976).

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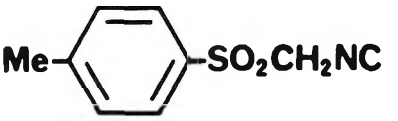

★ One-carbon elongation of ketones to acids, nitriles, etc.
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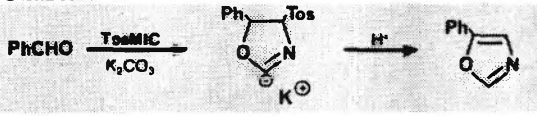
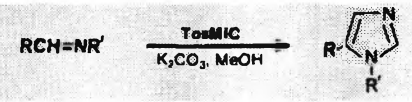
Tosylmethyl isocyanide (TosMIC) has been used extensively for the synthesis of diverse *5-membered heterocyclic systems.* Some representative examples are shown in equations 1-4.

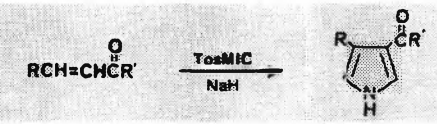
Oxazoles[1]



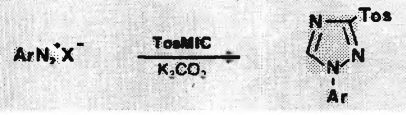
Imidazoles[2]



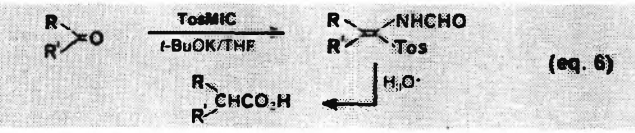
Pyrroles[3]

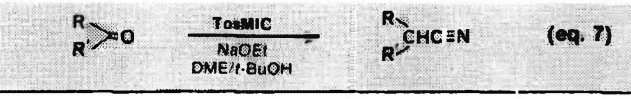


1,2,4-Triazoles[4]

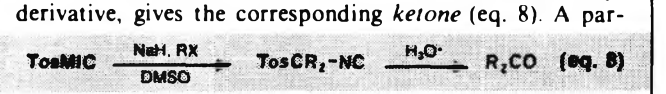


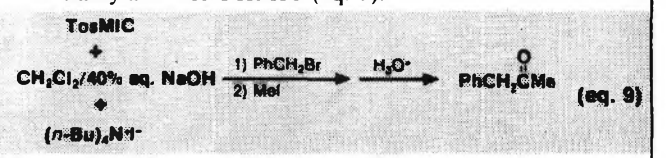
4-Ethoxyoxazolines[5] are formed by the reaction of **TosMIC** with ketones in the presence of thallous ethoxide; acid hydrolysis affords *α-hydroxyaldehydes* (eq. 5).[6] Reaction of a ketone with the conjugate base of **TosMIC** in THF gives the corresponding 1-formylamino-1-tosylalkene. Subsequent hydrolysis affords the *carboxylic acid* (eq. 6).[7] The same reaction performed in dimethoxyethane/*t*-butanol gives nitriles (eq. 7).[8]



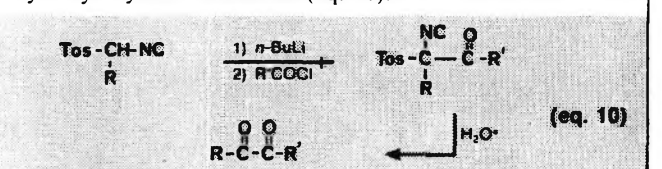


Recent developments in the use of **TosMIC** as a synthetic reagent have focused on its properties as a masked formaldehyde equivalent with *umpolung* of normal carbonyl reactivity. Thus, dialkylation of the conjugate base of **TosMIC**, followed by hydrolysis of the resulting dialkyl derivative, gives the corresponding *ketone* (eq. 8). A particularly convenient one-pot synthesis of *unsymmetrical ketones* employs phase-transfer catalysis to achieve sequential dialkylation of **TosMIC** (eq. 9).[9]





Similarly, the conjugate base of monoalkylated **TosMIC** can be acylated to provide an acyclic product, which upon hydrolysis yields a *diketone* (eq. 10).[10]



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10) D. van Leusen and A.M. van Leusen, *ibid.*, 4233 (1977).

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