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Conformation of Acyclic Vicinal Dinitriles and Diacids. Carbon-13 Nuclear Magnetic Resonance Correlations

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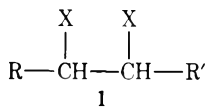
The conformations of certain acyclic dinitriles of the general structure RCH(CN)CH(CN)R′ were studied using ^{1}H NMR techniques in conjunction with dipole moment techniques. The conformation of the dinitriles was markedly solvent sensitive. Under conditions in which the carbons bearing CN become less conformationally pure, an R′ = benzyl group attains a greater conformational purity. The relative stabilities of the isomeric dinitriles were determined (the threo isomer was usually the more stable). The diacids analogous in structure to the dinitriles were considerably more conformationally pure. In deuteriochloroform, the conformation of the diacids was very sensitive to 1,8-bis(dimethylamino)naphthalene. ^{13}C coupling constants were determined for various compounds for certain CN or CH_3 groups; other groups gave indistinct or difficultly interpreted splitting patterns. The ^{13}C data for methyl groups were generally in accord with other data with regard to conformation.

The nature of the interaction of two electronegative groups X (as in structure 1) has received considerable attention. Lowe[1] and Wolfe[2] and their respective co-workers were among the first to call attention to the widespread preference of many types of groups X for a gauche conformation.[3] Abraham and co-workers have calculated and experimentally determined the conformational preferences for a variety of molecules having electronegative groups.[4,5] Phillips and Wray have commented upon the fact that Wolfe's "gauche effect" fails for certain molecules in which Abraham's approach is successful, and vice versa.[3-6] Phillips and Wray have correlated the tendency for a molecule to have gauche X groups with the total electronegativity of the two groups. In one case, Kagarise and co-workers have shown that bond angle changes are an important consideration.[6c] Furthermore, it seems fairly clear that certain polar groups, e.g., carbonyl groups, do not necessarily prefer a gauche conformation. Zefirov and co-workers have shown that second-row periodic chart atoms have a much lower tendency to be near one another in space than first-row atoms.[7] Rouvier and co-workers showed that cyano and amino groups prefer a trans orientation by a small amount.[8] Chen and Lin have shown that 3-methoxypropionitrile is more stable in the gauche conformation.[9]



1

Eliel and Kaloustian attributed the tendency for oxygen containing groups X to be near one another in space to van der Waals attractions.[10] Later, Eliel discussed the conformation of 1,3-dioxanes having other electronegative groups X in terms of the interesting idea of mutual solvation.[11]

Pople et al. have advanced a hyperconjugative explanation to account for the tendency of vicinal fluoride groups to be gauche, but they consider the interaction of the fluoride groups themselves to be repulsive.[12] Apparently Hoffman entertains similar ideas.[13] On the other hand, Epiotis considers the interaction of gauche fluoride groups to be attractive.[14] The interaction of the lone pairs on the two X's forms bonding and antibonding combinations of energy levels. The destabilizing effect of the antibonding combination is reduced owing to charge transfer from this orbital into an antibonding orbital of the ethanic skeleton. Since the destabilizing interaction is thus reduced, whereas the bonding interaction is unaffected, the net interaction of the two fluorides is attractive, according to Epiotis.

Neither the Pople hyperconjugation argument nor the Epiotis argument appears to be sufficient to explain the tendency for the two chlorine groups in 2,2′-dichlorobiphenyls to lie in virtual contact with one another.[15] Thus, the question remains whether some new all-encompassing explanation should be sought to explain all cases, or whether the biphenyls are an unrelated situation.

More recently, Abraham has reproduced the conformational preferences of a series of fluorocarbons using a conventional molecular mechanics program.[16] It was stated that no special explanations were necessary to account for the conformational preferences of the fluoride groups.

The purpose of this work was to study the conformational preferences in molecules having vicinal cyanide groups, in which the nonbonded pairs central to the Epiotis argument are lacking (although formation of bonding and antibonding combinations are still possible through interaction of the *bonded* π electrons).[17] In the cyanides, the position of highest electron density is closer to nitrogen, and not carbon. While we have no firm data, our impression is that

Table I
100-MHz ^{1}H NMR Data for 2–9

Compd	Solvent	Coupling constants, Hz[c]				Chemical shifts, ppm[c]					
		J_{AE}	J_{AB}	J_{BC}	J_{BD}	H_A	H_B	H_C	H_D	H_E	CH_3
						Ph—CH_A(CN)—CH_B(CN)—CH_3					
erythro-2	$CDCl_3$		7.4			4.07	3.13				1.52
	Pyridine		7.2			4.83	3.68				1.38
	Me_2SO		7.2			4.78	3.70				1.30
threo-3	$CDCl_3$		5.5			4.05	3.13				1.52
	Pyridine		5.8			4.73	3.65				1.46
	Me_2SO		5.8			4.77	3.70				1.40
						$(CH_3)_2CH_E$—CH_A(CN)—CH_B(CN)—CH_3					
erythro-4	$CHCl_3$	4.2	10.6			2.74	2.93			2.25	1.15, 1.19, 1.58
	Pyridine	4.8	9.2			3.09	3.24			~2.1	0.98, 1.01, 1.41
	Me_2SO	7.0	8.7			3.25	3.33			~2.0	1.03, 1.03, 1.39
threo-5	$CDCl_3$	8.2	5.2			2.48	3.02			2.15	1.12, 1.23, 1.5
	Pyridine	7.8	5.2			2.79	3.25			~2.0	0.96, 1.08, 1.3
	Me_2SO	7.4	5.5			3.02	3.34			1.96	1.02, 1.08, 1.3
						$(CH_3)_2CH_E$—CH_A(CN)—CH_B(CN)—CH_C(H_D)—Ph					
erythro-6	$CDCl_3$	~4	~11	*d*	*d*	~2.7	~2.5	~2.5	~2.5	2.26	
	Pyridine	4.5	9.9	4.3	9.7	3.22	3.68	3.35	3.11	2.25	
	Me_2SO	4.7	9.2	4.6	10.6	3.32	3.66	3.16	2.94	2.14	
threo-7	$CHCl_3$	8.8	4.2	~8	~8.8	2.34	2.98	3.23	3.06	2.14	
	Pyridine	8.2	4.8	6.9	8.9	2.94	3.63	3.31	3.19	2.14	
	Me_2SO	7.6	4.7	5.9	10.3	3.02	3.55	3.08	2.96	2.04	
						Ph—CH_A(CN)—CH_B(CN)—CH_C(H_D)—Ph					
erythro-8	$CDCl_3$		8.1	~5.2[d]	~8.8[d]	3.98	3.31	3.13	3.09		
	Pyridine		7.5	5.0	10.4	4.87	4.09	3.20	3.03		
	Me_2SO		7.2	4.8	11.1	4.81	4.07	3.06	2.75		
threo-9	$CDCl_3$[b]		5.0	*a*	*a*	4.24	3.37	3.16	3.15		
	Pyridine		5.4	*a*	*a*	4.87	3.97	3.29	3.29		
	Me_2SO		5.6	5.6	11.1	4.87	3.89	3.13	2.96		

[a] May be "deceptively simple". [b] Some CH_3CN added to separate the resonances of B from C and D. [c] These solutions were usually 5.0% w/v. In the one case tested (*threo*-7), J_{AB} diminished by ca. 0.2 Hz in moving from a 5% to a 20% solution. [d] Nearly superposed resonances prevent obtainment of accurate values.

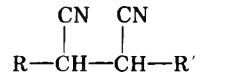
the interaction of the electrons in the two vicinal cyanides would be smaller than in the fluorides, owing to greater separation of the nitrogens from one another. Several workers have commented upon the presumed attractive nature of gauche CN groups. In a recent intensive study, Bodot and co-workers considered the interaction to be weakly attractive.[18] Peterson showed, however, that the interaction was strong enough to affect relative isomer stability.[19]

In this study, we hoped to compare ^{13}C techniques for conformational analysis to the more widely used ^1H and dipole moment techniques,[20–24] since the cyanide group is particularly convenient for study by ^{13}C NMR. A secondary objective of this work was to study the conformational preferences of the benzyl group. The type of compounds of interest is indicated in structure **1** (X = CN; R or R′ = alkyl, aryl, or benzyl). The ^1H NMR data are listed in Table I. The conformations of these compounds will be interpreted in terms of the conformers shown in Scheme I, in which the dihedral angles are arbitrarily shown as 60°. As before, J_{AB} values of 10–13 Hz are taken as indicative of predominately trans hydrogens, whereas J_{AB} values of 1–3 Hz are taken as indicative of gauche hydrogens.[25] Intermediate values usually indicate weighted means of these conformations. In Scheme I, the notation E_T signifies the conformer of the erythro diastereomer having trans hydrogens, etc.

Magnitude of the Dipole Moments. Comparison to NMR Results. In succinonitrile, the dipole moment of the conformer having gauche CN functions is 5.6 D, owing to the partial reinforcement of the individual CN group vectors.[20] The conformer having trans CN groups will have a resultant moment of near 0 D (however, owing to librational effects the actual moment will probably be larger, ca. 0.3 D).[20]

In the case of *erythro*-**2** (R = Ph; R′ = CH_3; structure

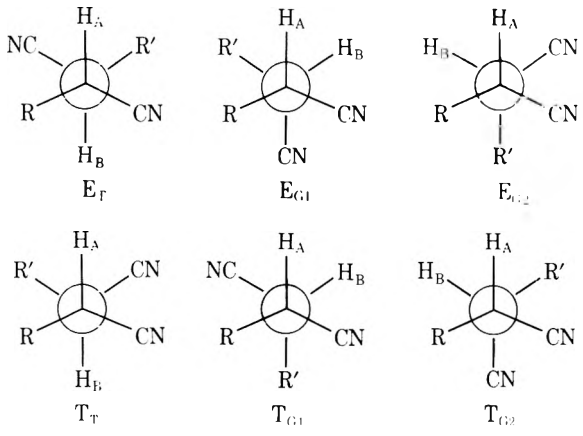
Table II
Dipole Moment and Equilibration Data of the Isomeric Dinitriles



Compd	R	R′	μ_{obsd}	μ_G	μ_T	% E_T or % T_{G1}		Equilibrium % erythro[b]
erythro-2	Ph	CH_3	3.7	5.75–5.0	1.0	53 ± 7		41
threo-3	Ph	CH_3					(35)[a]	41
erythro-4	i-C_3H_7	CH_3	2.2	5.8	0.3	86 ± 2		50
threo-5	i-C_3H_7	CH_3	5.3	5.8–5.6	0.4		18 ± 4	50
erythro-6	i-C_3H_7	CH_2Ph	1.6	5.8–5.6	0.5	92 ± 4		42
threo-7	i-C_3H_7	CH_2Ph	5.3	5.7–5.6	0.3		12 ± 2	42
erythro-8	Ph	CH_2Ph	3.3	5.6–5.0	0.7	63 ± 5		40
threo-9	Ph	CH_2Ph	4.3	5.6–4.9	0.9		32 ± 10	40

[a] Estimated from NMR data. [b] % erythro of an erythro–threo mixture produced by $NaOCH_3$ catalyzed equilibration of the individual diastereomers (average of duplicate runs); confidence level ± 3%.

Scheme I



given in Table I), the observed dipole moment is 3.7 D (Table II), indicating a sizable population of conformers with gauche CN groups (E_{G1} and/or E_{G2}). The NMR J_{AB} value in $CDCl_3$ (7.6 Hz) is indicative of a sizable population of conformers having gauche hydrogens (also E_{G1} and/or E_{G2}). The theoretical maximum dipole moment should be adjusted to account for the varying effect of the R and R′ groups. The dipole vector for Ph is directed toward Ph, and its magnitude is 0.8 D.[20] The vector for CH_3 is directed from CH_3 toward the ethanic backbone, and its magnitude is smaller, 0.3 D. Calculations, taking into consideration the angles these subsidiary dipoles make with the CN dipoles, give 5.75 D as the moment expected for E_{G1}, and 5.0 D for E_{G2}. The fraction of molecules having trans CN groups, N_T (which is the population of E_T), may be calculated from eq. 1[20] using both extreme values for the magnitude of the dipole of conformers having gauche CN's, and averaging the results.

$$N_T = \frac{\mu_G^2 - \mu_{obsd}^2}{\mu_G^2 - \mu_T^2} \quad (1)$$

Thus, the weight of E_T for *erythro*-2 is 0.53 ± 0.07, in agreement with the NMR data which suggests about 50% E_T.

For *erythro*-4 (R = i-C_3H_7; R′ = CH_3), a much larger J_{AB} value is observed in $CDCl_3$ (10.6 Hz) indicative of a very strong preference for E_T. Correspondingly, the dipole moment (2.2 D) for 4 is much smaller than for 2 since the CN groups are trans in the predominant conformer, E_T. Either E_{G1} or E_{G2} would have the same moment, 5.8 D. Using eq 1, the weight of E_T is calculated to be 0.86.

For *erythro*-6 (R = i-C_3H_7; R′ = $PhCH_2$), the dipole moments for the various conformers are approximated as indicated in Table II. Conformer E_T is calculated to have a weight of 0.92 ± 0.04. The J_{AB} value, ca. 11 Hz, is in agreement with the high predominance of E_T. For *erythro*-8 (R = Ph and R′ = $PhCH_2$), the weight of E_T is much lower (0.63 ± 0.05), also in agreement with NMR data. Thus, compounds having R = Ph show a much smaller preference for E_T than compounds having alkyl or benzyl substituents. The error limits indicated above may be somewhat low, since the above analysis utilizes dihedral angles of 60°, which is an idealized value, seldom present.

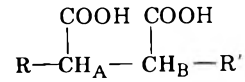
An exact identification of the limiting NMR coupling constant for pure trans protons (J_T) or pure gauche protons (J_G) is not possible. However, using the weights of the individual conformers determined from dipole moment data, and using the theoretical prediction[26] that the ratio of J_T to J_G is 5.5, the calculated values for J_T and J_G may be checked for consistency. For **8**, J_T is calculated to be 11.8 ± 0.7 Hz, and J_G 2.1 ± 0.2 Hz (**8** has the highest uncertainty); for **2**, J_T = 12.0, and J_G = 2.2 Hz; for **4**, J_T = 12.2, and J_G = 2.2 Hz; and for **6**, J_T = 11.8 and J_G = 2.1 Hz. The consistency of J_T and J_G suggests that the geometry of the trans or gauche conformers in **2, 4, 6,** and **8** is not grossly different.

For the threo isomers, the dipole moment data also may be used to calculate the weight of the conformers having trans CN groups (T_{G1}). These data are indicated in Table II. In order to roughly differentiate between T_T and T_{G2}, the average values for J_T and J_G roughly determined for the erythro isomers were used in a set of simultaneous equations using the weight of T_{G1} determined by dipole moment studies. The weights of T_T, T_{G1}, and T_{G2} are found to be 0.4, 0.2, and 0.4 for **5**; 0.3, 0.1, and 0.6 for **7**; and 0.4, 0.3, and 0.3 for **9**, with confidence limits of ca. ±0.1.[27] The conformer having trans CN groups (T_{G1}) is most frequently the minor conformer. However, none of these threo isomers show really strong conformational preferences.

Equilibration Studies. Equilibrium was approached from erythro and from threo extremities using methoxide as catalyst. The results are tabulated in Table II. In all cases except **3**, the threo isomer predominated at equilibrium.[19,28] It is noteworthy that the threo isomers usually contain a greater weight of the conformers having gauche CN groups.

Solvent Effects on Conformation. A change to solvents of increased polarity results in sharply reduced J_{AB} values for the erythro isomers **4, 6,** and **8**. *erythro*-**2**, which is already highly conformationally mixed, undergoes only a small change. As others have noted,[3,4,11,18,29] polar solvents are able to support conformers having large dipole mo-

Table III
100-MHz ^{1}H NMR Coupling Constants (J_{AB}, Hz) of the Isomeric Diacids



			$CDCl_3$ solvent			D_2O solvent				
Compd	R	R′	Free acid	DAN[d]	AP[e]	DAN[a,b]	AP[c]	NH_4^+[f] (pH 8)	Na^+[g] (pH 9)	Ba^{2+}[h] (pH 11)
erythro-12	Ph	CH_3	11.3	6.2	10.3	12.0	10.8	10.1	11.1	~10.7[a]
threo-13	Ph	CH_3	10.6	3.5	6.6	10.2	11.5	11.5	11.5	11.6
erythro-14	*i*-C_3H_7	CH_3	8.4	3.8	4.6	9.0	10.9	9.2	10.8	*a*
erythro-16	Ph	CH_2Ph	11.0[i]						11.2[i]	
threo-17	Ph	CH_2Ph	11.2[i]	~3	5.2				11.2[i]	11.4

[a] Insolubility was a severe problem. [b] Excess DAN [1,8-bis(dimethylamino)naphthalene] present. [c] Excess AP (2-aminopyridine) present. [d] One equivalent of DAN present. [e] One equivalent of AP present. [f] The diammonium salts were prepared and dissolved in D_2O. [g] Anhydrous Na_2CO_3 added to acid until pH ~9. [h] BaO added to pH ~11; the solution was filtered before use. [i] Very similar to the data of Opara and Read, ref 38f.

ments better than nonpolar solvents, since dipole–dipole repulsion is reduced by solvation of the individual dipoles. Thus, conformers such as E_{G1} become more important in polar solvents. The threo isomers appear to undergo a slight change in J_{AB} to higher values indicative of a slightly greater preference for T_T. This conformer permits a closer contact of CN with solvent.

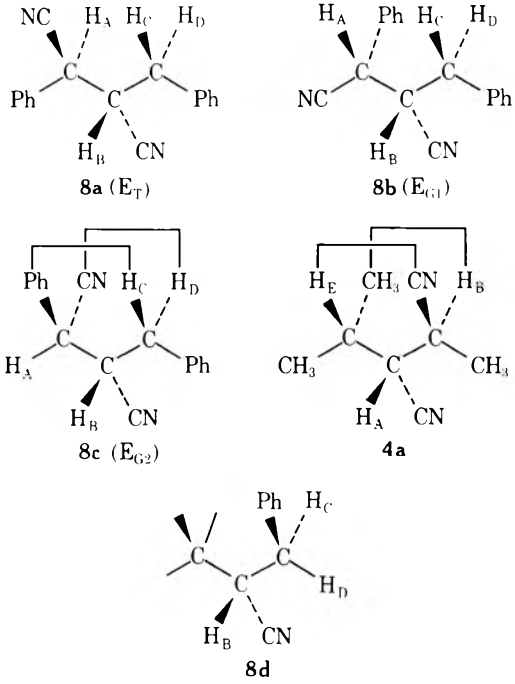
Conformation of the Benzyl Group. In earlier work, and in several compounds of this study, whenever part of a molecule assumes greater conformational purity (through a change in solvent or temperature), other parts of the molecule do the same.[30] For example, in *erythro*-**4**, the magnitude of J_{AB} (10.6 Hz) is near maximum, and the magnitude of J_{AE} (4.2 Hz) is near minimum. Cooling the sample to −57° results in a further increase in J_{AB} (10.9 Hz) and a decrease in J_{AE} (3.6 Hz).[31]

Similar unified changes occur on solvent variation. Thus, for *erythro*-**4**, J_{AB} varies from 10.6 ($CDCl_3$) to 8.7 Hz (Me_2SO) whereas J_{AE} changes from 5.2 ($CDCl_3$) to 7.0 Hz (Me_2SO). The origin of these variations in J_{AB} and J_{AE} in opposite directions has been discussed earlier in terms of minimization of 1,3 interactions between large groups (cf. **4a**).[30,32] A similar variation might have been expected for J_{BC} and J_{BD} of the benzyl group in compounds **6–9**.[33] The extended conformational diagrams in Scheme II illustrate the conformational possibilities for **8**. As the polarity of the solvent is increased (see Table I), J_{AB} for **8** moves toward the averaged value of 7 Hz, showing that E_{G1} and possibly E_{G2} become present in sizable concentrations. *However, as conformational purity diminishes at the carbons bearing CN, the conformational purity of the benzyl group appears to increase.* A change in J_{BD} from 5.2 ($CDCl_3$) to 4.8 Hz (Me_2SO), coupled with a change in J_{BD} from ca. 8.8 ($CDCl_3$) to 11.1 Hz (Me_2SO), is observed. Thus, conformations of the benzyl group as in **8d** (Scheme II) appear to become increasingly excluded. The rather incomplete data for *erythro*-**6** and *threo*-**7** suggest similar behavior.

Although an explanation similar to Brown's "windshield wiper" is possible in which rotational changes at the carbons bearing CN would tend to exclude certain regions of space from the phenyl group of benzyl,[34] it is difficult to believe that rotation about one C–C bond of a propane skeleton could be that much faster than rotation about a less sterically hindered C–C bond.

Although no certain explanation seems readily evident, we suggest that the effect of the solvent molecules as they aggregate near the CN functions may tend to restrict the benzyl group.[29] It is noteworthy that a large change in chemical shift of H_A and H_B occurs in moving to polar solvents, whereas the chemical shifts of H_C and H_D change but slightly.

Scheme II



To the extent that conformers such as **8c** become more important in polar solvents, the benzyl group would be forced to occupy the position shown (and not that shown in **8d**) in order to minimize 1,3 interactions.

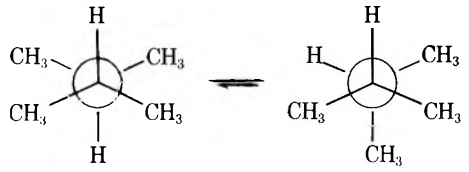
With regard to effective size, the benzyl group appears rather similar to methyl (compare compounds **2** and **8** and compounds **4** and **6**), rather than phenyl owing to the nature of the carbon attached to the ethanic skeleton.

Conformation of the Diacids. Table III lists the NMR data for certain diacids of similar structure to the dinitriles discussed earlier. It is evident that a considerably higher degree of conformational purity is present in the diacids. Specifically, E_T and T_T are now strongly favored.[35] The data also show that compounds having R or R′ = Ph now have a higher degree of conformational purity than R or R′ = alkyl.

The strong preference and E_T or T_T is quite common for compounds having carbonyl groups,[30b] and other sp^2-hybridized groups such as phenyl[30] or groups such as halogen,[23,35] sulfoxide,[36] sulfone,[37] phosphine oxide,[37] and oth-

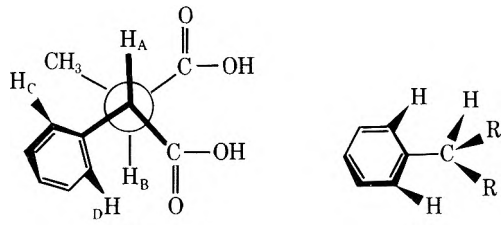
ers.[38] Generally, the preference for the conformer having trans vicinal hydrogens (E_T or T_T), termed type II behavior, is found for compounds having few alkyl groups attached to the ethanic backbone. Compounds with R and R′ = alkyl frequently show a preference for the conformer with trans alkyl groups (E_T or T_{G2}).[39] This behavior, termed type I, minimizes the quite large repulsion between the alkyl groups.[40] Both type I and type II behavior may be overridden if substantial attractive interactions occur between various substituents, such as intramolecular hydrogen bonding.[41]

Many subtle changes in molecular geometry occur between different compounds, and between different conformers of the same compounds. Crystal structures and other absolute methods are slowly clarifying these changes. For example, Allinger and co-workers showed that the conformer with gauche hydrogens in 2,3-dimethylbutane is preferred owing to a widening of the dihedral angle between geminal methyl groups.[6c] Thus, the interaction between vicinal methyl groups is worsened in **10a**, leading to a preference for **10b**.[42]



10a **10b**

However, in studies of a considerable number of tetrasubstituted ethanes, no general tendency for gauche hydrogens was noted. A large number of compounds, such as the diacids **12**, **13**, **16**, and **17**, prefer trans hydrogens.[38] We tentatively suggest that an angle contraction between geminal groups may be present as in structure **11a**. The highly



11a **11b**

polarizable π electron clouds on phenyl and carboxyl may not result in the degree of repulsion found in geminal methyl groups in 2,3-dimethylbutane. The contracted dihedral angle would reduce the repulsion between vicinal COOH–COOH or Ph–CH_3 groups. The diminished dihedral angle would require that the smallest group possible, namely hydrogen, be situated between Ph and COOH. This, in turn, would result in trans vicinal hydrogens.

The frequent involvement of phenyl in type II behavior may be due to a second factor, which is the result of the distinctive shape of phenyl. One ortho hydrogen of phenyl is eclipsed with one geminal substituent (probably another hydrogen); the other ortho hydrogen bisects the angle between the R groups as shown in **11b**.[43] In **11a**, if H_C is eclipsed with H_A, H_D extends toward the center of the ethanic skeleton and impinges upon one of the vicinal substituents. The least unfavorable interaction would occur with H_B. Again the result is a preference for a conformer having trans hydrogens H_A and H_B.

The cyanides **2**–**9** do not easily fit into type I or type II behavior patterns. The anomalous behavior is very likely the result of the weak attraction between cyanides, and due to the fairly small size of cyanide. However, compounds **4** and **6** strongly prefer E_T. Thus, the repulsion of the alkyl groups overcomes any attractive interaction of the two cyanides.[44]

A phenyl group and an alkyl group will tolerate a gauche orientation much more readily than two alkyl groups. Thus, **2** and **8** show a much higher population of the conformers with gauche CN functions (E_G) as indicated by the smaller J_{AB} values and dipole moments. The attraction of the cyanides may release the compound from any angle contractions associated with type II behavior, and the small size of cyanide may permit the ortho hydrogen of phenyl to be eclipsed with cyanide rather than H_A (cf. **11b**).

For the threo isomers, the optimum arrangement presumably should be trans alkyl groups and gauche cyanides as found in T_{G2}. This conformer is indeed highly populated for **7**, which has the largest alkyl groups. However, the reason for the general lack of conformational purity in other compounds remains obscure.

Effect of Ionization upon Conformation. In Table III, it is seen that the dianions of *erythro*-**12** and *threo*-**13** in D_2O have approximately the same conformational preference as the free acids in $CDCl_3$, namely for E_T or T_T.[45] The divalent cation, barium, does not draw the carboxylate anions together in the erythro isomer, since a decrease in J_{AB} was not observed in the presence of this cation. The concentration of di–di ion pairs is sizable at the concentrations of substrate utilized, but the separation of the barium cation from the organic dianion would be on the order of 8–14 Å.[46] Thus, several water molecules may separate the cation from the anion, and both the attraction between the cation and dianion and the repulsion between the carboxylates is reduced.

The most dramatic change observed recently in our laboratory occurred upon addition of 1,8-bis(dimethylamino)naphthalene (DAN) to solutions of the diacids in $CDCl_3$. For *erythro*-**12**, the J_{AB} value diminished from 11.3 to 6.2 Hz upon addition of 1 equiv of DAN (an additional though smaller decrease was observed upon addition of excess DAN). For *threo*-**13**, a decrease in J_{AB} from 10.6 to 3.5 Hz was observed.

The exact state of ionization of these diacids in the presence of DAN remains uncertain. To test whether hydrogen bonding, and not ionization, might be the cause of these strong changes in J_{AB}, 2-aminopyridine (AP) was utilized in parallel experiments. A small decrease in J_{AB} was observed for **12**, but sizable decreases were observed for **13**, **14**, and **17**. The pyridine derivative, AP, is a bifunctional hydrogen bond acceptor, but it is not sufficiently basic to cause ionization. On the other hand, DAN, although bifunctional, is not expected to be a good double hydrogen bond acceptor, because of steric hindrance to proper orientation of the lone pairs. DAN (proton sponge) is, of course, a strong base.[47]

We tentatively suggest that the monoanion is formed to a significant extent in the DAN solutions. Intramolecular hydrogen bonding is believed to hold the COOH and COO^- in a gauche conformation in the monoanion. In the AP solutions, hydrogen bonding to the bifunctional base also would lead to gauche carboxyl functions. In aqueous solutions, neither DAN or AP has a large effect upon the conformation of **12** or **13**, since water is the primary agent for solvation or hydrogen bonding.

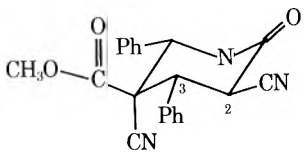
The threo isomers also undergo pronounced changes upon addition of DAN or AP, even though the preferred conformation in $CDCl_3$ (T_T) already has gauche carboxyl groups. The reason for the change of conformation (probably to T_{G2}) is not immediately obvious. Possibly the intramolecular hydrogen bonding between carboxyl functions

releases the molecule from the angle deformations (as in structure 11) that gave rise to the preference for T_T.

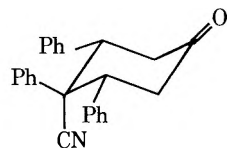
^{13}C NMR Data. The ^{13}C chemical shifts for the compounds of this study are shown in Table IV. The chemical shifts show the expected changes as structure is varied, and these will not be considered further.

It was possible to determine ^{13}C–H coupling constants between certain types of carbons and vicinal hydrogens. Perlin and co-workers have indicated that a Karplus type of relationship exists for the dihedral angle between ^{13}C and a vicinal hydrogen and the magnitude of the coupling constant $^3J_{CH}$.[48] For trans nuclei, ^3J was found to be ca. 8 Hz, whereas for gauche nuclei, ^3J was ca. 1 Hz. These values were considered to be quite sensitive to such internal factors as strain, electronegativity, etc., as indeed was shown by the earlier work of Karabatsos and co-workers.[48d] For carbonyl-hydrogen coupling constants, $^3J_T \sim 13$, $^3J_G \sim 2$ Hz.[48f]

In order to apply ^3J values to problems in conformation, it is necessary to observe these values for compounds of near conformational purity having functional groups similar to **2–9** and **12–17**. Compounds **18** and **19** were used to partially satisfy this objective.



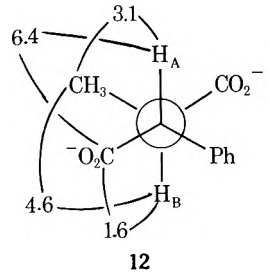
18



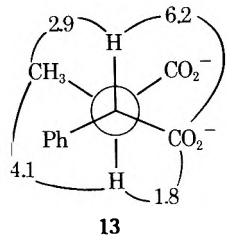
19

In studies on **18** and **19** and a number of similar compounds coupling constants from trans (diaxial) cyanide and hydrogen groups were 9.2 ± 0.5 Hz. In **18**, the equatorial cyanide at C-2 showed a coupling constant to H-3 of 1.7 Hz. This value should be reasonably characteristic of gauche nuclei.

The diacids **12** and **13** showed very high J_{AB} values in ^1H spectra, and these molecules are also close to conformational purity. Observation of the ^{13}C spectrum of the methyl group in **12** and **13** (disodium salts in D_2O) showed splittings of 3.1 and 4.6, and 2.9 and 4.1 Hz, respectively, in addition to the larger splitting due to the directly bound hydrogens ($^1J_{CH}$ = 128 Hz). These values are considered good to ±0.4 Hz. The smaller splitting (~3 Hz) is believed to be due to $^3J_{CH}$, and the larger due to $^2J_{CH}$ (this assignment was made on the basis of consistency with other results from our laboratory). The small ^3J is in qualitative agreement with the large J_{AB} in requiring a very high population of conformers E_T and T_T as shown in structure **12** and **13**.



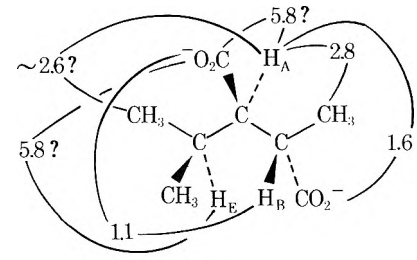
12



13

For **12** and **13**, it was also possible to obtain sharp spectra for certain carboxyl groups. In **12**, the carboxyl nearest methyl was poorly resolved, but the carboxyl nearest Ph was a double doublet from which assignments of ^2J = 6.4 and ^3J = 1.4 Hz were made (**18** gave similar values). The latter is in agreement with the preference for E_T since gauche COOH and H_B nuclei would be in evidence.

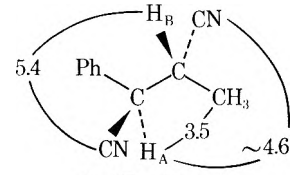
In **14**, a double-triplet splitting pattern was observed for one carboxyl, most likely the carboxyl nearest isopropyl. This carboxyl must have one two-bond coupling and two three-bond couplings. The proton spectrum indicates a predominance of E_T (redrawn in **14a**).



14a

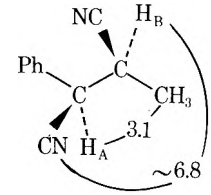
In agreement with **14a**, the coupling constant between methyl and H_A was found to be 2.8 Hz, indicative of gauche nuclei. For the carboxyl one possible assignment is $^3J_{CO-H_B}$ = 1.1, $^3J_{CO-H_E} \sim 5.8$, and $^2J_{CO-H_A} \sim 5.8$ Hz. The coupling to H_B is consistent with conformer **14a**, but the coupling to H_E seems much too low.[48f] A similar double-triplet pattern was noted for compounds **4–6** (i.e., through observation of one CN in each compound). It is difficult to believe that $^3J_{CH}$ would be equivalent to $^2J_{CH}$ in so many compounds, and we have reservations about the implications from these double triplets. Computer simulation of the spectra showed that larger or smaller coupling constants resulted in splittings of nearly the proper magnitude in the simulated spectra, however.

For the dinitriles **2–5**, the J_{AB} values indicated a greater mixture of conformers than for the diacids. In *erythro*-**2**, the weight of E_T is roughly 0.5. It was of interest to see how closely the carbon couplings agree with this population and the conformational weights in other structures. In **2**, the cyanide couplings, $^3J_{CH-H_B}$ = 5.4 and $^3J_{CN-H_A} \simeq 4.6$ Hz, do indeed indicate considerable conformation averaging. If the weight of E_T is taken as 0.5 and using a set of simultaneous equations with ^3J_T = 9 Hz, the weights of E_{G1} and E_{G2} are roughly 0.2 and 0.3. Observing the methyl group of **2**, $^3J_{CH_3-H_A}$ is 3.5 Hz, which is consistent with the low population of E_{G2}.



2a (E_T shown)

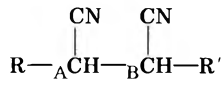
For *threo*-**3**, $^3J_{CN-H_B} \simeq 6.8$ and $^3J_{CH_3-H_A}$ = 3.1 Hz. These data are consistent with sizable populations of T_T and T_{G2} but a very low population of T_{G1}.



3a (T_{G2} shown)

For *erythro*-**4**, a multiplet was found for one cyanide and a double triplet for the other. One possible assignment of the coupling constants is shown in the diagram (**4a**). In this case, the cyanide couplings are in good agreement with the conformation suggested from the proton spectra and dipole moment (ca. 86% E_T). Of the minor conformers, E_{G2} is ex-

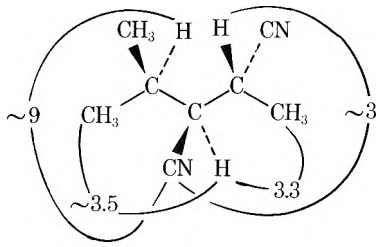
Table IV
^{13}C Chemical Shifts



Isomer	R	R′	δ R	δ R′	δ CA	δ CB	δ CN
erythro-2	Ph	CH_3		15.5	40.9	31.5	117.9, 118.1
threo-3				16.1	40.9	31.9	117.0, 118.5
erythro-4	*i*-C_3H_7	CH_3	CH 28.6 CH_3 17.1 CH_3 17.3	16.7	43.2	26.5	116.8, 119.1
threo-5	*i*-C_3H_7	CH_3	CH 29.3 CH_3 19.9 CH_3 20.2	16.9	43.3	26.5	117.3, 118.7
erythro-6	*i*-C_3H_7	CH_2Ph	CH_3 28.6 CH_3 17.1 CH_3 21.3	36.4[a]	40.9	34.7	117.3, 117.8
threo-7	*i*-C_3H_7	CH_2Ph	CH 29.6 CH_3 20.1 CH_3 20.6	37.2[a]	40.9	34.3	
erythro-8	Ph	CH_2Ph		35.8[a]	39.6[b]	39.2[b]	117.1, 118.9
threo-9	Ph	CH_2Ph		36.6[a]	39.1	40.3	117.0, 118.5

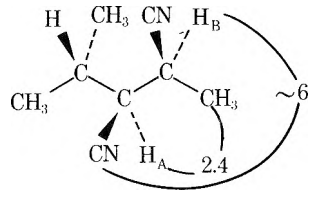
[a] Chemical shift of the benzylic carbon. [b] Tentative assignment.

pected to be the more important as R isopropyl is very hindered in E_{G1}. Rough calculations bear this out, suggesting that E_{G2} is about 14% populated.



4a

In *threo*-**5**, the coupling constants $^3J_{CN-H_B} \simeq 6$ and $^3J_{CH_3-H_A} = 2.4$ Hz were determined. These data are in agreement with the data of Table II, which indicate that the weight of T_{G1} (which has trans CH_3 and H_A groups) is quite small (~20%).



5a (T_{G2} shown)

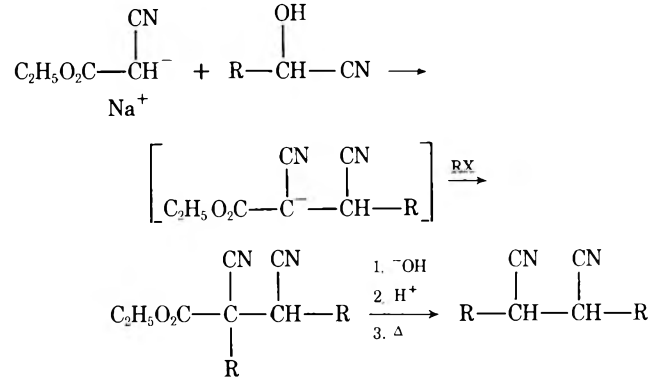
In conclusion we would point out that ^{13}C coupling constants involving methyl groups are in good qualitative agreement with conformational preferences derived from ^{1}H and dipole moment data. Some reservations have been indicated above about ^{13}C couplings involving cyanide or COOH, but agreement is satisfactory in many cases with other lines of evidence. As greater understanding of ^{13}C–H coupling constants is attained, these data should become as important as H–H couplings as a conformational probe. The ^{13}C couplings have an added advantage that a number of different carbons in a given molecule may be studied in contrast to the more limited proton couplings.

The conformational weights derived from ^{1}H and dipole moment data can be accommodated with trans and gauche $^3J_{CN-H}$ couplings of 9–9.5 and 2–3 Hz, respectively, and by $^3J_{CH_3-H}$ couplings of 6–7 and 2–3 Hz. It does seem that the carbon coupling constants are subject to rather wide variations from compound to compound. Thus far, only methyl groups among alkyl groups can be successfully studied in our hands (benzyl carbons are extensively coupled to protons in the ring).

All three lines of evidence suggest a preference for conformers having gauche CN groups in the threo isomers, and a strong contribution from such conformers in certain erythro isomers, especially in polar solvents. With regard to the Pople et al. hyperconjugative explanation of the reason for gauche X groups,[12] no consistent preference is noted for conformers such as T_{G2} (which has hydrogen trans to cyanides) over T_T.[49] It is rather difficult to assess the Epiotis explanation for gauche X groups, but, as discussed earlier, the positions of greatest electron density (nitrogen of the cyanides) tend to be rather distant from one another even if the cyanides are gauche, and it is questionable whether the interaction of the electrons would be large enough to account for the tendency for cyanides to be gauche.

Experimental Section

The general method of synthesis was the condensation of an appropriately substituted ethyl cyanoacetate with the cyanohydrin of the appropriate aldehyde. The resulting product was hydrolyzed and decarboxylated according to the following equations.



The general method was that of Higson and Thorpe.[50]

1,2-Dicyano-1-phenylpropane (2 and 3). Procedure A. To a 500-ml flask fitted with condenser and magnetic stirrer was added 5.8 g (0.25 g-atom) of sodium metal and 100 ml of absolute ethanol. After reaction, 28 g (0.25 mol) of ethyl cyanoacetate was added to the cooled solution followed by 32.8 g (0.247 mol) of benzaldehyde cyanohydrin (the latter was added gradually with stirring and cooling). The solid sodium salt of ethyl cyanoacetate gradually

went into solution during addition of the cyanohydrin, leaving a brown solution at the end of addition. The resulting solution was allowed to stand for 12 hr at room temperature. To this solution, 42.6 g (0.3 mol) of methyl iodide was added with cooling, and the mixture was warmed on a water bath until a test portion was neutral to litmus. The reaction mixture was poured into water. The oil that separated was extracted into ether. The ether solution was washed with water, dried ($MgSO_4$), and evaporated to give the crude product, ethyl 2-methyl-3-phenyl-2,3-dicyanopropionate, yield 22.4 g (75%). The NMR spectrum of the crude product showed it to be a roughly equal mixture of erythro and threo isomers.

Procedure B. In a 250-ml round-bottom flask fitted with a condenser, 10 g of potassium hydroxide in 100 ml of dry methanol was added plus 24.2 g (0.1 mol) of ethyl 2-methyl-3-phenyl-2,3-dicyanopropionate. The mixture was stirred overnight, during which time a precipitate formed. The precipitate was filtered off and washed with ether, and then dissolved in water. The aqueous solution was acidified with concentrated hydrochloric acid, which yielded a heavy oil which was extracted into ether. The ether solution was washed with water, dried ($MgSO_4$), and evaporated. The gummy oil that resulted was decarboxylated by heating under reduced pressure. When gas evolution ceased, the remaining oil was dissolved in a small amount of chloroform and added to a chromatography column [150 g of silica gel (Baker)]. From the fourth fraction of 75 ml (chloroform eluent), 5 g of a mixture of diastereomeric products was collected. The diastereomers were separated by repeated crystallization from chloroform and petroleum ether. The erythro isomer (2) separated as small white needles, mp 76–78° (lit.[50] mp 80°), mass spectrum *m/e* 170 (parent ion).

Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.64; H, 5.88. Found: C, 77.77; H, 5.93.

The threo isomer separated as a brown oil, contaminated with ca. 20% of the erythro isomer. Repeated attempts at separation from the erythro isomer were unsuccessful.

Anal. Calcd for $C_{11}H_{10}N_2$; C, 77.64; H, 5.88. Found: C, 77.73; H, 5.88.

4-Methyl-2,3-dicyanopentane (4 and 5). Ethyl 2,4-dimethyl-2,3-dicyanopentanoate was prepared by the procedure A as outlined above. From 6.25 g (0.27 g-atom) of sodium, 28.25 g (0.25 mol) of ethyl cyanoacetate, 24.9 g (0.25 mol) of isobutyraldehyde cyanohydrin, and 42.4 g (0.3 mol) of methyl iodide, 27.8 g (54%) of the product ester was obtained, by 115–117° (4 mm).

The above ester was hydrolyzed by mixing 26 g (0.13 mol) of the ester with 15 g of potassium hydroxide in 100 ml of dry methanol, following procedure B. After the solvent was removed the remaining oil was distilled, during which the vigorous evolution of carbon dioxide occurred. The product was collected at 105° (2.5 mm), giving 3.5 g of the mixed diastereomers as determined by NMR. The diastereomers were separated using preparative VPC techniques (specifically, using a 1.5-m, 9.4-mm diameter column packed with Chromosorb W having ca. 10% QF-1 as the liquid phase at 200°). In a larger scale run, the diastereomers were separated by using a 50-cm spinning band distillation column. The fraction collected at 92° (2.3 mm) proved to be the erythro isomer (ca. 57% of the total mixture), mass spectrum (70 eV) *m/e* 136 (parent ion).

Anal. Calcd for $C_8H_{12}N_2$: C, 70.59; H, 8.82. Found: C, 70.32; H, 9.09.

The threo isomer distilled at 110° (2.3 mm), and accounted for ca. 43% of the mixture, mass spectrum (70 eV) *m/e* 136 (parent ion).

Anal. Calcd for $C_8H_{12}N_2$: C, 70.59; H, 8.82. Found: C, 70.37; H, 9.09.

1-Phenyl-4-methyl-2,3-dicyanopentane (6 and 7). According to procedure A, 12.5 g (0.54 g-atom) of sodium, 56.5 g (0.5 mol) of ethyl cyanoacetate, 49.5 g (0.5 mol) of isobutyraldehyde cyanohydrin, and 63.1 g (0.5 mol) of benzyl chloride were allowed to react to form 100 g (70%) of crude ethyl 2-benzyl-4-methyl-2,3-dicyanopentanoate.

The above ester was hydrolyzed by procedure B using 28.4 g (0.1 mol) of the above ester mixed with 10 g of potassium hydroxide in 100 of dry methanol. After decarboxylation under vacuum, the residue was taken up with carbon tetrachloride and chloroform. On cooling some crystals appeared which were filtered off and recrystallized from carbon tetrachloride and chloroform, yielding 9.5 g of product, mp 90–98°. However, the NMR spectrum showed this material to be a mixture of diastereomers. Chromatography on 75 g of silica gel (Baker) using benzene as eluent afforded a solid, mp 99–101°, in fractions 4 and 5 (75 ml each). This material was recrystallized from the same solvents, giving a material later identified as the erythro isomer, mp 104–107°, mass spectrum (70 eV) *m/e* 212 (parent ion).

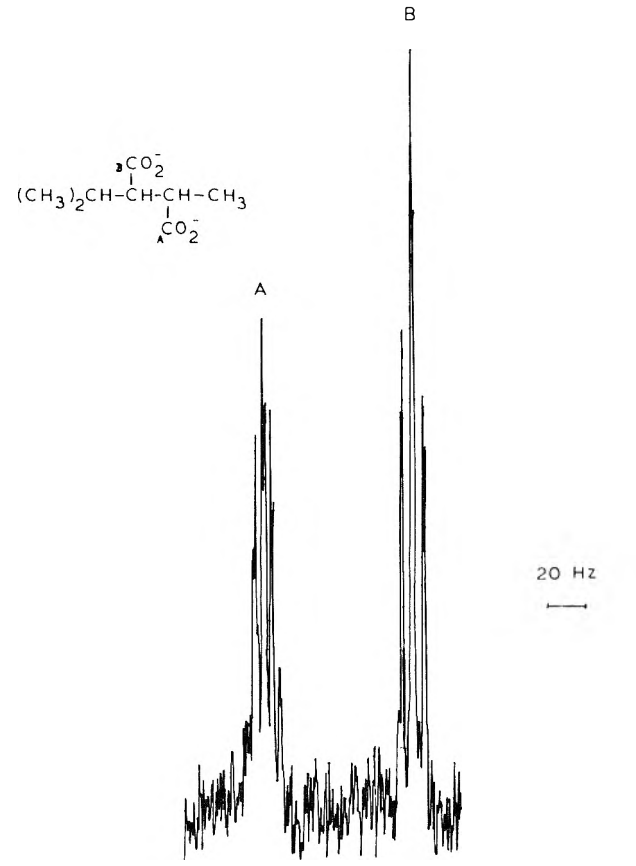


Figure 1. Coupled spectrum of 14 in D_2O (carbonyl region only).

Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.25; H, 7.55. Found: C, 79.07; H, 7.74.

Fraction 8 of the chromatography contained the threo isomer, mp 70–72°, mass spectrum (70 eV) *m/e* 212 (parent ion).

Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.25; H, 7.55. Found: C, 79.17; H, 7.65.

1,3-Diphenyl-1,2-dicyanopropane. According to procedure A, 5.8 g (0.25 g-atom) of sodium, 28 g (0.25 mol) of ethyl cyanoacetate, 32.9 g (0.25 mol) of benzaldehyde cyanohydrin, and 31.3 g (0.247 mol) of benzyl chloride yielded 73 g (93%) of the crude ethyl 2-benzyl-3-phenyl-2,3-dicyanopropionate.

According to procedure B, the above ester (31.8 g, 0.10 mol), was mixed with 10 g of potassium hydroxide in 100 ml of dry methanol. After decarboxylation in vacuo, the remaining oil was taken up in hot ethanol. Upon cooling, a material subsequently shown to be the erythro isomer separated as long needles (3.2 g) mp 138–140°, mass spectrum (70 eV) *m/e* 246 (parent ion).

Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.93; H, 5.65. Found: C, 83.06; H, 5.69.

The filtrate was evaporated to yield a gummy oil which was dissolved in a 3:1 mixture of chloroform and carbon tetrachloride. On cooling, the threo isomer separated as long needles (2.7 g), mp 85–87°, mass spectrum (70 eV) *m/e* 246.

Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.93; H, 5.65. Found: C, 82.88; H, 5.57.

3-Methyl-2-phenylbutanedioic Acid (12 and 13). Ethyl 2-methyl-3-phenyl-2,3-dicyanopentanoate (22.0 g, 0.091 mol) was refluxed in 200 ml of concentrated hydrochloric acid for ca. 12 hr. The product (a mixture of the two diastereomers) appeared as crystals upon cooling. There were filtered off, and yielded 9.0 g (48%) of the crude diacids, mp 175–185°. The crystals were dissolved in dilute sodium hydroxide and the solution was neutralized to pH 5 with dilute hydrochloric acid. The monosodium salt of the erythro succinic acid crystallized out, mp >320°. The free acid was recovered by redissolving the monosodium salt in dilute sodium hydroxide and acidifying to pH 1, followed by recrystallization from ether: mp 199–201° (lit.[51] mp 192–193°); NMR ($CDCl_3$–TFA) δ 1.11 (d, 3, CH_3), 3.34 (m, 1, $CHCH_3$), 3.86 (d, 1, CHPh), and 7.34 (s, 5, Ph); ir (KBr) 3200–3500, 1710 cm^{-1}.

After removing the erythro monosodium salt, the filtrate was acidified to pH ca 1. Crystals formed which proved to be about 80% threo and 20% erythro diacid. The pure threo isomer was obtained by repeating the dissolution in base, and precipitation of the erythro monosodium salt, followed by acidification to precipitate the mixture enriched in the threo form. The pure *threo*-**13** had mp 197–199° (lit.[51] mp 170–178°); NMR ($CDCl_3$–TFA) δ 1.49 (d, 3, CH_3), 3.48 (dq, 1, $CHCH_3$), 3.98 (d, 1, CHPh), and 7.38 (s, 5, Ph); ir (KBr) 3200–2500, 1710 cm^{-1}; mass spectrum (70 eV) *m/e* 208 (parent ion).

In another run, 1.6 g (0.093 mol) of *erythro*-**2** was mixed with 50 ml of concentrated hydrochloric acid and 0.1 ml of hydrogen peroxide (30%). The mixture was heated at reflux for 48 hr. The reaction mixture was cooled and diluted with a large volume of water, whereupon the product precipitated, mp 184–186°. The NMR spectrum showed that this material was ca. 90% of the erythro diacid. The diacid was dissolved in ca. 30 ml of water and made basic to a pH of 11; the solution was filtered. To the filtrate was added barium acetate in increments until no further precipitation seemed evident. The mixture was digested upon the steam bath for ca. 1 hr, allowed to cool, and then filtered. The mother liquor was treated with additional barium acetate, but only a slight precipitation occurred. The precipitate was treated with concentrated hydrochloric acid in ca. 30 ml of water. The resulting precipitate was vigorously stirred and filtered. The resulting diacid **12** was air dried, giving 0.9 g (54%) of product, mp 198.5–199.5°.

2-Methyl-3-isopropylbutanedioic Acid (14 and 15). This compound can be prepared from hydrolysis of **5** or **6**, or by hydrolysis of ethyl 2,4-dimethyl-2,3-dicyanopentanoate. In a typical run, 3 g (0.022 mol) of a mixture of **5** and **6** in 20 ml of concentrated hydrochloric acid was refluxed overnight (ca. 12 hr), after which some white crystals were noticeable. The solution was cooled and the crystals were collected by filtration, yielding 1.3 g of the erythro product (34% yield): mp 178–180° (lit.[52] mp 171°); NMR ($CDCl_3$–TFA) δ 1.06 (d, 3, CH_3), 1.08 [d, 3, $(CH_3)_2CH$], 1.36 [d, 3, $(CH_3)_2CH$], 2.05 [m, 1, $(CH_3)_2CH$], 2.78 (dd, 1, CH-*i*-Pr), and 3.04 (dq, 1, $CHCH_3$); ir (KBr) 3200–2500, 1700 cm^{-1}.

The filtrate was evaporated to dryness giving the impure threo isomer, **15**, which was exceedingly difficult to purify or handle (this isomer appeared to be quite water soluble).

2-Phenyl-3-benzylbutanedioic Acids (16 and 17). Hydrolysis of ethyl 2-benzyl-3-phenyl-2,3-dicyanopropanoate with hydrochloric acid, or with combinations of various acids, was not successful. This material was prepared by hydrolysis of the dinitriles **8** or **9**. To a solution of 80 ml of concentrated hydrochloric acid, 40 ml of concentrated sulfuric acid, and 40 ml of concentrated acetic acid (these must be *mixed with care*, as gaseous hydrochloric acid is evolved) was added 1.5 g (0.006 mol) of **9** and the mixture was refluxed for ca. 12 hr. On cooling the diacids (1.75 g) precipitated. In other runs some phenyl benzylsuccinimide, mp 126–130°, mass spectrum (70 eV) *m/e* 265 (parent ion), was also formed.

The best purification of these acids was belatedly found to be by means of preferential precipitation of the barium salt of one isomer. In a typical run, 2.5 g of the mixture of **16** and **17** (mp 178–180°) (shown by NMR to be a ca. 35–65% mixture) was dissolved in dilute sodium hydroxide solution. The calculated molar equivalent of barium acetate (with respect to the minor component), ca. 1 g, was added to the solution of the diacids. An immediate precipitate formed, and the mixture was digested on a steam bath for ca. 0.5 hr, allowed to cool, and filtered. Additional barium acetate was added in the same manner in increments followed by filtration, until no further material precipitated. The first two crops of precipitate were used and the much smaller third and fourth crops were discarded. This barium salt was acidified with dilute hydrochloric acid, and the resulting precipitate stirred for ca. 0.5 hr and filtered. This material was readded to dilute sodium hydroxide and precipitated again as the barium salt. The barium salt was washed with water and acidified. The free acid was collected by filtration, giving 0.5 g of **16** as the first crop, mp 184–187°, and 0.55 g as the second crop, mp 182–184°.

The mother liquor from the original barium salt precipitations was acidified to pH 1 with hydrochloric acid, and the fluffy precipitate was filtered off and allowed to air dry, mp 196–203°. This acid (**17**) was redissolved in dilute sodium hydroxide, and additional barium acetate was added in increments; and the precipitates (very slight) were discarded. Reacidification and filtration gave 1.4 g of **17**: mp 200–202° (lit.[38h,53] mp 176°); NMR ($CDCl_3$–TFA) δ 2.85 (m, 2, CH_2Ph), 3.6 (m, 1, $CHCH_2Ph$), 4.02 (d, 1, CHPh), and 7.0–7.5 (m, 10, Ph). The threo diacid **17** from other runs, purified by a recrystallization route, had mp 172–175°, very close to the literature value. The NMR spectrum was very similar to the mp 200° material.

In another run, *erythro*-**8** (1.5 g, 0.059 mol) was heated in 40 ml of concentrated hydrochloric acid, 20 ml of acetic acid, and 20 ml of sulfuric acid at reflux for 48 hr. On cooling, a precipitate appeared which was collected by filtration. The NMR spectrum showed it to be mostly **16**. The acid was dissolved in dilute sodium hydroxide, and precipitated as the barium salt as described above; this was done twice. The resulting diacid, **16** (1.35 g, 80%), had mp 187–189° (lit.[38h] mp 183°); NMR ($CDCl_3$–TFA) δ 3.1 (m, 2, CH_2Ph), 3.6 (m, 1, $CHCH_2Ph$), 4.05 (d, 1, CHPh), and 7.2–7.5 (m, 10, Ph).

Dipole Moments. The dipole moments were determined using a WSW DM 01 Dipolmeter. The cell was calibrated using benzene, cyclohexane, and carbon tetrachloride solvent pairs. Five solutions of the unknown compound were made up in carbon tetrachloride as solvent. The dielectric constant of these solutions were determined using the calibration as determined above.[20] The refractive indices of these solutions were determined on an Abbe' refractometer. The dipole moment was calculated from eq 2, where a_ϵ is the slope of the plot of change in dielectric constant relative to pure solvent vs. weight fraction of substrate, and a_n is a plot of change in refractive index (quantities squared) vs. weight fraction of substrate.

$$\mu^2 = \frac{27kT}{4\pi N_2 d_1} \frac{1}{(\epsilon_1 + 2)^2} (a_\epsilon - a_n) M_2 \quad (2)$$

NMR Data. The NMR data was taken on a Varian XL-100 instrument, or less often, on a Varian A-60D. The coupling constants were determined from 100-Hz expansions of the spectral region in question. The spectra were simulated at 500 and at 100 Hz using the LAOCOON III program.[54] Variations of the parameters were made until the computer-generated plot was superimposable on the original spectrum, although in some cases a good fit of the original spectrum was not possible either due to the complexity of the spectra or due to extreme closeness of certain chemical shifts; cases in point were **7** and **2** in $CDCl_3$. The vicinal coupling constant J_{AB} is good to ±0.3 Hz, however. The data have been omitted from Table I where the uncertainty was large.

The ^{13}C data were also determined on the XL-100 spectrometer (at 25.2 MHz). In normal runs (data given in Table IV), a 5K spectral width was used with a 0.4-sec acquisition time and a 0.2-sec pulse delay. From 5 to 10K of transients were collected. The sample solutions were as concentrated as possible, usually from 0.1 to 0.3 g of substrate per 3.0 ml of $CDCl_3$. The maximum resolution as indicated by the computer was 0.09 ppm. Assignments were made by observation of the splittings determined from undecoupled spectra.

The coupling constants were determined using highly concentration solutions. The "gated" mode of operation of the decoupler was used or, less frequently, the decoupler was simply not used. A typical run (**13**, carbonyl region) involved a 1K spectral width, a 2.5-sec acquisition time, a 2.0-sec pulse delay (gated mode of decoupler operation), and a 40-μsec pulse width. Considerable difficulty was encountered in these spectra from folded peaks, and only the clearest examples are reported in this paper. For this particular sample 10.2K of transients were collected. The spectrum resulting from a similar run is given in Figure 1. The ^{13}C splittings were also simulated using the LAOCOON program.[54] The splittings were first order for the carbonyl groups of the acids **9** and **10**, and almost first order for **11** (i.e., the line separations taken from the spectrum reproduced the spectrum when fed back into the computer program). First-order splittings were observed for certain CN spectra, and not for others. In some cases, computer simulation was impossible owing to an insufficient number of spins in the program. Coupling constants that were not simulated for this or other reasons and coupling constants whose exact value is unclear are indicated with an approximate sign.

The decisions as to which line separations were related to ^2J and which were ^3J were aided by the study of model compounds. Thus, observation of the cyanide carbon of phenylacetonitrile showed a triplet pattern (two-bond couplings to the CH_2 unit) of 10.8 Hz. The larger splittings of CN in **2–5** were assigned as ^2J. For propanoic acid, observation of the methyl showed a ^2J of ca. 4 Hz, and the methylene gave a similar value. Observation of the carbonyl gave $^2J_{CO\text{-}CH_2}$ as 6.9 Hz and $^3J_{CO\text{-}CH_3}$ as 5.8 Hz.

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Registry No.—**2**, 56908-39-5; **3**, 56908-40-8; **4**, 56908-41-9; **5**, 56908-42-0; **6**, 56908-43-1; **7**, 56908-44-2; **8**, 56908-45-3; **9**, 56908-46-4; **12**, 56908-47-5; **13**, 56908-48-6; **14**, 56943-30-7; **15**, 56908-49-7; **16**, 56908-50-0; **17**, 56908-51-1; ethyl cyanoacetate, 105-56-6; benzaldehyde cyanohydrin, 532-28-5; ethyl 2-methyl-3-phenyl-2,3-dicyanopropionate, 29840-39-9; ethyl 2,4-dimethyl-2,3-dicyanopentanoate, 56908-52-2; isobutyraldehyde cyanohydrin, 15344-34-0; ethyl 2-benzyl-4-methyl-2,3-dicyanopentanoate, 56908-53-3; ethyl 2-benzyl-3-phenyl-2,3-dicyanopropionate, 56908-54-4; ethyl 2-methyl-3-phenyl-2,3-dicyanopentanoate, 56908-55-5.

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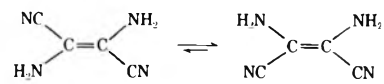

By comparison, Lewis and Mayo [*J. Am. Chem. Soc.*, **70**, 1533 (1948)] report roughly 76% fumaronitrile at equilibrium, whereas Mommaerts [*Bull. Soc. Chim. Belg.*, **52**, 79 (1943)] reports 50% of the trans isomer.
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Silane Reductions in Acidic Media. IV. Reductions of Alkyl-Substituted Cyclohexanones by Mono-, Di, and Trialkylsilanes. Stereochemistry of Alcohol and Ether Formation[1a,b]

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Stereochemical results from the reduction of 4-*tert*-butyl-, 4-methyl-, 3-methyl-, 2-methyl-, and 3,3,5-trimethylcyclohexanones by mono-, di-, and tri-*n*-alkylsilanes and by α-, β-, and γ-branched trialkylsilanes in aqueous sulfuric acid–ethyl ether and trifluoroacetic acid media are reported. Alcohols are formed by silane reductions in aqueous sulfuric acid–ethyl ether. Both trifluoroacetates and symmetrical ethers are produced in trifluoroacetic acid media; alkyl branching at the α positions of alkylsilanes or of cyclohexanones and increasing the number of *n*-alkyl groups bonded to silicon dramatically decreases the relative yield of ether products. Steric factors govern the stereochemical outcome of silane reductions of ketones to alcohols and alcohol derivatives. Increasing the number, but not the length, of linear carbon chains and increasing the branching at the α and β positions of alkylsilanes increases the relative yield of the thermodynamically less stable alcohol. Factors influencing the stereoselectivity of hydride transfer to *O*-alkyloxonium ions resulting in symmetrical ethers have also been determined. The stereoselectivities in organosilane reductions are compared to those from other hydride reducing agents, and the relative importance of conformational equilibria on the stereoselectivity in reductions of methylcyclohexanones is discussed.

Stereoselective control of reaction products in the reduction of cyclic ketones has been the subject of numerous investigations.[2] Hydride reducing agents, such as lithium aluminum hydride, sodium borohydride, and their alkoxy derivatives, undergo predominant axial attack on the relatively unhindered carbonyl group of cyclic ketones, such as 4-*tert*-butylcyclohexanone, to give predominantly the more stable alcohol;[3] diborane and aluminum hydride similarly produce a preponderance of the more stable equatorial alcohol.[4] Mixtures of isomeric alcohols are usually obtained in these reductions. However, nearly exclusive production of the more stable alcohol (>95%) from cyclic ketones has been achieved in dissolving metal reductions using lithium in ammonia.[5]

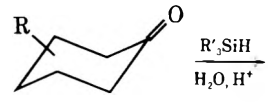
Few reducing agents are capable of effecting stereoselective control in ketone reductions that result in a preponderance of the less stable alcohol. The general approach that has been successfully applied to reductions of cyclic ketones to the less stable axial alcohol has been to increase the steric bulk of the reducing agent. Trialkyl- and diarylborohydrides,[6] for example, have shown marked success in reversing the usual tendency for hydride transfer to the carbonyl group from the axial direction.[7]

Like the more commonly used aluminum and boron hydrides, silicon hydrides are effective reducing agents for the carbonyl group of ketones.[1a] However, except for the light-induced hydrosilation of cyclic ketones with trichlorosilane,[8] there has been no report on the stereoselectivity of ketone reductions by silanes. Alkylsilanes are conveniently prepared by substitution reactions at silicon using chlorosilanes and organometallic compounds; in these reactions the steric bulk of alkyl substituents can be varied widely. Consequently, the effect of increasing the steric bulk of silane reducing agents on the stereoselectivity of ketone reductions can be examined systematically. Such a study of the structural variations of alkyl-substituted organosilanes on the stereoselectivity of product formation is expected to provide information essential to the proper design of truly highly selective reducing agents.

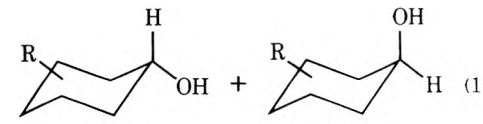
Unlike the more commonly used aluminum and boron hydrides, ketone reductions by the silicon hydrides are catalyzed by Bronsted acids. Activation of the carbonyl carbon by an acid is required before hydride transfer can occur. In order to determine the stereoselectivity in ketone reductions by organosilanes we have examined the reductions in protonic acid media of alkyl-substituted cyclohexanones by mono-, di-, and trialkylsilanes having different steric requirements.

Results

Reductions in Aqueous Sulfuric Acid–Ethyl Ether Mixtures. Aldehydes and ketones are conveniently reduced to alcohols without structural rearrangement by alkylsilanes in aqueous sulfuric acid using ethyl ether as the solvent.[1a] The alkylsilanes are, in turn, oxidized to the corresponding alkylsilanols. The relative yields of the thermodynamically less stable alcohol from the reductions of selected alkyl-substituted cyclohexanones by mono-, di-, and trialkylsilanes in aqueous sulfuric acid–ethyl ether media (eq 1) are presented in Table I. With the exception of re-



Ia, R = 4-*t*-Bu
b, R = 4-Me
c, R = 3-Me
d, R = 2-Me
e, R = 3,3,5-TriMe



ductions by triethylsilane, the rapidly stirred reaction mixtures were heterogeneous. Ketone reductions under the reaction conditions reported in Table I were generally complete within 24 hr at room temperature.

n-Butylsilane is capable of three individual hydride transfer reactions. However, only two of the three hydrogens are rapidly transferred in reductions of carbonyl compounds. When 1 molar equiv of *n*-butylsilane was used to reduce the ketones listed in Table I, nearly 0.3 equiv of *n*-butylsilane remained unreacted. When 0.36 molar equiv of *n*-butylsilane (1.1 molar equiv of hydride) was employed

Table I
Stereoselectivities of Organosilane Reductions of Alkyl-Substituted Cyclohexanones in Aqueous Sulfuric Acid–Ethyl Ether Mixtures[a]

Registry no.	Silane (mmol)	mmol of ketone	mmol of acid	Relative yield, % cyclohexanol[b,c] *cis*-4-*tert*-Butyl-[d]	*cis*-4-Methyl-	*trans*-3-Methyl-	*cis*-2-Methyl-	*trans*-3,3,5-Trimethyl-
1600-29-9	*n*-$BuSiH_3$ (5.5)	5.0	3.5	10	18	19	31	74
	(1.8)	5.0	3.5	13				
542-91-6	Et_2SiH_2 (5.0)	5.0	3.5	20	26	29	41	85
617-86-7	Et_3SiH (6.0)	5.0	3.5	32	35	39	54	(90)[e]
998-41-4	*n*-Bu_3SiH (5.5)	5.0	3.5	22	25	35	51	(89)[e]
2929-52-4	*n*-Hex_3SiH (10)	5.0	3.5	21		32		

[a] Reactions were run at room temperature (28 ± 3°). Aqueous sulfuric acid (0.5 g of a 73 g % solution of aqueous sulfuric acid prepared from 0.5 mol of 96% H_2SO_4 and 1.0 mol of water) was added to the silane and ketone in 0.6 ml of ethyl ether. [b] Unless indicated otherwise the yield of alcohol products was essentially quantitative. Recovered yields of alcohol products after work-up approaching 90% could be attained in these small-scale reactions. [c] The precision of analysis is within ±1% from duplicate runs. [d] The yield of *cis*-4-*tert*-butylcyclohexanol from the reduction of 4-*tert*-butylcyclohexanone with phenylsilane was 9% and with tetramethyldisiloxane was 21% using similar reaction conditions. [e] Observed relative yield of alcohol product. Olefinic products are also obtained.

Table II
Stereoselectivities of Organosilane Reductions of Alkyl-Substituted Cyclohexanones in Trifluoroacetic Acid[a]

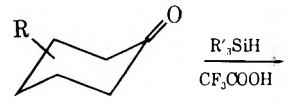
Registry no.	Silane (mmol)	mmol of ketone	mmol of CF_3CO_2H	Relative yield, % cyclohexanol[b,c] *cis*-4-*tert*-Butyl-	*cis*-4-Methyl-	*trans*-3-Methyl-	*cis*-2-Methyl-	*trans*-3,3,5-Trimethyl-
	n-$BuSiH_3$[d] (5.0)	5.0	34	16				
		5.0	34	21				
13154-66-0	*n*-$PrSiH_3$[e] (2.5)	2.4	5.0	20			37	
	Et_3SiH[f] (6.0)	5.0	34	32	36	42	48[g]	84
	n-Hex_3SiH (6.0)	5.0	10				44	
17922-08-1	*i*-$Pent_3SiH$ (4.0)	3.0	20	30	33	38	48	83
33729-87-2	c-$Pent_3SiH$ (4.0)	3.0	21	44	48	51	59	95
6485-81-0	*i*-Bu_3SiH (3.0)	2.5	17.5	55	56	61	62[g]	93
6531-11-9	*sec*-Bu_3SiH[h] (2.5)	2.2	5.1	56			64	
	(2.5)	3.0	21	(55)[i]	(58)[i]	(67)[i]	(64)[j]	96
30736-07-3	*t*-Bu_3SiH_2 (2.5)	2.5	18	(68)[i]	(67)[i]	(73)[i]	(66)[k]	89

[a] Reactions were run at room temperature (28 ± 3°). The ketone in trifluoroacetic acid was added to the silane. [b] Relative yield of alcohol products; symmetrical ethers are also formed (see Tables III and IV). [c] The precision of analysis is within ±1% from duplicate runs. [d] At −20° the relative yield of *cis*-4-*tert*-butylcyclohexanol was only 3% (44 hr reaction time). [e] Using a 14-fold excess of CF_3CO_2H the yield of *cis*-4-*tert*-butylcyclohexanol was 17%. With PMHS the yield of *cis*-4-*tert*-butylcyclohexanol was 19%. [f] Identical results from 4-*tert*-butylcyclohexanone were observed when only 1 equiv of acid was employed. [g] Less than 1% methylcyclohexane (formed from 1-methylcyclohexene by ionic hydrogenation) was observed. [h] The yield of *cis*-4-*tert*-butylcyclohexanol was 58% when 5 mmol of ketone and silane were used with 34 mmol of acid. [i] 3 mol % olefin product(s) obtained. [j] 4 mol % methylcyclohexane. [k] 30 mol % methylcyclohexane.

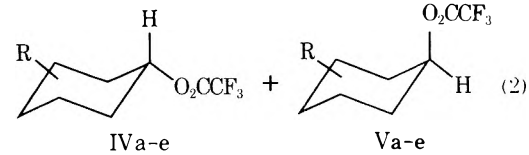
for the reduction of 4-*tert*-butylcyclohexanone (Table I), 72% of the ketone was reduced within 4 hr; an additional 40 hr was required to reduce the remaining 28% of 4-*tert*-butylcyclohexanone. The silane compound formed from *n*-butylsilane after two hydride transfer reactions was a relatively unreactive solid polymeric siloxane from which the reduction products were conveniently isolated. Since unreacted *n*-butylsilane (bp 54–56°) can be easily separated from alcohol products by fractional distillation, the use of *n*-butylsilane provides a simple, convenient method for producing the more stable alcohol isomer predominantly in reductions of relatively unhindered cyclic ketones.

With trisubstituted branched-chain alkylsilanes, such as tri-*sec*-butylsilane, and trialkylsilanes possessing more than 12 carbon atoms, such as tri-*n*-hexylsilane, reaction times for reductions of cyclic ketones are greater than 24 hr. In addition, in these reductions acid-catalyzed dehydration of the alcohol products becomes important. Such difficulties can be circumvented if reductions with these more bulky silanes are carried out in trifluoroacetic acid media.

Reductions in Trifluoroacetic Acid Media. The relative yields of the thermodynamically less stable alcohol from the reductions of alkyl-substituted cyclohexanones by mono-, di-, and trialkylsilanes in trifluoroacetic acid (eq 2)



Ia, R = 4-*t*-Bu
b, R = 4-Me
c, R = 3-Me
d, R = 2-Me
e, R = 3,3,5-TriMe



IVa-e Va-e (2)

are presented in Table II. The reaction solutions were homogeneous, and the reactions were, with the exception of those using di-*tert*-butylsilane and tri-*sec*-butylsilane, noticeably exothermic. The trifluoroacetate derivatives formed in these reductions[1a] were usually converted by a mild hydrolysis procedure to the corresponding alcohols. Analysis of the trifluoroacetate products prior to hydrolysis, and of the alcohol products after hydrolysis, showed

Table III
Symmetrical Ether and Trifluoroacetate Product Distributions in Triethylsilane Reductions of Alkylcyclohexanones[a]

Ketone	Trifluoroacetates % yield	Trifluoroacetates % V/% IV	Symmetrical ethers % Yield	Symmetrical ethers % axial/% equatorial[b]
Ia	83	0.47	17	1.04
Ib	83	0.56	17	*c*
Ic	87	0.72	13	*c*
Id	>99	0.92	<1	*c*
Ie	84	8.1	16	3.65

[a] Reductions were run at room temperature using 1.0 mmol of ketone, 0.8 mol of triethylsilane, and 6.5 mmol of trifluoroacetic acid. Reaction time was 24 hr. [b] Ratio of axial to equatorial alkyl substitution of oxygen determined by ^{1}H NMR spectroscopy or by GLC analysis. [c] Could not be determined.

amount of ether formation is dependent on the structures of both the ketone and silane. Organosilane reductions of cyclohexanones with alkyl substituents in remote positions with respect to the carbonyl group, 4-*tert*-butyl-, 4-methyl-, 3-methyl-, and 3,3,5-trimethylcyclohexanones, give a substantially higher proportion of symmetrical ethers than 2-methylcyclohexanone, a ketone having an alkyl group that can effectively shield the carbonyl group. Reduction of 2-methylcyclohexanone by *n*-butylsilane in trifluoroacetic acid, for example, gives 46% symmetrical ethers, compared to 74% symmetrical ethers from the reduction of 4-*tert*-butylcyclohexanone by *n*-butylsilane under similar reaction conditions. The relative yield of symmetrical ethers is also dependent on the nature of alkyl substitution of the organosilane; the greater the number of alkyl groups and the greater the branching of the alkyl groups, especially at the α position, the less is the relative proportion of symmetrical ethers formed during reduction. Significant con-

Table IV
Symmetrical Ether and Trifluoroacetate Product Distributions in Reductions of 4-*tert*-Butylcyclohexanone by Organosilanes[a]

Silane (mmol)	mmol of ketone	mmol of CF_3CO_2H	Trifluoroacetates[b,c] % yield[d]	Trifluoroacetates[b,c] % *cis*/% *trans*	Symmetrical ethers[c] % yield[d]	Symmetrical ethers[c] *trans,-trans*, %*f,i*	Symmetrical ethers[c] *cis,trans* %*f,j*	Symmetrical ethers[c] *cis,cis* %*f,k*	Symmetrical ethers[c] % *cis*/% *trans*[e]
n-$BuSiH_3$ (5.0)	5.0	34	37	0.19	63	44	46	10	0.49
(1.8)	5.0	34	40	0.27	60	50	43	7	0.40
(50)	50	125	26	0.031[g]	74	67	29	4	0.23[g]
n-$PrSiH_3$ (2.5)	2.4	5.0	50	0.25	50	53	40	7	0.37
PMHS (4.0)	5.0	34	66	0.23	34	30	55	15	0.76
Et_3SiH (18)	18	135	83	0.49	17	25	48	27	1.04
(22)	20	20	93	0.53	7	19	45	36	1.41
c-$Pent_3SiH$ (4.0)	3.0	21	89	0.79	11	13	35	52	2.28
i-Bu_3SiH (2.7)	2.5	17.5	86	1.08	14	18	43	39	1.53
sec-Bu_3SiH (2.5)	3.0	21	94	1.22	6	3	24	73	5.67
t-Bu_2SiH_2 (5.2)	5.2	35	97[h]	2.12	0				

[a] See footnote *a*, Table II. [b] Analyzed as the alcohol unless indicated otherwise. [c] See footnote *c*, Table II. [d] Unless indicated otherwise, trifluoroacetates and symmetrical ethers were formed in nearly quantitative yields. [e] 2(% *cis,cis*-) + % *cis,trans*-/2(% *trans,trans*-) + % *cis,trans*-. [f] Relative yield of isomeric ether; duplicate runs show that the precision of analysis is within ±2% of the reported value. [g] Reaction was run at −20° for 44 hr; isolated yield of ethers was 74%. [h] 3% cycloalkene. [i] Registry no., 56889-95-3. [j] Registry no., 56942-33-7. [k] Registry no., 56942-34-8.

that no change in the isomeric ratio of products occurred during the hydrolysis procedure. The primary silane products were the corresponding silyl trifluoroacetates which formed mixtures of silanols and disiloxanes upon hydrolysis.

Organosilane reductions of Ia–e were generally complete within 2–4 hr when 7 molar equiv of trifluoroacetic acid was used. However, more than 2 days were required for complete reduction of 3- and 4-methylcyclohexanones by di-*tert*-butylsilane (1 molar equiv of silane), and reaction times of more than 12 days were necessary for complete reduction of 2-methyl- and 3,3,5-trimethylcyclohexanones by the same reducing agent. *In ketone reductions di-tert-butylsilane was approximately 100 times less reactive than tri-sec-butylsilane.* When 2 hydride equiv of di-*tert*-butylsilane per ketone were employed, the silane products consisted of di-*tert*-butylsilyl trifluoroacetate (4%) and either di-*tert*-butylsilanediol or its trifluoroacetate derivative (96%). After hydrolysis of the reaction mixture di-*tert*-butylsilanediol was isolated in 91% yield. Thus the second hydride transfer is more rapid than the first, and both hydrides per molecule of di-*tert*-butylsilane are effective in reducing ketones.

In trifluoroacetic acid media symmetrical ether formation is a major competing reaction in ketone reductions (eq 3).[1a] As shown by the data in Tables III and IV, the relative

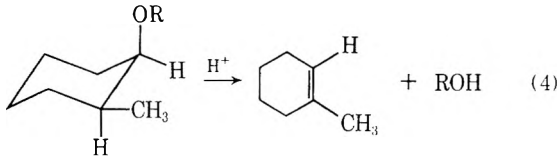
trol over reaction products can be achieved in these reductions by proper choice of silane, temperature (low temperatures favor the ether), and acid concentration (high concentrations favor the ether) so that ether or alcohol products can be produced selectively.

$$(m + 2n)\ R_2C{=}O \xrightarrow[CF_3COOH]{R'_3SiH} m R_2CHOOCCF_3 + n R_2CHOCHR_2 \quad (3)$$

With the exception of those ethers formed in reductions of 2-methylcyclohexanone, symmetrical ethers were not noticeably converted to trifluoroacetates under the reaction conditions employed, and the trifluoroacetates did not form symmetrical ethers. Symmetrical ethers were not formed in the reductions of alkyl-substituted cyclohexanones in aqueous sulfuric acid–ethyl ether.

When the 2-methylcyclohexyl ethers having an isomeric cis to trans ratio of 1.02 were treated with 6.0 equiv of trifluoroacetic acid at room temperature for 24 hr, only 61% of the ethers (cis/trans = 0.73) was recovered. Both *cis*- and *trans*-2-methylcyclohexyl trifluoroacetates were produced (39% yield) in an isomeric ratio (cis/trans = 0.98) nearly identical with that of the reactant ethers, and 1-methylcyclohexyl trifluoroacetate was also formed in 39% yield. These results indicate that cleavage of the 2-methylcyclo-

hexyl ethers occurs by elimination, that only the cis-substituted 2-methylcyclohexyl ring of the symmetrical ethers undergoes elimination, and that the unique ether cleavage reaction occurs with both *cis,cis*- and *cis,trans*-2-methylcyclohexyl ethers but not with the trans,trans isomer (eq 4).

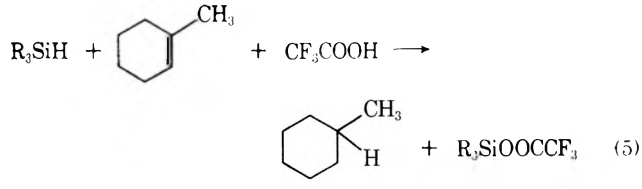


(4)

Table IV reports the relative yields of the three isomeric symmetrical ethers formed in the organosilane reductions of 4-*tert*-butylcyclohexanone. Like the relative yield of symmetrical ethers in these reductions, the cis to trans ratio for the ether products reflects the nature of alkyl substitution of the organosilane. The cis to trans ratio for the ethers magnifies the corresponding ratio for trifluoroacetate products. Within experimental limits no changes in the relative yields of the isomeric ether products were observed when the reduction of 4-*tert*-butylcyclohexanone was monitored at intervals over a 27-hr period.

Except in reductions by tri-*sec*-butylsilane or di-*tert*-butylsilane and of 2-methylcyclohexanone, elimination products were not observed during the reductions of alkyl-substituted cyclohexanones by organosilanes. Approximately 3 mol % of cycloalkene was observed in reductions of 4-*tert*-butyl-, 4-methyl-, and 3-methylcyclohexanones by tri-*sec*-butylsilane and di-*tert*-butylsilane when 7 molar equiv of trifluoroacetic acid was used. The olefin or olefins produced in each of these reductions were relatively stable toward addition of trifluoroacetic acid under the reaction conditions employed; no change in the yield of olefin was observed over a 20-hr period after complete reduction of each of the 3- and 4-substituted cyclohexanones.[10] From the results in Table II for the tri-*sec*-butylsilane reduction of Ia in which only 2 equiv of acid was used, and in which no elimination–addition occurs, an estimate of a maximum of 3–4% olefin formation in reductions of Ia–c is reasonable. Cycloalkene products were not obtained from the reductions of 3,3,5-trimethylcyclohexanone by any of the organosilanes listed in Table II.[11]

The preferred orientation in elimination reactions of 2-methylcyclohexanol derivatives results in the formation of 1-methylcyclohexene.[12] Subsequent reduction of 1-methylcyclohexene by organosilanes[13] forms methylcyclohexane under the reaction conditions employed for reduction of 2-methylcyclohexanone (eq 5). The yields of methylcyclohexane from organosilane (given in parentheses) reductions of 2-methylcyclohexanone were <1% (Et_3SiH), <1% (*i*-Bu_3SiH), 4% (*sec*-Bu_3SiH), and 30% (*t*-Bu_2SiH_2). No 1-methylcyclohexyl trifluoroacetate, the expected addition product from 1-methylcyclohexene and trifluoroacetic acid, was observed.

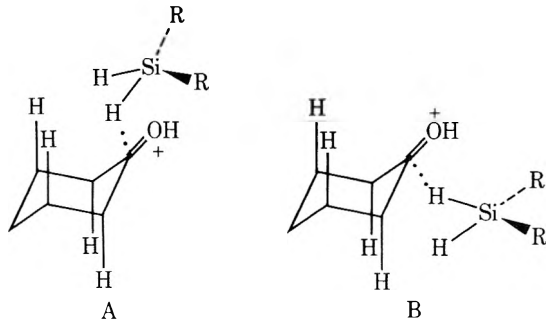


(5)

Discussion

Stereoselectivity of Alcohol Formation. The results reported in Tables I and II describe the importance of steric factors from both the ketone and the silane reducing agent in determining the stereochemical outcome of organosilane reductions of alkyl-substituted cyclohexanones. Increasing the steric bulk of the organosilane reducing agent increases the relative yield of the thermodynamically less stable alcohol or alcohol derivative.

The relative yield of the less stable isomer, IIIa–e or Va–e, increases with increasing substitution of n-alkyl groups at silicon. An increase of approximately 10% in the proportion of hydride transfer that results in the production of axial alcohol occurs with each successive *n*-alkyl substitution at silicon when silane reductions are performed in aqueous sulfuric acid–ethyl ether; smaller increases are observed when the corresponding reductions occur in trifluoroacetic acid. In general, the effect of increasing *n*-alkyl substitution is additive, suggesting that steric interference to hydride transfer is dependent on the composite steric bulk of the organosilane and that hydride transfer does not occur preferentially from fixed geometries, such as A and B, in which the larger alkyl substituents, especially of mono- and dialkylsilanes, are positioned to avoid steric crowding with the ketone during hydride transfer.[14]



Branching at the α and β positions of trialkylsilanes increases the relative yield of the less stable alcohol product in ketone reductions. Only small differences in product yields from reductions of Ia–e in trifluoroacetic acid were observed with triisobutylsilane and tri-*sec*-butylsilane (Table II). However, when the relatively free rotation of each of the alkyl groups of an α-branched trialkylsilane is restricted, as in tricyclopentylsilane, the increase in the relative yields of Va–e is significantly less than the corresponding yields in reductions by tri-*sec*-butylsilane. As with the effect of increasing the chain length of tri-*n*-alkylsilanes, the effect of tricyclopentylsilane compared to tri-*sec*-butylsilane (α branching) on the stereoselectivity of ketone reductions is most evident with 3- and 4-alkylcyclohexanones. Branching at the γ position of trialkylsilanes is not effective in altering the relative yields of Va–e from those obtained using triethylsilane.

n-Butylsilane and di-*tert*-butylsilane rapidly undergo two hydride transfer reactions; the third hydride transfer from *n*-butylsilane is relatively slow. A comparison of the results from Tables I and II for reduction of Ia by 1.1 and 0.36 molar equiv of *n*-butylsilane show a 3–5% increase in the relative yield of IIIa or Va due to the transfer of the third hydride. Although the exact stereochemical outcome from the transfer of the first hydride is unknown, these results are predictably similar to those observed by Rickborn and Wuesthoff for reductions of sodium borohydride:[3b] *in successive hydride transfer reactions from polyhydride reducing agents, the transfer of the first hydride results in the higher yield of the more stable alcohol isomer.*

The stereochemical outcome of reductions of alkyl-substituted cyclohexanones by *n*-alkylsilanes in aqueous sulfuric acid–ethyl ether or in trifluoroacetic acid is comparable to similar results from reductions with boron and aluminum hydrides (Table V). Equatorial attack is preferred in reductions of 3,3,5-trimethylcyclohexanone because of the steric interference toward attack from the axial side due to

Table V
Comparative Stereoselectivities of Boron, Aluminum, and Silicon Hydrides

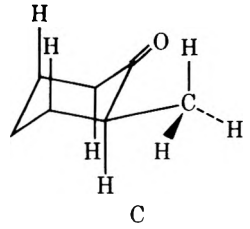
Reducing agent	Relative yield, % cyclohexanol				
	cis-4-*tert*-Butyl-	*cis*-4-Methyl-[c,d]	*trans*-3-Methyl-[c,e]	*cis*-2-Methyl-	*trans*-3,3,5-Trimethyl-
$LiAlH_4$, Et_2O	11[3d]	17[6a] (16)	16[6a] (16)	24[3d]	55
$NaBH_4$, *i*-PrOH, 0% reaction[3b]	—	11	13	25	58
$NaBH_4$, *i*-PrOH, 100% reaction[3b]	20[16]	24 (25)	24 (25)	40	62
B_2H_6[4b,c]	10	15	12 (17)	25	66
n-$BuSiH_3$[a]	10	18	19 (16)	31	74
AlH_3	13,46[4e]			26	88[17]
$LiAlH(O\text{-}t\text{-}Bu)_3$[3e]	10	14	17 (18)	37	88,94[3f]
Et_2SiH_2[a]	20	26	29 (27)	41	85
Et_3SiH[a]	32	35	39 (38)	54	90
Et_3SiH[b]	32	36	42 (37)	48	84
$LiAlH(OMe)_3$	41[18]			69[3d]	73[19]

[a] Data taken from Table I. [b] Data taken from Table II. [c] Values in parentheses are calculated using the conformational energies for conformers of methylcyclohexanones[21] with the values from reductions of 4-*tert*-butylcyclohexanone as the model for the equatorial conformer and 5α-cholestan-3-one[20] or 3,3,5-trimethylcyclohexanone as the model for the axial conformer. [d] Calculated yield = 0.94 (% *cis*-4-*tert*-butyl-) + 0.06 (% β-3-cholestanol). [e] Calculated yield = 0.90 (% *cis*-4-*tert*-butyl-) + 0.10 (% *trans*-3,3,5-trimethyl-).

the axial methyl group in the 3 position.[2] Hydride transfer which avoids torsional strain[2,15] is generally predominant in reductions of Ia–d.

The relative yields of the less stable alcohol from reductions of 4-methyl- and 3-methylcyclohexanones are consistently greater than those from 4-*tert*-butylcyclohexanone. Unlike the conformationally biased 4-*tert*-butylcyclohexanone, conformations of methylcyclohexanones in which the alkyl substituent is in the axial position are not negligible.[21] For example, in the equilibrium mixture at room temperature the equatorial-methyl chair conformer of 3-methylcyclohexanone is present to the extent of only 90%; the axial-methyl chair conformer accounts for more than 9% of 3-methylcyclohexanone. If the assumption is made that hydride transfer to the equatorial-methyl conformer of 3-methylcyclohexanone occurs with the same ratio of axial to equatorial attack as 4-*tert*-butylcyclohexanone and that the model for the axial-3-methyl conformer is 3,3,5-trimethylcyclohexanone, the relative yields of alcohol products from reductions of 3-methylcyclohexanone can be predicted within ±1% for the majority of the reducing agents in Table V.[22] Using suitable model compounds the same procedure can be applied to estimate the product yields from reductions of 4-methylcyclohexanone.

The relative yields of the less stable cis isomer from reductions of 2-methylcyclohexanone are uniformly 10–30% greater than those from the corresponding reductions of 4-*tert*-butylcyclohexanone. In the equatorial conformation the 2-methyl substituent has an additional axial β hydrogen (C) which increases the steric requirement for axial attack. Stereochemical results from reductions of a model compound, *cis*-2-methyl-4-*tert*-butylcyclohexanone,[23] in which the 2-methyl substituent is fixed in the equatorial position indicate, however, that the effect of the additional axial β hydrogen cannot completely account for the higher yields of the less stable isomer found in reductions of 2-methylcyclohexanone. Nor can the conformational equilibrium of the reactant ketone completely account for the observed higher yields of cis alcohol. Ashby has shown that complexation with the carbonyl group in reductions of 2-methylcyclohexanone by complex metal hydrides causes an increase in the relative yield of *cis*-2-methylcyclohexanol. This increase has been explained as being due to a change in the relative proportion of the metal ion complexed axial-2-methylcyclohexanone conformer with the increasing bulk of the complexing agent.[23] In silane reductions utilizing Bronsted acids, protonation of the ketone carbonyl group may also change the conformational equilibrium of the reactant 2-methylcyclohexanone.



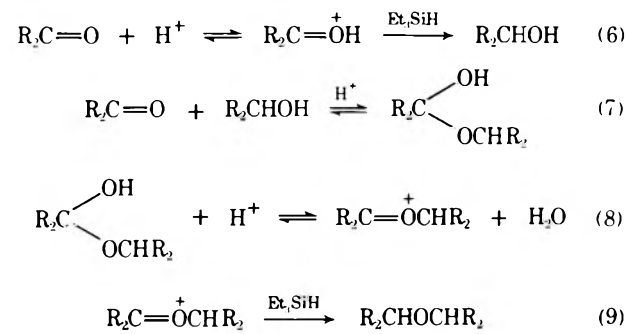
C

Strikingly different stereochemical results are obtained in reductions of alkyl-substituted cyclohexanones by bulky boron and silicon hydrides. The boron hydrides are especially sensitive toward 3,3,5-trimethylcyclohexanone and 2-methylcyclohexanone, yielding the thermodynamically less stable isomer in high stereochemical purity. In contrast, the silicon hydrides show no such differentiation and, in fact, exhibit less ability to discriminate stereochemically between alkyl-substituted cyclohexanones as the steric requirement of the silane is increased. Unlike boron hydrides, such as lithium tri-*sec*-butylborohydride and lithium perhydro-9b-boraphenalylhydride (LiPBPH), whose approach to the carbonyl group of 4-*tert*-butylcyclohexanone appears to be influenced by remote alkyl substituents, silicon hydrides show no similar steric influence in reductions of 4-*tert*-butylcyclohexanone. The differences in the stereoselectivities of the bulky boron and silicon hydrides is explained by the differences in the mechanisms for borohydride and silane reductions and will be discussed in a subsequent paper.[25]

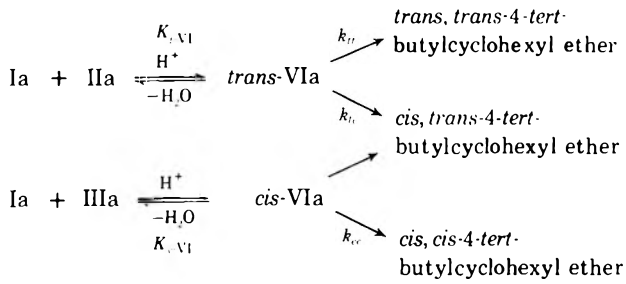
Stereoselectivity of Ether Formation. The yields of symmetrical ethers and trifluoroacetates reported in Table III indicate the relative importance of steric effects on ether formation in the triethylsilane reduction of alkyl-substituted cyclohexanones. The relative yields of ethers formed in reductions of cyclohexanones having alkyl substituents in the 3 and 4 positions are nearly identical (13–17%). In contrast, reduction of 2-methylcyclohexanone by triethylsilane gives less than 1% of symmetrical ethers.[26]

We have previously described ether formation as occurring by hydride transfer to the oxonium ion, VI, formed from the nucleophilic addition of an alcohol to the protonated carbonyl group, followed by elimination of a molecule of water (Scheme I).[1a,27] Ether formation competes with trifluoroacetolysis of the alcohol. The decreased yield of ethers from the reduction of 2-methylcyclohexanone (Id)

Scheme I



Scheme II



compared to that from 4-*tert*-butylcyclohexanone indicates either (1) that steric factors in reactions leading to VI decrease the effective concentration of VI, (2) that there is steric hindrance to hydride transfer from triethylsilane to VI, or (3) that the decreased yield of ethers is due to a combination of 1 and 2. Since reduction of Id by *n*-butylsilane gives a 46% yield of symmetrical ethers, the lower yield of ethers in silane reductions of Id indicates that there is indeed steric hindrance to hydride transfer from alkylsilanes to VI.

As seen from the data in Tables III and IV, the isomeric ratio of symmetrical ether products is also governed by the steric requirement of the organosilane. With the exception of the triethylsilane reduction of 3,3,5-trimethylcyclohexanone, the cis to trans ratio for ethers magnifies the cis to trans alcohol ratio. Among the trialkylsilanes in reductions of 4-*tert*-butylcyclohexanone this magnification is on the order of two to three. The cis to trans ratio of ethers in reductions of Ia by triisobutylsilane, however, is only a factor of 1.5 times that of the alcohol, possibly reflecting different steric requirements for hydride transfer to protonated ketone and VI in this case.

Since two isomeric alcohols are formed in silane reductions of alkyl-substituted cyclohexanones, two isomeric oxonium ion intermediates are formed in the reaction scheme leading to ether formation. Reduction of the two isomeric oxonium ions gives three isomeric ethers (Scheme II). If there is no discrimination in oxonium ion formation ($K_{t\text{-VIa}} = K_{c\text{-VIa}}$) the yields of symmetrical ethers will reflect the relative concentrations of alcohol products formed by silane reduction, and the relative rates of hydride transfer to each oxonium ion (k_{tc}/k_{tt} and k_{cc}/k_{ct}) can be determined. Table VI lists the selectivity ratios, k_{tc}/k_{tt} and k_{cc}/k_{ct}, which were calculated by assuming that [IIIa]/[IIa] = [*cis*-VIa]/[*trans*-VIa].[28]

Comparison of the isomeric ratios in Table VI shows that hydride transfer to VIa is much more sensitive to the steric bulk of the organosilane reducing agent than is hydride transfer to the corresponding protonated ketone, and that reduction of *cis*-VIa gives a higher yield of the less stable isomer than does the reduction of *trans*-VIa.[29] Thus *changing the steric bulk of the acid required to activate the carbonyl group in silane reductions dramatically affects the stereoselectivity of hydride transfer.* Similar effects are becoming increasingly evident in reductions by metal hydrides[6b,23,30] and by metal alkoxides.[31]

Table VI
Stereoselectivities of Organosilane Reductions of *trans*-VIa and *cis*-VIa in Reductions of 4-*tert*-Butylcyclohexanone

Silane (mmol)	mmol of ketone	mmol of CF_3-COOH	IIIa[a]/IIa	k_{tc}/k_{tt}[b]	k_{cc}/k_{ct}[c]
n-$BuSiH_3$ (5.0)	5.0	34	0.19	0.91	1.7
(1.8)	5.0	34	0.27	0.58	2.0
(50)	50	125	0.031	0.45	*d*
n-$PrSiH_3$ (2.5)	2.4	5.0	0.25	0.51	0.54
PMHS (4.0)	5.0	34	0.23	1.4	3.8
Et_3SiH (18)	18	135	0.49	1.7	4.5
(22)	20	20	0.53	2.6	*d*
c-$Pent_3SiH$ (4.0)	3.0	21	0.79	3.3	*d*
i-Bu_3SiH (2.7)	2.5	17.6	1.08	1.4	2.3
sec-Bu_3SiH (2.5)	3.0	21	1.22	14	*d*

[a] Data taken from Table IV. [b] k_{tc}/k_{tt} = (% IIa − % trans,trans ether)/% trans,trans ether. [c] k_{cc}/k_{ct} = (% IIIa − % cis,cis ether)/% cis,cis ether. [d] % cis,cis ether > % IIIa; does not necessarily imply that the reducing agent discriminated in favor of *cis*-VIa; in nearly every case either the yield of the cis,cis isomer was relatively low or the total yield of ethers was low and the experimental yields obtained relatively uncertain.

Experimental Section

Instrumentation. Infrared spectra were obtained on a Perkin-Elmer Model 621 grating spectrophotometer. Mass spectra were obtained using a Finnigan Model 1015 gas chromatograph–mass spectrometer operated at 70 eV. Proton magnetic resonance spectra were obtained with a Varian Model A-60A spectrometer; chemical shifts are reported in δ units using tetramethylsilane as the internal reference. Analytical GLC analyses were performed on Varian Aerograph Models 1864 and 2720 gas chromatographs using thermal conductivity detectors. Use was made of 5-ft columns of 10% SE-30, 25% glycerol, and 20% Carbowax 20M and 10-ft columns of 20% Carbowax 20M, all on Chromosorb P. Melting points were obtained on a Thomas-Hoover apparatus and were uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Materials. Commercial samples of 3- and 4-methylcyclohexanones were used without further purification. 2-Methylcyclohexanone and 4-*tert*-butylcyclohexanone were purified by distillation prior to use. A sample of 3,3,5-trimethylcyclohexanone was prepared by a standard Jones oxidation procedure from commercially available 3,3,5-trimethylcyclohexanol. Isomeric mixtures of each of the methylcyclohexanols and 4-*tert*-butylcyclohexanol were commercially available and used without further purification. A mixture of 3,3,5-trimethylcyclohexanols (52% cis, 48% trans) was prepared by a lithium aluminum hydride–ether reduction of 3,3,5-trimethylcyclohexanone. Diethyl-, triethyl-, tri-*n*-butyl-, and tri-*n*-hexylsilanes, polymethylhydrogensiloxane (PMHS), and tetramethyldisiloxane were commercially available and used without further purification. Phenyl-, *n*-butyl-, and *n*-propylsilanes were prepared by standard lithium aluminum hydride reductions of the corresponding organotrichlorosilanes.[1a] Triisobutyl- and triisopentylsilanes were prepared by standard methods from the corresponding Grignard reagents and trichlorosilane. Tri-*sec*-butyl- and tricyclopentylsilanes were prepared by standard methods from organolithium reagents and trichlorosilane. The preparation of di-*tert*-butylsilane has been described.[32] The physical constants and spectra of organosilanes prepared by these methods were consistent with their structure and with the reported literature values.

2-Methylcyclohexyl Ether. To a solution of 5.60 g (50.0 mmol) of 2-methylcyclohexanone and 1.76 g (20.0 mmol) of *n*-butylsilane cooled at 0° was added dropwise 9.2 ml (125 mmol) of trifluoroacetic acid over a 40-min period. The flask containing the homogeneous reaction solution was then stoppered and stored in a freezer at −40° for 144 hr, at which time ^1H NMR analysis indicated that all of the ketone had been reduced. Excess sodium hydroxide (50 ml of 3 *N* NaOH) was added, and the reaction mixture was stirred rapidly for 5 hr. The organic materials were extracted five

Table VII
^{1}H NMR Absorptions of Reaction Products from Silane Reductions of Ia–e in Trifluoroacetic Acid

Alkylcyclohexanone	Chemical shift, δ[a]				
	Cycloalkene	Trifluoroacetates[b]		Symmetrical ethers[b]	
		IV	V	Axial[c]	Equatorial[d]
Ia	5.71	5.37	4.97	4.05	3.62
Ib	5.70	5.37	5.04	4.1–3.8[e]	
Ic	5.67	5.47	5.08	4.15	3.8
Id	*f*	5.31	4.74	3.79	3.18
Ie	5.53	5.46	5.2	4.08	*g*

[a] Relative to internal Me_4Si in trifluoroacetic acid; temperature 37°. [b] Multiplet absorptions; peak width ±0.1 ppm for axial-substituted isomers, ±0.2 ppm for equatorial-substituted isomers. [c] Contribution from axial–axial and axial–equatorial substituted isomers. [d] Contribution from axial–equatorial and equatorial–equatorial substituted isomers. [e] Broad unresolvable absorptions. [f] Not observed in trifluoroacetic acid owing to formation of 1-methylcyclohexyl trifluoroacetate. [g] Not observed owing to broad linewidth and low concentration of this isomer.

times with 10-ml portions of pentane, and the combined pentane extract was stirred over solid potassium hydroxide for 3 hr. The potassium hydroxide was filtered, and the pentane solution was concentrated under reduced pressure. Vacuum distillation gave 2.41 g (11.5 mmol, 46% yield) of 2-methylcyclohexyl ether: bp 76.5–78.0° (0.3 Torr); ir (film) 1075 cm^{-1} (C–O–C); ^{1}H NMR (CCl_4) multiplets centered at δ 3.43 and 2.79 (1 H) and complex absorptions between δ 0.7 and 2.1 (12 H); mass spectrum *m/e* (rel intensity) 211 (0.033, P + 1), 210 (0.20, parent ion), 114 (3.9), 97 (27), 55 (100).

Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H. 12.46. Found: C, 79.72; H, 12.35.

4-*tert*-Butylcyclohexyl Ether. To a stirred solid–liquid mixture of 7.70 g (50.0 mmol) of 4-*tert*-butylcyclohexanone and 4.40 g (50.0 mmol) of *n*-butylsilane at 0° was added 0.2 ml (125 mmol) of trifluoroacetic acid dropwise over a 60-min period. The heterogeneous mixture slowly became homogeneous during the addition of trifluoroacetic acid. After complete addition of trifluoroacetic acid the reaction mixture was cooled to −40° for 44 hr, at which time ^{1}H NMR analysis indicated complete reduction of 4-*tert*-butylcyclohexanone. Vacuum distillation of the reaction mixture at 30 Torr removed trifluoroacetic acid, water, and unreacted *n*-butylsilane. Continued distillation at 0.3 Torr gave 5.34 g (18.5 mmol, 74% yield) of 4-*tert*-butylcyclohexyl ether, bp 147–160° (0.3 Torr). GLC analysis on a 2-ft 20% Carbowax 20M column at 205° gave three peaks with retention times of 2.9, 4.9, and 7.4 min and having relative peak areas of 4, 29, and 67%, respectively. Each of these compounds was collected and analyzed separately.

***cis,cis*-4-*tert*-Butylcyclohexyl ether** was a viscous liquid: 2.9 min retention time; ir (film) 1398, 1370, 1240 (*tert*-butyl), and 1050 cm^{-1} (C–O–C); ^{1}H NMR (CCl_4) δ 3.58 (m, 2 H), 1.9 (m, 4 H), 1.75–1.1 (m, 14 H), and 0.87 (s, 18 H); mass spectrum *m/e* (rel intensity) 295 (0.04, P + 1), 294 (0.17, parent ion), 156 (2.0), 139 (5.8), 123 (6.0), 99 (14), 83 (30), and 57 (100).

Anal. Calcd for $C_{20}H_{38}O$: C, 81.56; H, 13.00. Found: C, 81.70; H, 13.04.

***cis,trans*-4-*tert*-Butylcyclohexyl ether** was a white solid: mp 61.0–62.2°; 4.9 min retention time; ir (film) 1399, 1370, 1240, 1230 (*tert*-butyl), and 1085 cm^{-1} (C–O–C); ^{1}H NMR (CCl_4) δ 3.62 (m, 1 H), 3.10 (m, 1 H), 1.9 (m, 4 H), 1.67–0.9 (m, 14 H), and 0.87 (s, 18 H); mass spectrum *m/e* (rel intensity) 295 (0.025, P + 1), 294 (0.09, parent ion), 156 (0.83), 139 (5.5), 123 (6.0), 99 (11.5), 83 (28.5), 57 (100).

Anal. Calcd for $C_{20}H_{38}O$: C, 81.56; H, 13.00. Found: C, 81.77; H, 13.00.

***trans,trans*-4-*tert*-Butylcyclohexyl ether** was a white solid: mp 85.2–86.0°; 7.4 min retention time; ir (KBr) 1395, 1370, 1240, 1225 (*tert*-butyl) and 1090 cm^{-1} (C–O–C); ^{1}H NMR (CCl_4) δ 3.55 (m, 2 H), 1.83 (m, 8 H), 1.6–0.9 (m, 10 H), and 0.85 (s, 18 H); mass spectrum *m/e* (rel intensity) 295 (0.01, P + 1), 294 (0.048, parent ion), 156 (0.42), 139 (4.7), 123 (6.2), 99 (9.5), 83 (35), 57 (100).

Anal. Calcd for $C_{20}H_{38}O$: C, 81.56; H, 13.00. Found: C, 81.43; H, 12.96.

4-*tert*-Butylcyclohexyl Trifluoroacetate. To 7.80 g (50.0 mmol) of 4-*tert*-butylcyclohexanol (mixture of isomers) was added 11.40 g (100.0 mmol) of trifluoroacetic acid. The homogeneous reaction solution was allowed to remain at room temperature for 24 hr and was then quenched with an excess of a saturated sodium bicarbonate solution. The organic materials were extracted twice with 25-ml portions of ether. The combined ether extract was dried over anhydrous magnesium sulfate, and the ether was removed under reduced pressure after filtering the magnesium sulfate. Vacuum distillation gave 7.10 g (28.0 mmol, 56% yield) of 4-*tert*-butylcyclohexyl trifluoroacetate (36% cis and 64% trans by GLC analysis): bp 97–102 (18 Torr); ir (film) 1785 cm^{-1} (C=O); ^{1}H NMR (CCl_4) δ 5.24 and 4.83 (m, 1 H), 2.35–1.0 (m, 9 H), and 0.90 (s, 9 H). Trifluoroacetate esters of other alkyl-substituted cyclohexanols were prepared by a similar procedure.

General Reduction Procedure in Aqueous Sulfuric Acid–Ethyl Ether. The reduction of 4-*tert*-butylcyclohexanone by triethylsilane illustrates the general reduction procedure. To a rapidly stirred solution of 0.78 g (5.0 mmol) of 4-*tert*-butylcyclohexanone and 0.70 g (6.0 mmol) of triethylsilane in 0.6 ml of ether was added 0.5 g of aqueous H_2SO_4 (prepared by adding 0.5 mol of 96% sulfuric acid to 1.0 mol of H_2O) at room temperature. The exothermic, initially heterogeneous reaction mixture became homogenous after several minutes. The reaction solution was quenched with 25 ml of a saturated sodium bicarbonate solution 15 min after the addition of aqueous sulfuric acid and was extracted three times with 16-ml portions of ether. The combined ether extract was dried over and filtered from anhydrous magnesium sulfate, and the magnesium sulfate filter cake was rinsed several times with small portions of ether. The combined ether washes and extract was concentrated under reduced pressure. GLC analysis of the product mixture indicated the presence of unreacted triethylsilane, triethylsilanol, and a 90% recovered yield of 4-*tert*-butylcyclohexanol (32% cis, 68% trans); no other compounds were evident.

The optimum acid concentration used in these reductions was selected as 3.5 mmol of sulfuric acid (0.50 g of 73 g % aqueous H_2SO_4) per 5.0 mmol of I, when 0.6 ml of ethyl ether was used, based on reaction times for the reduction of 4-*tert*-butylcyclohexanone by triethylsilane. When 1.75 mmol of sulfuric acid was used, complete reduction was observed only after 20 hr at room temperature. With 3.5 mmol of sulfuric acid reduction was complete within 1 hr; and when 5.25 mmol of sulfuric acid was employed, less than 15 min reaction times were required. No change in the ratio of *cis*- to *trans*-4-*tert*-butylcyclohexanol was observed over the period of time required for each of these reductions.

General Reduction Procedure in Trifluoroacetic Acid. The reduction of 3,3,5-trimethylcyclohexanone with tri-*sec*-butylsilane illustrates the general reduction procedure. To a stirred solution of 0.70 g (5.0 mmol) of 3,3,5-trimethylcyclohexanone and 1.10 g (5.5 mmol) of tri-*sec*-butylsilane was added 2.5 ml (34 mmol) of trifluoroacetic acid at room temperature. The mildly exothermic, initially heterogeneous reaction mixture became homogeneous within 5 min. Reduction was complete in 2 hr by ^{1}H NMR analysis. Analysis by ^{1}H NMR spectroscopy indicated 98% 3,3,5-trimethylcyclohexyl trifluoroacetate (only the trans isomer was observed) and 2% ether products.[33] Excess 3 *N* sodium hydroxide was added to the reaction solution and the mixture was rapidly stirred for 12 hr. The organic materials were extracted three times with 15-ml portions of ether. The combined ether extract was dried over and filtered from anhydrous magnesium sulfate, and the magnesium sulfate filter cake was rinsed several times with small portions of ether. The combined ether washes and extract was concentrated under reduced pressure. Analysis by GLC gave a 90% recovered yield of 3,3,5-trimethylcyclohexanol (4% cis, 96% trans). An alternate procedure, adding the silane to a stirred solution of ketone and trifluoroacetic acid, gave identical results.

Product Analyses. Reaction solutions from reductions in triflu-

oroacetic acid were analyzed by ^{1}H NMR spectroscopy prior to quenching. Reaction products were identified from the chemical shifts and characteristic splittings of absorptions in the δ 3–6 spectral region (Table VII). Structural assignments were verified by GLC analysis followed by GLC collection and identification of products in those cases where particular standards were not available.

Product yields were determined by GLC analyses for the vast majority of reactions reported in this study. Isomeric alcohols from 2-, 3-, and 4-methylcyclohexanone reductions were separated and analyzed on 5-ft, 25% glycerol columns at 100°. Isomeric alcohols from 4-*tert*-butylcyclohexanone reductions were separated and analyzed on a 5-ft 20% Carbowax 20M column programmed from 135 to 180° at 4°/min. Isomeric alcohols from 3,3,5-trimethylcyclohexanone reductions were separated and analyzed on a 10-ft 20% Carbowax 20M column at 180°. In each separation the axial isomer eluted first, as determined by the agreement between ^{1}H NMR and GLC analyses and by ^{1}H NMR analyses of the separate isomers of 4-methylcyclohexanol and 2-methylcyclohexanol from GLC collections. The individual thermal conductivities of alcohol, symmetrical ether, and trifluoroacetate products were determined and used to obtain absolute yields. The thermal conductivities of the geometrical isomers of each alcohol were assumed to be identical;[34] those of symmetrical ether and trifluoroacetate geometrical isomers were identical within experimental error. GLC results were reproducible within ±1% on duplicate runs.

Yields of olefinic products were determined by ^{1}H NMR spectroscopy through comparison with the known absolute yields of alcohol products. For many reactions product yields were determined both by GLC analysis and by ^{1}H NMR spectroscopy. Yields from ^{1}H NMR spectral analyses were calculated from averaged integrations of proton absorptions by comparison to an internal standard. Excellent agreement between ^{1}H NMR and GLC yields was observed; for example, compared to the results from GLC analyses, the relative percent of alcohol isomers from ^{1}H NMR analyses agreed within 2% for 2-methyl- and 4-*tert*-butylcyclohexanone reductions.

Control experiments and specific product analyses are included as supplementary material.[35]

Reduction of 4-*tert*-Butylcyclohexanone by Di-*tert*-butylsilane. Silane Products. Di-*tert*-butylsilane (3.0 mmol) and 4-*tert*-butylcyclohexanone (2.5 mmol) were added to 17.5 mmol of trifluoroacetic acid, and the reaction mixture was kept at room temperature for 91 hr. A product identified as di-*tert*-butylsilyl trifluoroacetate by ^{1}H NMR analysis of the reaction mixture (Si-H, s, δ 4.63) was observed in low yield (3.5% of reacted silane). Di-*tert*-butylsilanediol was isolated in 91% yield from the reaction mixture after quenching with aqueous sodium bicarbonate and extraction with ether as a white, crystalline solid, mp 151.5–152.0° (lit.[36] mp 152°).

Acknowledgment. Support of this work by the Research Corporation is gratefully acknowledged. We wish to thank Nancy Ball, Stephen Donnelly, and Abayomi Odubela for their contributions to this study.

Registry No.—Ia, 98-53-3; Ib, 589-92-4; Ic, 591-24-2; Id, 583-60-8; Ie, 873-94-9; IIa, 21862-63-5; IIc, 7443-55-2; IIe, 767-54-4; IIIa, 937-05-3; IIIb, 7731-28-4; IIId, 7443-70-1; IVa, 7600-15-9; IVb, 31003-54-0; IVc, 31003-46-0; IVd, 31003-41-5; IVe, 56889-89-5; Va, 7556-86-7; Vb, 31003-53-9; Vc, 31123-86-1; Vd, 31003-40-4; Ve, 56889-88-4; *trans*-IIa, 56889-93-1; *cis*-VIa, 56889-94-2; trifluoroacetic acid, 76-05-1; *cis,cis*-3,3,5-trimethylcyclohexyl ether, 56889-96-4; *cis,trans*-3,3,5-trimethylcyclohexyl ether, 56942-35-9; *trans,trans*-3,3,5-trimethylcyclohexyl ether 56942-36-0; 2-methylcyclohexyl ether, 56889-97-5.

Supplementary Material Available. Control experiments for reactions performed in aqueous sulfuric acid–ethyl ether and specific product analyses for reductions in trifluoroacetic acid will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3821.

References and Notes

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(10) However, cyclohexene and 4-*tert*-butylcyclohexene do undergo addition of trifluoroacetic acid under the reaction conditions usually employed for organosilane reductions (5–7 equiv of CF_3COOH); after 22 hr at room temperature cyclobexene produced cyclohexyl trifluoroacetate in 80% yield and 4-*tert*-butylcyclohexene gave 3- and 4-*tert*-butylcyclohexyl trifluoroacetates in 89% yield. The unreacted cycloalkenes accounted for the remainder of the material in each case. The production of these trifluoroacetates indicates that similar addition reactions of trifluoroacetic acid with alkylcyclohexenes can occur.

(11) Although no cycloalkene products were observed from the reduction of 3,3,5-trimethylcyclohexanone by either di-*tert*-butylsilane or tri-*sec*-butylsilane, elimination products would be expected by analogy to the corresponding reductions of 3-methylcyclohexanone. Because of the longer reaction times required for reductions of le, addition of trifluoroacetic acid to 3,3,5-trimethylcyclohexene may have occurred undetected to give a mixture of *cis*- and *trans*-3,3,5-trimethylcyclohexyl trifluoroacetates, the expected addition products.

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none was reduced by triethylsilane in the presence of a 6 molar equiv excess of 4-*tert*-butylcyclohexanol (26% cis, 75% trans) under reaction conditions similar to those reported in Table VI. Analysis of the reaction products after complete reduction (IIa, 73%, IIIa, 27%) showed that, within experimental error, no discrimination between IIa and IIIa had occurred in the formation of *cis*-VIa and *trans*-VIa. The observed relative yields of ether products, 24% *trans,trans*-, 52% *cis,trans*-, and 24% *cis,cis*-4-*tert*-butylcyclohexyl ethers, could be predicted within experimental error from the data for triethylsilane (6.7 equiv CF_3COOH reaction) in Table VI.

(29) The reduction of 3,3,5-trimethylcyclohexanone by triethylsilane provides the only exception to these generalizations. The symmetrical ethers, 67% *trans,trans*-, 23% *cis,trans*-, and 10% *cis,cis*-3,3,5-trimethylcyclohexyl ethers, constituted 16% of the reduction products. Using the observed isomeric ratio, IIIe/IIe = 6.2, the relative rates for hydride transfer were k_{tt}/k_{tc} = 3.5 and k_{ct}/k_{cc} = 0.40, significantly less than the ratio of IIIe to IIe.

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Silane Reductions in Acidic Media. V. Reductions of Alkyl-Substituted Cyclohexanones by Di- and Tri-*tert*-butylsilanes. Steric Hindrance to Nucleophilic Attack at Silicon in the Trifluoroacetolysis of Silyl Alkyl Ethers[1a,b]

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Results are reported for the reductions of alkyl-substituted cyclohexanones by di-*tert*-butylsilane, di-*tert*-butylmethylsilane, and tri-*tert*-butylsilane in trifluoroacetic acid. The reactivities of di- and tri-*tert*-butylsilanes reflect the steric bulk of the *tert*-butyl groups. However, the inductive effect of alkyl substituents is pronounced; tri-*tert*-butylsilane reacts faster than di-*tert*-butylsilane in reductions of cyclohexanones. The thermodynamically less stable isomers are formed predominantly in *tert*-butylsilane reductions of cyclic ketones with remote substituents. However, silyl alkyl ethers formed in these reductions undergo trans elimination of silanol in competition with nucleophilic displacement at silicon. The relative rate for elimination increases with the increased steric bulk of alkyl groups bonded to silicon.

The reactivities of organosilicon compounds are strongly influenced by the steric bulk of *tert*-butyl substituents.[2-4] The *tert*-butyl group shields silicon from nucleophilic reagents that normally attack silicon.[4a] This steric effect should also be evident in the relative rates for reduction of ketones by *tert*-butylsilanes and in the stereoselectivities of these reductions. Indeed, in reductions of alkyl-substituted cyclohexanones di-*tert*-butylsilane is observed to be approximately 100 times less reactive than tri-*sec*-butylsilane.[1a]

Silyl alkyl ethers have been observed previously in organosilane reductions of carbonyl compounds when limited amounts of Bronsted acids are employed, and are presumed intermediates in these reactions.[5] Such compounds, which have proven to be highly useful in protecting the alcohol functional group in synthetic transformations,[6] are quantitatively solvolyzed in acidic media to alcohols. Alkoxy-*tert*-butyldimethylsilanes,[6c] although significantly more stable toward solvolysis, also react quantitatively with nucleophilic reagents to form alcohols. Nucleophilic attack at silicon in silyl alkyl ethers occurs in preference to attack at carbon. However, when silicon is shielded by more than one bulky *tert*-butyl group the rate of nucleophilic substitution at silicon may be sufficiently low so as to allow alternate pathways to become dominant.

In this paper we wish to report that highly hindered di- and tri-*tert*-butylsilanes do undergo selective hydride transfer reactions with alkyl-substituted cyclohexanones but that these reactions are complex owing to reactions caused by the shielding of silicon by *tert*-butyl groups. A novel elimination reaction of di- and tri-*tert*-butylsilyl alkyl ethers occurs in these reactions in competition with nucleophilic substitution at silicon.

Results

Di-*tert*-butylmethylsilane. The reactions of alkyl-substituted cyclohexanones with di-*tert*-butylmethylsilane are significantly and unexpectedly faster than those with di-*tert*-butylsilane. Using 6.6 equiv of trifluoroacetic acid, reductions of 4-*tert*-butyl, 4-methyl-, 2-methyl-, and even 3,3,5-trimethylcyclohexanone are complete within 20 hr at room temperature. Di-*tert*-butylmethylsilane is 20 to 40 times more reactive than di-*tert*-butylsilane in these reactions.

In Table I product yields from reductions of alkyl-substituted cyclohexanones by di-*tert*-butylmethylsilane are presented and compared to those from reductions by di-*tert*-butylsilane under the same reaction conditions. Only cycloalkene and cyclohexyl trifluoroacetate products are observed at 20 hr in reductions of alkylcyclohexanones by di-*tert*-butylmethylsilane when 6.6 equiv of trifluoroacetic acid is used. Cycloalkene formation is significant when di-*tert*-butylmethylsilane is employed under these reaction conditions and occurs to a greater extent than in reductions by di-*tert*-butylsilane. The relatively high yield of olefinic products in these reactions is surprising since under the same reaction conditions elimination processes are minimal (<1%) when less bulky silane reducing agents are used.[1a]

To determine the source of elimination processes in ketone reductions, lower acid concentrations were employed in order to decrease the rate of reduction and of solvolysis of the presumed silyl ether intermediates. Prior determinations had shown that alcohol, alkyl ether, and trifluoroacetate reaction products could not be the source of the alkenes formed in reductions by *tert*-butylsilanes. 4-*tert*-Butylcyclohexanone was treated with di-*tert*-butylmeth-

Table I
Di-*tert*-butylmethylsilane and Di-*tert*-butylsilane Reductions of Alkylcyclohexanones

Registry no.	Alkycyclohexanone	% yield from $(t\text{-Bu})_2MeSiH$[a, b]			% yield from $(t\text{-Bu})_2SiH_2$[b, c]		
		% cyclo-alkene[d]	% trifluoro-acetate	Rel % *cis*-trifluoro-acetate	% cyclo-alkene[d]	% trifluoro-acetate	Rel % *cis*-trifluoro-acetate
98-53-3	4-*tert*-Butyl-	13[g]	87	67	3	97	68
589-92-4	4-Methyl-	5	95	65	3	97	67
583-60-8	2-Methyl-	60[e, h]	40	35	30[f]	70	66
873-94-9	3,3,5-Trimethyl-	40[i]	60	<1	0	100	11

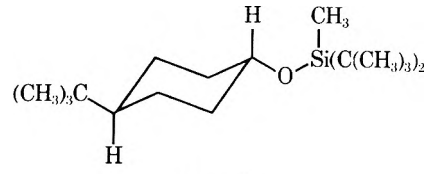
[a] Reductions were run at room temperature with 1.5 mmol of ketone, 1.5 mmol of silane, and 9.9 mmol of trifluoroacetic acid. Reaction times were 20 hr. Reduction of 4-*tert*-butylcyclohexanone was complete within 2 hr at room temperature. [b] No reaction products other than alkenes and trifluoroacetates were observed. [c] Reaction times for complete reduction varied from 72 hr (4-methylcyclohexanone) to more than 300 hr (2-methyl- and 3,3,5-trimethylcyclohexanone). [d] Absolute yield. [e] Sum of methylcyclohexane and 1-methylcyclohexyl trifluoroacetate. [f] Analyzed as methylcyclohexane; no 1-methylcyclohexyl trifluoroacetate was observed. [g] Registry no., 2228-98-0. [h] Registry no., 591-49-1. [i] Registry no., 503-45-7.

Table II
Di-*tert*-butylmethylsilane Reduction of 4-*tert*-Butylcyclohexanone[a]

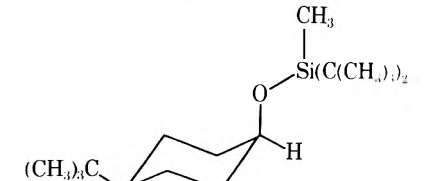
Time, hr	Relative yield, %[b]					
	cis-I (56889-82-8)	*trans*-I (56889-83-9)	*cis*-II + *cis*-IV	*trans*-II + *trans*-IV	III	Σ *cis*-I, II, IV, + III
0.6	70	27	1.8	0.5	0.7	72.5
21	41	18	27	7	6	74
46	28	10	38	16	8	74
96	27	8	39	20	8	73

[a] Reduction was run at room temperature with 3.0 mmol of 4-*tert*-butylcyclohexanone, 3.5 mmol of di-*tert*-butylmethylsilane, and 9.0 mmol of trifluoroacetic acid and was complete within 3 hr. [b] Product yields based on GLC analyses and consistent with those obtained by ^1H NMR analyses at 15, 105, and 270 min and at 96 hr. Corrections have been made for the amounts of addition products from trifluoroacetolysis of III; at 96 hr the yield of 3-*tert*-butylcyclohexyl trifluoroacetates was 3%.

ylsilane at room temperature in the presence of 1.0, 1.5, and 3.0 equiv of trifluoroacetic acid, and these reactions were followed with time. The isomeric 4-*tert*-butylcyclohexyl di-*tert*-butylmethylsilyl ethers (I) and 4-*tert*-butyl-



trans-I



cis-I

cyclohexanols (II) were observed in addition to 4-*tert*-butylcyclohexene (III) and the isomeric 4-*tert*-butylcyclohexyl trifluoroacetates (IV). Typical results are given in Table II for the reduction in which 3.0 equiv of trifluoroacetic acid was used. The silyl ethers, *cis*- and *trans*-I, are, by far, the predominant reduction products from these reactions; subsequent transformations of the silyl ethers yield the trifluoroacetate and alkene products observed in organosilane reductions of ketones in trifluoroacetic acid media (Table I).

The stereoselectivity in the reduction of 4-*tert*-butylcyclohexanone by di-*tert*-butylmethylsilane should be constant with time.[7] However, from Table II the observed sum of cis products (*cis*-I + *cis*-II + *cis*-IV) decreases with increasing time, but the sum of the relative yields of *cis*-I, *cis*-II, III, and *cis*-IV is constant within experimental error throughout the 96-hr period during which the reaction products were analyzed. These results, which were confirmed by similar comparisons for reductions run with 1.0 equiv of trifluoroacetic acid, indicate that 4-*tert*-butylcyclohexene is formed specifically from *cis*-I.

Table III
Stereoselectivities in Cyclohexanone Reductions by Di-*tert*-butylsilane and Di-*tert*-butylmethylsilane in Trifluoroacetic Acid[a]

Alkylcyclohexanone	% less stable isomer[b]	
	$(t\text{-Bu})_2MeSiH$	$(t\text{-Bu})_2SiH_2$
4-*tert*-Butyl	72	69
4-Methyl-	67	68
2-Methyl-	74	76
3,3,5-Trimethyl-	>99	89[c]

[a] Calculated by assuming that olefin products result solely from diaxial elimination of silyl cyclohexyl ethers. [b] From the data in Table I. [c] Although alkene products were not observed in this reaction, olefin formation with subsequent addition of trifluoroacetic acid may have occurred during the long reaction time required for complete reduction. Such a process might explain the unexpectedly low selectivity in this reduction.

The yield of 4-*tert*-butylcyclohexene was sensitive to both the concentration of acid, ranging from 13% (6.6 equiv of CF_3CO_2H) to 6% (1.0 equiv of CF_3CO_2H), and to the reaction temperature, 11% at 25° and 4% at −40° (3.0 equiv of CF_3CO_2H). However, the stereoselectivity in forming *cis*-4-*tert*-butylcyclohexyl products, calculated by assuming that 4-*tert*-butylcyclohexene is formed solely from *cis*-I, did not change over the range of reaction conditions employed and averaged 72 ± 1%. Similar calculations permit an estimate of the stereoselectivities in reductions of other

Table IV
Trifluoroacetolysis of 4-*tert*-Butylcyclohexene

CF_3CO_2H/4-*tert*-butylcyclohexene	Temp, °C	Yield, %[a] *trans*-V (31003-52-8)	*cis*-V (31003-51-7)	*cis*-IV (7556-86-7)	*trans*-IV (7600-15-9)	*trans*-V/*cis*-V	*cis*-IV/*trans*-IV	IV/V
20	25[b]	53	9	30	8	5.9	3.7	0.61
4.0	25[c]	50	9	31	10	5.6	3.1	0.70
2.0	80[b]	45	15	28	12	3.0	2.3	0.67

[a] Relative product yields based on ^{1}H NMR and GLC analyses. No products other than those reported were observed in significant yields. [b] Analyzed after 24 hr; 11% olefin remained unreacted. [c] Analyzed after 120-hr reaction time; 18% cycloalkene was unreacted.

Table V
Reduction of 4-*tert*-Butylcyclohexanone by Tri-*tert*-butylsilane[a,f]

Time, hr	% reduction[b]	Relative yield, %[c] VI	II[d]	III	*cis*-IV	*trans*-IV[e]	*trans*-V	*cis*-V[e]
21	50	64	9	5.5	10	8.0	3.0	0.5
27	53	57	10	7.4	12	9.3	3.7	0.6
93	85	51		22	13	9.0	4.2	0.8
264	94	20		50	13	9.3	6.5	1.2
720	97	10		38	21	10	18	3.0

[a] Reduction was run at room temperature with 2.5 mmol of 4-*tert*-butylcyclohexanone, 3.0 mmol of tri-*tert*-butylsilane, and 7.5 mmol of trifluoroacetic acid. [b] Based on tri-*tert*-butylsilane. [c] Product yields based on ^{1}H NMR analyses. GLC analyses of the quenched reaction solutions gave results which agreed substantially with the ^{1}H NMR data. Yields obtained at 145, 436, and 693 hr reaction time were in agreement with trends observed at reaction times reported here. [d] Only *cis*-II was observed. The relative yield of *trans*-II was not determined. [e] ^{1}H NMR analysis was used to give the sum of *trans*-IV and *cis*-V. The yields of the individual products were calculated using the *trans*-V/*cis*-V ratio in Table IV. [f] Registry no., 18159-55-2.

alkyl-substituted cyclohexanones. These calculations are given for both di-*tert*-butylsilane and di-*tert*-butylmethylsilane in Table III.

In the reduction of 2-methylcyclohexanone by di-*tert*-butylmethylsilane the elimination process from the cis alkyl silyl ether yielding 1-methylcyclohexene is dominant (60%); subsequent trifluoroacetolysis and ionic hydrogenation[8] of the 1-methylcyclohexene gives 1-methylcyclohexyl trifluoroacetate (23%) and methylcyclohexane (37%), respectively.[9] Neither 3-methylcyclohexene nor the 3-methylcyclohexyl trifluoroacetates were detected. Di-*tert*-butylmethylsilanol, di-*tert*-butylmethylsilyl trifluoroacetate, and the 2-methylcyclohexyl di-*tert*-butylmethylsilyl ethers are the only silane products.

Trifluoroacetolysis of 4-*tert*-Butylcyclohexene. Since olefin production is significant in reductions of 4-*tert*-butylcyclohexanone by *tert*-butylsilanes in trifluoroacetic acid, the selectivities of the addition of trifluoroacetic acid to 4-*tert*-butylcyclohexene were investigated. No previous study of the trifluoroacetolysis of alkylcyclohexenes has been reported; and, consequently, the stereoselectivities of trifluoroacetate products observed in silane reductions could be thought to reflect the stereoselectivities of the products from trifluoroacetolysis of alkyl-substituted cyclohexenes.

Trifluoroacetolysis of 4-*tert*-butylcyclohexene produces the geometrical isomers of both 3-*tert*-butylcyclohexyl trifluoroacetate (V) and the 4-*tert*-butylcyclohexyl trifluoroacetate (IV). The yields of these products under conditions comparable to those used in reductions of 4-*tert*-butylcyclohexanone are given in Table IV. Addition preferentially occurs to give V, and axial-trifluoroacetate products are favored over equatorial-substituted trifluoroacetates. The ratio of the yields of IV to V are not affected within experimental limits either by changes in the concentration of trifluoroacetic acid or by changes in temperature. The cis to trans ratio of V and IV, however, does reflect changes in temperature but not changes in trifluoroacetic acid concentration.

The low yield of 3-*tert*-butylcyclohexyl trifluoroacetate products in reductions of 4-*tert*-butylcyclohexanone by either di-*tert*-butylsilane or di-*tert*-butylmethylsilane under reaction conditions reported earlier indicates that trifluoroacetic acid addition to 4-*tert*-butylcyclohexene is not an important process in 4-*tert*-butylcyclohexyl trifluoroacetate production. This is further substantiated by the results from the reduction of 4-*tert*-butylcyclohexanone by di-*tert*-butylmethylsilane using 3 equiv of trifluoroacetic acid; the yield of 3-*tert*-butylcyclohexyl trifluoroacetate, after a reaction time of 96 hr, is only 3% (Table II).

Tri-*tert*-butylsilane. Among the *tert*-butylsilanes silicon is shielded to the greatest extent in tri-*tert*-butylsilane.[4a] Yet nearly complete reduction of 4-*tert*-butylcyclohexanone (>95%) by this highly hindered silane occurs within 95 hr at room temperature when 4 equiv of trifluoroacetic acid is employed. The rate of hydride transfer from tri-*tert*-butylsilane is greater than that from di-*tert*-butylsilane. The reaction products, however, are composed almost solely of 4-*tert*-butylcyclohexene (31%) and the 3- and 4-*tert*-butylcyclohexyl trifluoroacetates (64%), indicating that the elimination process, observed as a competing reaction in reductions by the di-*tert*-butylsilanes, is the dominant reaction in reductions by tri-*tert*-butylsilane.

The yields of products from the reduction of 4-*tert*-butylcyclohexanone by tri-*tert*-butylsilane using 3 equiv of trifluoroacetic acid were obtained by ^{1}H NMR and GLC analyses of the reaction mixture at various times and are reported in Table V. Relatively low yields of 4-*tert*-butylcyclohexanol (~5%) were observed at reaction times of less than 30 hr (~50% reduction); at longer reaction times this alcohol could not be detected. The isomeric 4-*tert*-butylcyclohexyl tri-*tert*-butylsilyl ethers (VI) were predominant initially (<100 hr) but were slowly converted to 4-*tert*-butylcyclohexene and to trifluoroacetate products. The rel-

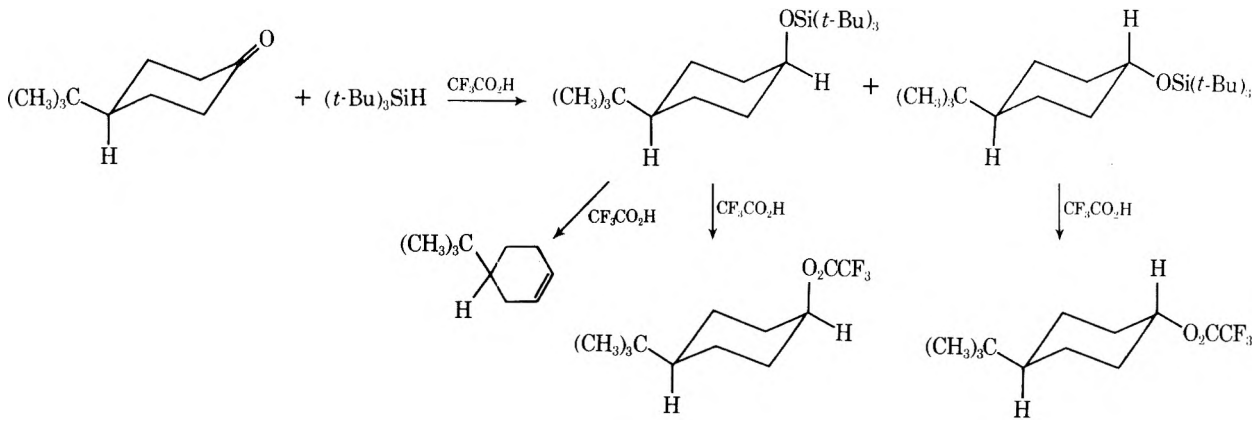
ative yields of *cis*-VI at 21, 93, 168, and 720 hr were 96, 95, 94, and 73%, respectively, indicating that the rate of solvolysis of *cis*-VI is comparable to that of *trans*-VI.

Trifluoroacetolysis of 4-*tert*-butylcyclohexene accounts for the production of 3-*tert*-butylcyclohexyl trifluoroacetate (V) and for a fraction of the 4-*tert*-butylcyclohexyl trifluoroacetate (IV) obtained in the reduction process. Using the product ratios from Table IV for IV/V and for *cis*-IV/*trans*-IV the relative yields of the isomeric 4-*tert*-butylcyclohexyl trifluoroacetates resulting from trifluoroacetolysis of 4-*tert*-butylcyclohexene can be calculated and substracted from the observed values given in Table V. Using this method the relative yields of *cis*-IV (9.2 ± 1.7%) and *trans*-IV (7.6 ± 1.5%) are found to be relatively constant over the 720 hr reaction period; no trend is detectable. The yield of *trans*-IV is identical, within experimental error, with that of *trans*-VI (4–6%), indicating that under the reaction conditions employed *trans*-VI is converted solely to *trans*-IV and does not undergo elimination to 4-*tert*-butylcyclohexene. Similar results were obtained when 4-*tert*-butylcyclohexanone was treated with tri-*tert*-butylsilane at room temperature using 4.0 and 2.0 equiv of trifluoroacetic acid and at 80° using 2.0 equiv of trifluoroacetic acid.

Tri-*tert*-butylsilane reductions were run at −30° in an attempt to minimize olefin formation. Using 4 equiv of trifluoroacetic acid the silane reduction of 4-*tert*-butylcyclohexanone gave after 2 months reaction time 71% VI (97% cis), 23% IV (65% cis), and 6% III. The sum of the yields of *cis*-VI and those products resulting from *cis*-VI, *cis*-IV, and III was 90%. Similarly, the tri-*tert*-butylsilane reduction of 4-methylcyclohexanone under comparable conditions gave 78% 4-methylcyclohexyl tri-*tert*-butylsilyl ether (93% cis), 20% 4-methylcyclohexyl trifluoroacetate (65% cis), and 2% 4-methylcyclohexene (2 months reaction time). The sum of the yields of *cis*-VII and those products resulting from *cis*-VII, *cis*-4-methylcyclohexyl trifluoroacetate and 4-methylcyclohexene, was 88%. The major silicon product from these reductions was tri-*tert*-butylsilanol.

Attempts to displace the tri-*tert*-butylsilyl group from VI without elimination by alternative procedures were unsuccessful. The method successfully employed to remove the *tert*-butyldimethylsilyl protecting group did not affect VI even when significantly longer reaction times were used. Similarly, lithium aluminum hydride failed to reduce the tri-*tert*-butylsilyl ether even after heating at 55° for 4 days.

Scheme I



Discussion

Organosilane Reductions. The reactivities of di- and tri-*tert*-butylsilanes in ketone reductions reflect both the steric bulk of the *tert*-butyl group and the inductive effect of alkyl substituents. Qualitatively, the rates of cyclohexanone reductions by tri-*sec*-butylsilane are faster than those by di-*tert*-butylmethylsilane, which are greater than those by tri-*tert*-butylsilane. The rates for reductions by di-*tert*-butylsilane, however, are slower than those for similar reductions by tri-*tert*-butylsilane; *an increase in the number of alkyl substituents dramatically increases the reactivity of alkylsilanes in reduction processes.* An estimate of the relative reactivities of hindered organosilanes (given in parentheses) can be made through a comparison of reaction times for reduction: *sec*-Bu_3SiH (100), *t*-Bu_2MeSiH (30), *t*-Bu_3SiH (3), *t*-Bu_3SiH_2 (1).[10]

Reductions of alkyl-substituted cyclohexanones by di- and tri-*tert*-butylsilanes yield predominantly the less stable cyclohexyl derivative, either the cyclohexyl trifluoroacetate or silyl ether. The selectivity for the less stable isomer increases in the order *sec*-Bu_3SiH < $(t\text{-Bu})_2SiH_2$, $(t\text{-Bu})_2MeSiH$ < $(t\text{-Bu})_3SiH$. Indeed, the stereoselectivity for hydride transfer in tri-*tert*-butylsilane reductions of 4-*tert*-butylcyclohexanone (90% cis products) and 4-methylcyclohexanone (88% cis products) is similar to that achieved by either lithium tri-*sec*-butylborohydride[11] or lithium dimesitylborohydride bis(dimethoxyethane).[12] The usefulness of tri-*tert*-butylsilane in ketone reductions, however, is severely limited by the same factor which provides the exceptionally high degree of stereoselectivity in hydride transfer. The bulky *tert*-butyl groups not only provide steric hindrance to hydride transfer from the axial direction in cyclohexanone reductions but, also, effectively shield silicon from nucleophilic attack.

The dominant reaction pathway for silyl ethers produced in the reduction of 4-*tert*-butylcyclohexanone by tri-*tert*-butylsilane at or above room temperature is elimination. In this process elimination of the elements of tri-*tert*-butylsilanol occurs in acidic media only from *cis*-VI (Scheme I). Reductions by di-*tert*-butylmethylsilane and, to a lesser extent, di-*tert*-butylsilane also occur with elimination competing with substitution at silicon.[13] The relative importance of the elimination reaction increases with an increase in the steric bulk about silicon. The relative rates for substitution at silicon (k_s) compared to those for elimination (k_e) can be determined from the ratios of *cis*-trifluoroacetate to alkene and are estimates for the shielding of silicon by *tert*-butyl groups. In reductions of 4-*tert*-butylcyclohexanone the ratios, k_s/k_e, from *cis*-4-*tert*-butylcyclohexyl silyl ethers are observed to be 22 for $(t\text{-Bu})_2SiH_2$, 4.5 for $(t\text{-Bu})_2MeSiH$, and 0.11 for $(t\text{-Bu})_3SiH$. For reductions of 2-methylcyclohexanone similar calculations of k_s/k_e for $(t\text{-Bu})_2SiH_2$ (1.5) and $(t\text{-Bu})_2MeSiH$ (0.23) show qualitative agreement with those from reductions of 4-*tert*-butylcyclo-

hexanone. Nucleophilic substitution is, therefore, highly sensitive to the steric environment about silicon, more so than are the rates for ketone reductions.

The observation of exclusive elimination from cis alkyl silyl ethers formed in silane reductions of 4-*tert*-butylcyclohexanone is consistent with a trans-elimination mechanism and implies that, if the chair cyclohexane conformer is assumed, the 4-*tert*-butyl group is conformationally larger than the $-OSiR_3$ substituent. In agreement with this prediction, the ^1H NMR spectrum of the isomeric mixture of 4-*tert*-butylcyclohexyl di-*tert*-butylmethylsilyl ethers (I) exhibits two proton absorptions for the $-Si(t\text{-}Bu)_2-$ groups with intensities expected from the relative amounts of axial- and equatorial-substituted isomers; only one signal for the 4-*tert*-butyl group is observed. The chemical shifts of the methine hydrogens (CHOSi) of I are δ 4.08 (*cis*-I) and 3.64 (*trans*-I), respectively, substantially the same as those from the isomeric 4-*tert*-butylcyclohexyl triethylsilyl ethers, δ 4.00 (cis isomer) and 3.57 (trans isomer). In contrast, the corresponding methine hydrogen of *cis*-VI absorbs at δ 4.37 and those of VII absorb at δ 4.33 (*cis*-VII) and 3.77 (*trans*-VII). The downfield shift for the methine hydrogen of tri-*tert*-butylsilyl ethers of alkylcyclohexanols can be explained by a long-range deshielding effect by the conformationally restricted tri-*tert*-butylsilyl group. Similar effects have been noted in other molecular systems.[14,15] However, molecular models of either VI or VII do not provide a clear distinction between the chair cyclohexane conformation and alternate conformations, and the observed chemical shift difference between VI or VII and I may be due to a change in ring conformation.

Trifluoroacetolysis of 4-*tert*-Butylcyclohexene. Although addition reactions have received considerable attention in the literature, there have been few studies of the stereochemical outcome of addition reactions and none of the addition of carboxylic acids to cycloalkenes. Trifluoroacetolysis of 4-*tert*-butylcyclohexene (III) produces the geometrical isomers of both 3- and 4-*tert*-butylcyclohexyl trifluoroacetates. The preference for the production of 3-*tert*-butylcyclohexyl trifluoroacetate (Table IV) indicates that the remote *tert*-butyl group plays a directive role in the addition process. The addition of diborane to III,[16] on the other hand, does not occur with a similar directive influence.

The influence of the *tert*-butyl group is also observed in the axial/equatorial trifluoroacetate ratios for IV (3.4 at 25°) and V (5.8 at 25°). Although the reason for the difference between these values is not obvious from our present results, the high axial/equatorial ratios are consistent with an ionic mechanism for addition in which the *tert*-butylcyclohexyl cations are preferentially trapped from the axial side. Similar selectivities are not observed in either the hydroboration[16] or epoxidation[18] reactions of III.

Experimental Section

General. Instrumentation has been previously described.[1a] 4-*tert*-Butylcyclohexene was synthesized from 4-*tert*-butylcyclohexyl methanesulfonate using standard procedures. The syntheses of *tert*-butylsilanes, the general reaction procedure, and product analyses are described elsewhere.[1a,4a]

Reductions of 4-*tert*-Butylcyclohexanone by Di-*tert*-butylmethylsilane. Product Analyses. Reactions were run as previously described.[1a] 4-*tert*-Butylcyclohexene and the isomeric 3- and 4-*tert*-butylcyclohexyl trifluoroacetates were identified by ^1H NMR and GLC methods. Product yields based on the integration of characteristic ^1H NMR absorptions were within 2% of those obtained by the integration of GLC peaks assigned to the same products.

For reductions using di-*tert*-butylmethylsilane, di-*tert*-butylmethylsilanol and di-*tert*-butylmethylsilyl trifluoroacetate were identified by ^1H NMR and GLC comparison with authentic samples. The GLC peaks assigned to the isomeric 4-*tert*-butylcyclohexyl di-*tert*-butylmethylsilyl ethers (I) were collected together and analyzed: viscous, colorless liquid; ^1H NMR ($CDCl_3$) δ 4.08 and 3.64 (m, 1 H, 81% *cis*-I and 19% *trans*-I, respectively), 2.13–1.17 (m, 9 H), 0.98 and 0.96 (two sharp singlets, 18 H, 80 and 20%, respectively), 0.86 (s, 9 H), and 0.3 (s, 3 H); ir (film) 2950, 2890, 1440 and 1375 (CH_3), 1390 and 1365 (*t*-Bu), 1245 and 797 ($SiCH_3$), 1110 (C–O), and 1050 cm^{-1} (Si–O–C); mass spectrum *m/e* (rel intensity) 257 (0.45) 256 (1.60), 255 (7.00), 215 (0.45), 214 (1.74), 213 (8.50), 75 (100), 57 (23).

Anal. Calcd for $C_{19}H_{40}OSi$: C, 73.00; H, 12.90; Si, 8.98. Found: C, 73.08; H, 12.83; Si, 9.02.

Reduction of 2-Methylcyclohexanone by Di-*tert*-butylmethylsilane. Product Analyses. Methylcyclohexane, 1- and 2-methylcyclohexyl trifluoroacetates, di-*tert*-butylmethylsilanol, and di-*tert*-butylmethylsilyl trifluoroacetate were analyzed by ^1H NMR and GLC comparison with authentic samples. The GLC peak assigned to the 2-methylcyclohexyl di-*tert*-butylmethylsilyl ethers was collected and analyzed: ^1H NMR (CCl_4) δ 3.33 (m, 11 H), 2.2–1.2 (m, 12 H), 1.0 and 0.97 (singlets, 18 H), and 0.04 (s, 3 H).

Addition of Trifluoroacetic Acid to 4-*tert*-Butylcyclohexene. The following illustrates the reaction procedure and method of analysis for the isomeric 3- and 4-*tert*-butylcyclohexyl trifluoroacetates. To 0.160 g (1.15 mmol) of 4-*tert*-butylcyclohexene was added 2.61 g (23.0 mmol) of trifluoroacetic acid with stirring at room temperature. The initially heterogeneous light-orange mixture became homogeneous upon continued stirring and slowly turned to a red-brown color after 24 hr. ^1H NMR analysis of the reaction mixture indicated four trifluoroacetate products: 50% *trans*-V (δ 5.57), 28% *cis*-IV (δ 5.43), and 22% of a mixture of *cis*-V and *trans*-IV (δ 5.08). The 4-*tert*-butylcyclohexyl trifluoroacetates (IV) were identified from their characteristic chemical shifts by comparison with authentic samples; the identities of the 3-*tert*-butylcyclohexyl trifluoroacetates were inferred.

The reaction mixture was quenched with 25 ml of saturated aqueous sodium bicarbonate, and the resulting mixture was extracted five times with 5-ml portions of pentane. The combined pentane extract was dried over anhydrous magnesium sulfate and filtered, the filter cake was washed several times with small portions of pentane, and the combined pentane washes and extract were concentrated under reduced pressure. GLC analysis on a 5-ft 15% SE-30 column at 130° gave peaks for the following compounds (retention times given in parentheses): unknown (3.8%, 4.1 min), III (11.2%, 4.9 min), *trans*-V (45.0%, 9.0 min), *cis*-IV (25.5%, 9.7 min), *cis*-V (7.7%, 10.4 min), and *trans*-IV (6.8%, 11.2 min). The assignments of III and *cis*- and *trans*-IV were made by retention time comparisons and peak enhancements with authentic samples. The assignments for *cis*- and *trans*-V were consistent with the observation that the less stable isomer eluted prior to the more stable equatorial isomer.[1a]

Analyses of the alcohols formed after saponification of the worked-up reaction mixture using 3 *N* aqueous sodium hydroxide confirmed the results obtained by ^1H NMR and GLC analyses of the trifluoroacetate mixture. The use of the shift reagent 2,2,6,6-tetramethyl-3,5-heptanedioneeuropium(III) [Eu(Thd)$_3$] provided a superior method for determining product yields from the complex mixture. Enough Eu(Thd)$_3$ was added to a ^1H NMR sample to completely separate *trans*-V-OH and *cis*-IV-OH CHOH absorptions (570 and 595 Hz, respectively, relative to internal Me_4Si). The *cis*-IV-OH isomer experienced a larger shift than did the *trans*-V-OH isomer; the differential shift was easily observed upon successive additions of small portions of the shift reagent to the sample. The relative proportions of *trans*-V-OH and *cis*-IV-OH were obtained by integration of the shifted absorptions: 62 and 38%, respectively (compared with 64% *trans*-V and 36% *cis*-IV by GLC analysis).

GLC analysis of the saponification mixture on a 5-ft 20% Carbowax 20M column programmed at 4°/min from 130 to 180° gave two alcohol peaks (84 and 16%, respectively) having the same retention times as *cis*-IV-OH and *trans*-IV-OH. Assuming that both axial alcohols (*cis*-IV-OH and *trans*-V-OH) have the same retention time and that both equatorial alcohols, likewise, have the same retention times, there is excellent agreement between these results and the GLC results for the trifluoroacetates (overall, 83% axial and 17% equatorial isomers).

Reduction of 4-*tert*-Butylcyclohexanone by Tri-*tert*-butylsilane. Product Analyses. To 0.38 g (2.5 mmol) of 4-*tert*-butylcyclohexanone and 0.60 g (3.0 mmol) of tri-*tert*-butylsilane was added 0.90 g (7.5 mmol) of trifluoroacetic acid at room tempera-

ture. The homogeneous light yellow reaction mixture was analyzed by ^{1}H NMR spectroscopy and GLC at various times, and the identities and yields of reaction products were determined. Products not identified by retention time comparison and peak enhancement with authentic samples were collected and analyzed.

Tri-*tert*-butylsilanol (82% yield) was identified spectroscopically: ^{1}H NMR (CCl_4) δ 1.42 (s, 1 H) and 1.12 (s, 27 H); ir (film) 3720, 3680 (weak, sharp) and 3460 cm^{-1} (broad, strong).

Tri-*tert*-butylsilyl trifluoroacetate (18% yield) was also detected: ^{1}H NMR (CCl_4) δ 1.21 (s); ir (film), 1775 cm^{-1} (C=O).

The *cis*- and *trans*-4-*tert*-butylcyclohexyl tri-*tert*-butylsilyl ethers were assigned to two peaks separable on a 5-ft 10% FFAP column. A mixture consisting of 97% of the cis isomer was collected as a white, crystaline solid: mp 91–92°; ^{1}H NMR ($CDCl_3$) δ 4.37 (m, 1 H), 2.23–1.33 (m, 9 H), 1.13 (s, 27 H), and 0.86 (s, 9 H); ir (film) 1385, 1360 and 1225 (*t*-Bu), 1110 (C–O), 1055 (SiOC), and 810 cm^{-1} (Si–C); mass spectrum *m/e* (rel intensity) 297 (M − 57, 0.40), 255 (1.5), 213 (5.3), 75 (100), 73 (14), 57 (38), 41 (22), 29 (26).

Anal. Calcd for $C_{22}H_{46}OSi$: C, 74.50; H, 13.07; Si, 7.92. Found: C, 74.20; H, 12.97; Si, 8.16.

Reduction of 4-Methylcyclohexanone by Tri-*tert*-butylsilane. Product Analyses. To 0.11 g (1.0 mmol) of 4-methylcyclohexanone and 0.30 g (1.5 mmol) of tri-*tert*-butylsilane was added 0.46 g (4.0 mmol) of trifluoroacetic acid at 0°. The homogeneous, light yellow solution was transferred to a freezer (−30°). After cooling a viscous, colorless liquid separated to the top of the reaction mixture. After 2 months ^{1}H NMR analysis indicated approximately 60% reduction. The reaction mixture was quenched with an excess of 3 *N* sodium hydroxide and worked up in the usual manner. Analysis by GLC showed one peak that could not be identified by comparison with authentic samples. The unidentified peak, which was homogeneous on Carbowax 20M, SE-30, and FFAP columns, was collected as a colorless, viscous liquid and analyzed as 4-methylcyclohexyl tri-*tert*-butylsilyl ether: ^{1}H NMR ($CDCl_3$) δ 4.33 and 3.77 (multiplets, 1 H), 2.2–1.2 (m, 9 H), 1.13 (s, 27 H), and 0.92 (broadened s, 3 H); ir (film) 1387, 1360 and 1230 (*t*-Bu), 1130 (C–O), 1055 (SiOC), and 810 cm^{-1} (Si–C); mass spectrum *m/e* (rel intensity) 257 (0.09), 256 (0.34), 255 (1.7), 215 (0.42), 214 (1.1), 213 (5.8), 173 (1.1), 172 (3.8), 171 (22), 75 (100), 73 (16), 57 (14), 55 (21), 45 (13), 41 (17), and 29 (10).

Anal. Calcd for $C_{19}H_{40}OSi$: C, 73.00; H, 12.90; Si, 8.98. Found: C, 72.87; H, 12.77; Si, 8.77.

Registry No.—*cis*-II, 937-05-3; *trans*-II, 937-06-4; *cis*-VI, 56889-86-2; *trans*-VI, 56889-87-3; $(t\text{-Bu})_2$MeSiH, 56310-20-4; $(t\text{-Bu})_2SiH_2$, 30736-07-3; *cis*-4-methylcyclohexyl trifluoroacetate, 31003-53-9; *trans*-4-methylcyclohexyl trifluoroacetate, 31003-54-0; *cis*-2-methylcyclohexyl trifluoroacetate, 31003-40-4; *trans*-2-methylcyclohexyl trifluoroacetate, 31003-41-5; *cis*-3,3,5-trimethylcyclohexyl trifluoroacetate, 56889-88-4; *trans*-3,3,5-trimethylcyclohexyl trifluoroacetate, 56889-89-5; *cis*-2-methylcyclohexyl di-*tert*-butylmethylsilyl ether, 31003-40-4; *trans*-2-methylcyclohexyl di-*tert*-butylmethylsilyl ether, 31003-41-5; tri-*tert*-butylsilanol, 56889-90-8; tri-*tert*-butylsilyl trifluoroacetate, 56889-91-9; 4-methylcyclohexyl tri-*tert*-butylsilyl ether, 56889-92-0.

References and Notes

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Silane Reductions in Acidic Media. VI. The Mechanism of Organosilane Reductions of Carbonyl Compounds. Transition State Geometries of Hydride Transfer Reactions[1a,b]

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The hydride transfer step in reductions of carbonyl compounds by hindered organosilanes yields alkyl silyl ethers in a four-center process involving the silicon hydride and the protonated carbonyl group. Rapid equilibration between silyl ether, alcohol, and silyl trifluoroacetate occurs in trifluoroacetic acid when triethylsilane is employed. Subsequent reactions of alcohol, silyl ether, and silyl trifluoroacetate products are identified. The implications of these results for the stereoselectivities of hydride transfer to substituted cyclohexanones are discussed. The sensitivity of bulky reducing agents toward 2-methyl and axial 3,5 substituents is proposed to result from differences in the transition state geometries for the hydride transfer step. The mechanism for the formation of alkyl ethers in silane reductions is also discussed.

Organosilanes are effective reducing agents for the carbonyl group of aldehydes and ketones when these reactions are performed in acidic media. The nature of the hydride transfer step has not, however, been investigated. Such information would have particular relevance to an understanding of the stereoselectivity in ketone reductions by organosilanes[2] and to potential uses of organosilanes in selective syntheses.

Two mechanisms can be considered for the hydride transfer step in carbonyl group reductions by organosilanes performed in Bronsted acids, the media usually employed for these reactions. In Scheme I (counterion mechanism)

Scheme I

$$R_2C{=}O + HA \rightleftharpoons R_2C{=}OH^+ + A^- \quad (1)$$

$$R_2C{=}OH^+ + A^- + R'_3SiH \longrightarrow R_2CHOH + R'_3SiA \quad (2)$$

nucleophilic substitution by the counterion (A^-) of the acid used to catalyze the reaction is involved in the rate-limiting hydride transfer step (eq 2). When the anion of the Bronsted acid is relatively nonnucleophilic, an additional step, involving alcohol in the displacement of hydrogen from silicon through a chain process (eq 3), may be important. Either inversion or retention of configuration at silicon may be involved by analogy to the stereochemical course of hydride transfer in comparable organosilane reactions.[4-9]

$$R_2C{=}OH^+ + R_2CH\text{-}OH + R'_3SiH \rightarrow R_2CHOH + R'_3SiOCHR_2 + H^+ \quad (3)$$

In the alternate mechanism for alcohol formation (Scheme II, four-center mechanism) nucleophilic attack by

Scheme II

$$R_2C{=}O + HA \longrightarrow R_2C{=}OH^+ + A^- \quad (1)$$

$$R_2C{=}OH^+ + R'_3SiH \longrightarrow R_2CHOSiR'_3 + H^+ \quad (4)$$

$$R_2CHOSiR'_3 + HA \longrightarrow R_2CHOH + R'_3SiA \quad (5)$$

the oxygen of the carbonyl group occurs with hydride transfer to the carbonyl carbon. Subsequent solvolysis of the silyl alkyl ether forms the alcohol product. A similar mechanism for hydride transfer has been suggested for the deoxygenation of sulfoxides by silanes,[10] and to explain the retention of configuration at silicon observed in reductions of silyl derivatives by isobutylaluminum hydride.[11]

The fundamental difference between the mechanisms for silane reductions of carbonyl compounds in Schemes I and II is the nucleophile that displaces hydride from silicon. In Scheme II the nucleophile is the oxygen of the carbonyl group; the first-formed reaction product is an alkyl silyl ether. In Scheme I the anion of the protonic acid is the nucleophile; alcohol and R_3SiA are formed in the hydride transfer step. Alternatively, from eq 3, silyl ether should be the dominant reaction product; in this case, however, if a structurally different alcohol is employed in the ketone reduction, the nucleophilic alcohol need not be identical with that produced by hydride transfer. Thus the reaction products produced directly in the hydride transfer step differentiate between the pathways for silane reduction.

In this paper we wish to report the results of our studies on the mechanism of the hydride transfer step in silane reductions of carbonyl compounds and on the subsequent fate of reaction intermediates in trifluoroacetic acid media. The implications of these results for the stereoselectivities of hydride transfer to substituted cyclohexanones are discussed.

Results

The determination of the rate-limiting step in organosilane reductions is a complex problem owing to the nature of the reaction medium. The first-formed reduction products may subsequently react to form additional products suggestive of alternative mechanistic pathways. To minimize such difficulties trifluoroacetic acid was chosen as the Bronsted acid, and minimal amounts of this acid were employed in order to decrease the rates of reactions subsequent to the rate-limiting step.

An additional complication was suggested in studies at room temperature of the reduction of 4-*tert*-butylcyclohexanone by triethylsilane in which only 1 equiv of trifluoroacetic acid was employed. The data obtained from these studies[12] suggested that a exchange process of silyl alkyl ether and trifluoroacetic acid with alcohol and silyl trifluoroacetate (eq 6, R = 4-*tert*-butylcyclohexyl) was occurring.[13] The unsubstituted cyclohexyl system was chosen to examine this process in greater detail.

$$ROSiEt_3 + CF_3CO_2H \overset{K}{\rightleftharpoons} ROH + Et_3SiO_2CCF_3 \quad (6)$$

Either treatment of cyclohexyl triethylsilyl ether with trifluoroacetic acid or mixing cyclohexanol and triethylsilyl trifluoroacetate in trifluoroacetic acid resulted in the same equilibrium mixture of products (eq 6, R = cyclohexyl, K = 1.4 ± 0.2). When 10 equiv of trifluoroacetic acid based on either silyl ether or silyl trifluoroacetate was used, equilibrium was achieved within 25 sec; when 1 equiv of trifluoroacetic acid was used, equilibration occurred only after a reaction period of 5 min. Yields of solution components

Table I
Di-*tert*-butylmethylsilane Reduction of 4-*tert*-Butylcyclohexanone[a]

Time, min	% reduction[b]	Yield, % ROSiMe-(*t*-Bu)	ROH	Alkene[d]	RO_2CCF_3
35	62	54	8	<1	<1
60	88	68	5	4	11
160	91	68	3	5	15
344	94	63	2	7	22
22 hr	100	58	0	8	34

[a] Reduction was run at room temperature with 1.0 mmol of 4-*tert*-butylcyclohexanone (98-53-3), 0.75 mmol of di-*tert*-butylmethylsilane (56310-20-4), and 1.5 mmol of trifluoroacetic acid. [b] Based on reacted silane. [c] Actual product yields based on ^1H NMR analyses and confirmed by GLC methods. Isomeric yields were comparable to those previously observed.[1a] R = 4-*tert*-butylcyclohexyl. [d] 4-*tert*-Butylcyclohexene.

were determined at more than four different times for each of four separate reactions. The formation of cyclohexyl trifluoroacetate from cyclohexanol occurred at a slower rate than the interconversion between silyl ether and alcohol. Triethylsilyl trifluoroacetate was converted to hexaethyldisiloxane by the water produced from the trifluoroacetolysis of cyclohexanol.

The value of K obtained for the cyclohexyl system is nearly identical with that calculated for the 4-*tert*-butylcyclohexyl system ($K = 1.7 \pm 0.2$). In either system the alcohol product is favored over the silyl ether, and the equilibrium exchange described in eq 6 is rapidly attained even when minimal amounts of trifluoroacetic acid are used.

The rapid equilibration of triethylsilyl ether and alcohol in trifluoroacetic acid sets a severe limitation on the determination of the mechanism for hydride transfer in triethylsilane reductions. At equilibrium it is not possible to determine from which direction equilibration has been achieved. However, prior to equilibrium observation of a value for the ratio, $[ROH][Et_3SiO_2CCF_3]/[ROSiEt_3][CF_3CO_2H]$, that is greater than the equilibrium value would be suggestive of the counterion mechanism (Scheme I), whereas if the ratio is less than the equilibrium value, the four-center mechanism (Scheme II) or hydride transfer by eq 3 would be implied. Attempts to determine the direction from which equilibration occurs in the reduction of cyclohexanone by triethylsilane were unsuccessful. Equilibrium (eq 6, R = cyclohexyl) was established prior to 5 min reaction times (<2% reduction) even when only 0.5 equiv of trifluoroacetic acid was employed.

When the rate of equilibration of silyl ether–alcohol is comparable to the rate of reduction, as in the case of cyclohexanone reductions by triethylsilane, the mechanism of the hydride transfer step cannot be determined with confidence. However, a reliable distinction between Schemes I and II is attainable if (1) the rate of reduction is faster than the rate of equilibration and (2) the reduction product is not the predominant form at equilibrium. From previous studies both criteria appeared possible in reactions with *tert*-butylsilanes.[1a] Both di-*tert*-butylmethylsilane and tri-*tert*-butylsilane yield silyl ethers as the exclusive or nearly exclusive reduction product at short reaction times (<50% reduction) in reactions with cyclohexanones.

The reduction of 4-*tert*-butylcyclohexanone by di-*tert*-butylmethylsilane was performed and the reaction products analyzed at various times to determine the exact levels of silyl ether and alcohol present during reduction.[14] The results of this study are given in Table I and clearly show that silyl ether and alcohol are the initially formed reaction products. However, although the relative yield of the silyl ether is as high as 87%, indicating that this compound is the primary reduction product, the ratio of alcohol to silyl ether may in fact reflect the relative equilibrium concentrations of these two components under the reaction conditions employed.

To determine the extent of the silyl ether–alcohol interconversion (eq 7) di-*tert*-butylmethylsilyl trifluoroacetate was prepared and added to an equal amount of 4-*tert*-butylcyclohexanol (26% cis, 74% trans), followed by 3 equiv of trifluoroacetic acid. After 20 and 280 min, a longer time than was required for complete reduction of 4-*tert*-butylcyclohexanone,[1a] no 4-*tert*-butylcyclohexyl di-*tert*-butylmethylsilyl ether was observed. Only 4-*tert*-butylcyclohexanol, the corresponding trifluoroacetates, and the silyl trifluoroacetate were detected, indicating that, if equilibration occurred, the equilibrium constant for eq 7 must be greater than 50. In reductions of 4-*tert*-butylcyclohexanone by di-*tert*-butylmethylsilane under comparable conditions the product ratio from eq 7 was observed to be less than 0.005, a factor of 10000 from the minimum estimate of the equilibrium value. From these experiments, which show that the silyl ether is the first-formed reduction product, a distinction between Schemes I and II can be made. However, these data do not permit a choice between eq 3 and 4 for the hydride transfer step.

$$R_2CHOSiMe(t\text{-}Bu)_2 + CF_3CO_2H \rightleftharpoons R_2CHOH + (t\text{-}Bu)_2MeSiO_2CCF_3 \quad (7)$$

In a separate experiment 4-*tert*-butylcyclohexanone was reduced by di-*tert*-butylmethylsilane in the presence of 0.84 equiv of *trans*-4-methylcyclohexanol. Analysis of the reaction products throughout the time for complete reduction showed the presence of *cis*- and *trans*-4-*tert*-butylcyclohexyl di-*tert*-butylmethylsilyl ether (74% cis at 16% reduction) and other reaction components previously observed in the reduction of 4-*tert*-butylcyclohexanone. No trace of *trans*-4-methylcyclohexyl di-*tert*-butylmethylsilyl ether, the silyl ether product expected from eq 3, could be detected. Under the same reaction conditions 4-methylcyclohexanone yielded the isomeric 4-methylcyclohexyl di-*tert*-butylmethylsilyl ethers at levels comparable to those for the 4-*tert*-butylcyclohexyl silyl ethers observed in reductions of 4-*tert*-butylcyclohexanone.

Separate experiments were performed to determine if the symmetrical ethers formed by silane reductions in trifluoroacetic acid could be produced in reactions involving silyl alkyl ethers or alcohols. A mechanism for symmetrical ether formation has been previously described and requires hydride transfer to an O-alkylated carbonyl compound.[15] Symmetrical ethers were not produced within the limits of detectability from the reaction of alcohol with trifluoroacetic acid, from a mixture of alcohol and trifluoroacetic acid, from silyl alkyl ethers in trifluoroacetic acid, or from mixtures of silyl alkyl ethers and alcohols in trifluoroacetic acid. Symmetrical ethers are formed by reduction rather than by substitution on silyl alkyl ethers or alcohols.

Discussion

The mechanism for alcohol formation in reductions of carbonyl compounds by di- and tri-*tert*-butylsilanes is adequately described by Scheme II. The hydride-transfer step occurs in a four-center arrangement between the protonated carbonyl group and the silicon hydride and does not involve either the counterion of the acid employed or the alcohol formed during the reduction process. Owing to the rapid equilibration between alcohol and silyl ether (eq 6), however, the mechanism of the hydride transfer step with

less hindered silanes, such as triethylsilane, could not be directly determined with confidence by the same method successfully used with more hindered silanes.

The hydride transfer step resulting in symmetrical ethers is consistent with that of the counterion mechanism (eq 8, A^- = alcohol or conjugate base of acid). Neither silyl ethers nor alcohols are directly converted to ethers under the same reaction conditions used for reductions of carbonyl compounds. The relative yield of symmetrical ether is dependent not only on the concentration of alcohol, but also, on the relative rates for hydride transfer to protonated and O-alkylated carbonyl compound.

$$R_2C{=}OR' + R''_3SiH + A^- \rightarrow R_2CHOR' + R''_3SiA \quad (8)$$

A general mechanism for silane reductions of carbonyl compounds in Bronsted acids is given in Scheme III. Acti-

Scheme III

$$R_2C{=}O + HA \rightleftharpoons R_2C{=}OH + A^-$$

$$R_2C{=}OH + R'_3SiH \xrightarrow{A^-} R_2CHOSiR'_3 + H^+$$

$$R_2C{=}OH + R'_3SiH \xrightarrow{?} R_2CHOH + R'_3SiA$$

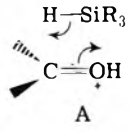
$$R_2CHOH + HA \rightleftharpoons R_2CHA + H_2O$$

$$R'_3SiA + H_2O \rightleftharpoons R'_3SiOH + HA$$

$$R'_3SiA + R'_3SiOH \longrightarrow (R'_3Si)_2O + HA$$

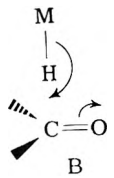
vation of the carbonyl group is usually required before hydride transfer can occur.[16] When protonic acids are used to catalyze silane reductions, these acids are also involved in subsequent reactions of the primary reduction products. These secondary reactions occur by displacement at silicon; displacement at carbon is not involved.[17] Lewis acids, such as zinc chloride[18] and aluminum chloride,[19] also catalyze silane reduction yielding mainly alkyl silyl ethers, presumably by a four-center mechanism; however, these reactions are similarly complicated by symmetrical ether and alkene product formation.

Previous studies have indicated that silicon–hydrogen bond breaking is not extensive in the transition state for hydride transfer.[9,10,20] The approach of organosilanes to the carbonyl group, therefore, should not be as sensitive to steric repulsions from substituents of the carbonyl compound as would be reagents for which closer approach occurs in the transition state. In addition, however, in the four-center mechanism the carbonyl oxygen is involved in the hydride transfer step, forming a bond to silicon as the hydride is released. This demands that the silicon atom be bent toward the carbonyl oxygen in the transition state (structure A). In contrast, metal hydride reductions are

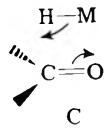


A

usually described by collinear C–H bond formation and M–H bond cleavage (structure B),[21] although such a geometry is not demanded (structure C).



B



C

Table II
Comparative Stereoselectivities of Bulky Boron and Silicon Hydrides

Reducing agent	Relative yield, % cyclohexanol: *cis*-4-*tert*-Butyl	*cis*-4-Methyl	*cis*-2-Methyl-	*trans*-3,3,5-Trimethyl
Et_3SiH[2]	32	36	48	84
IPC_2BH[a,22]	37	33	94	
LiPBPH[b,23]	54	52	97	99
sec-Bu_3SiH[2]	55	58	64	96
$(t\text{-Bu})_2SiH_2$[1a]	69	68	76	89
$(t\text{-Bu})_2MeSiH$[1a]	72	67	74	99
Li-*sec*-Bu_3BH, 0°[24]	93	80	99	99.8

[a] Diisopinocampheylborane. [b] Lithium perhydro-9b-boraphenalylhydride.

In reductions of substituted cyclohexanones, groups bonded to the metal will be significantly more sensitive to steric effects from axial 3,5 positions in the transition state described by structure B than in that described by structure C. Since the transition state geometry in reductions by hindered organosilanes parallels C rather than B, the stereoselectivities in silane reductions should provide a reasonable model for the transition state geometries of other structurally comparable reducing agents.

The relative yields of the less stable isomers from reductions of alkyl-substituted cyclohexanones by selected bulky boron and silicon hydrides are given in Table II. By comparison with the results from 4-*tert*-butylcyclohexanone or 4-methylcyclohexanone, the yields of the less stable alcohols from reductions of 2-methylcyclohexanone and 3,3,5-trimethylcyclohexanone by the alkyl borohydrides and diisopinocampheylborane are enhanced relative to those by the organosilanes. This difference in the sensitivities to axial 3-methyl and 2-methyl substituents is attributable to differences in the geometries of the reducing agents in the transition state for hydride transfer. The results for the boron hydrides in Table II are consistent with hydride transfer through a geometry resembling B rather than C.

Experimental Section

General. Instrumentation has been previously described.[2] A Varian Model 485 digital integrator was used to determine peak areas in GLC analyses; reported yields were calculated with the use of experimentally determined thermal conductivity ratios. Cyclohexyl triethylsilyl ether and 4-*tert*-butylcyclohexyl triethylsilyl ether were prepared from the respective alcohols and triethylsilyl chloride in dry pyridine. Organosilanes were obtained commercially or were prepared as previously described.[25]

Triethylsilyl Trifluoroacetate. Triethylsilane (15.0 g, 0.13 mol) was added to a stirred solution of trifluoroacetic acid (29.4 g, 0.26 mol) and trifluoroacetic anhydride (3 ml), causing an immediate exothermic reaction. After 72 hr no triethylsilane was detected. Distillation at 17 Torr through a 17-cm Vigreux column yielded 52% of triethylsilyl trifluoroacetate, bp 61–66° [lit.[26] bp 153° (760 Torr)]. Even at the low temperature used for distillation hexaethyldisiloxane was formed in measureable quantities; redistillation through a short-path column gave triethylsilyl trifluoroacetate which was >99% pure by GLC analysis.

Equilibrium Measurements. Stirred solutions of trifluoroacetic acid and cyclohexyl triethylsilyl ether or of trifluoroacetic acid, cyclohexanol, and triethylsilyl trifluoroacetate were analyzed by GLC at various times. Reactions using 1 and 10 equiv of trifluoroacetic acid (based on cyclohexyl triethylsilyl ether or equivalent amounts of cyclohexanol and triethylsilyl trifluoroacetate) were performed at 25°. Samples were quenched with excess saturated aqueous sodium bicarbonate and extracted twice with ether. (Control experiments showed that triethylsilyl trifluoroacetate was converted quantitatively to triethylsilanol by aqueous bicarbonate and that the silyl ether and cyclohexyl trifluoroacetate were not hydrolyzed during the work-up procedure.) The combined ether

extract was dried over anhydrous magnesium sulfate and filtered, and the ether was evaporated under reduced pressure. In a typical run samples were removed at 25 sec, 1, 5, 10, and 30 min. The equilibrium ratio from eq 6 was constant until cyclohexyl trifluoroacetate had begun to form (>10 min when 1 equiv of trifluoroacetic acid was used; 3 min when 10 equiv of acid was employed). When 1 equiv of trifluoroacetic acid was used the equilibrium ratio was attained at 5 min; equilibrium was achieved prior to the removal of the first sample (<30 sec) when 10 equiv of trifluoroacetic acid was employed.

Triethylsilane Reduction of Cyclohexanone. Product Analysis with Time. Trifluoroacetic acid (17.8 mmol) was added to a stirred solution of cyclohexanone (34.3 mmol), triethylsilane (33.5 mmol), and two GLC standards, phenylcyclohexane and 1-octyl ether. Aliquots were removed at intervals and quenched with excess "Tri-Sil", hexamethyldisilazane, trimethylchlorosilane in pyridine. This quenching procedure was used to enhance GLC separation of reaction components and to provide symmetrical peaks for analysis. Control experiments showed that cyclohexyl triethylsilyl ether and cyclohexyl trifluoroacetate were not affected by the quenching procedure and that cyclohexanol was quantitatively converted to the trimethylsilyl derivative. Quenched samples were stored in a freezer prior to analysis. At reaction times between 5 min and 6 hr GLC analysis gave product yields which corresponded to the equilibrium value for eq 6. Similar results were obtained using a quenching procedure similar to that described for the equilibrium studies, but analyses were significantly more difficult owing to unsymmetrical and overlapping peaks. For the aliquot removed at 250 sec the product ratio was determined to be 0.4; however, at this and shorter reaction times GLC peaks having similar areas to those of the reaction components (~0.2 mmol) and retention times overlapping with cyclohexyl trimethylsilyl ether interfered with the silyl ether and prevented an accurate determination of this compound. At no time was the level of cyclohexyl triethylsilyl ether greater than that of the trimethylsilyl derivative of cyclohexanol.

Di-*tert*-butylmethylsilanol and Di-*tert*-butylmethylsilyl Trifluoroacetate. Di-*tert*-butylmethylsilanol was prepared by the di-*tert*-butylmethylsilane reduction of acetone. The reaction mixture was quenched with excess 3 *N* sodium hydroxide, refluxed under the basic conditions for 24 hr, cooled, and extracted three times with pentane. The combined pentane extract was washed three times with water, dried over anhydrous magnesium sulfate, and filtered, and the pentane was evaporated under reduced pressure. The resulting solid was sublimed at 0.2 Torr to give a waxy white solid, mp 45–48° (46.5–48.5° after GLC purification), in 62% yield: ir (film) 3480 (broad, O–H), 1380, 1360 (*t*-Bu), 1250, and 800 cm^{-1}; ^1H NMR (CCl_4) δ 1.24 (s, 1 H, OH), 1.02 (s, 18 H, *t*-Bu), and 0.03 (s, 3 H, CH_3).

Anal. Calcd for $C_9H_{22}SiO$: C, 62.00; H, 12.72; Si, 16.11. Found: C, 62.18; H, 12.71; Si, 16.24.

Trifluoroacetolysis of di-*tert*-butylmethylsilanol with trifluoroacetic anhydride gave di-*tert*-butylmethylsilyl trifluoroacetate: ir (film), 1780, 1470, 1390, 1365 and 820 cm^{-1}; ^1H NMR (CCl_4) δ 1.09 (s, 18 H) and 0.42 (s, 3 H).

Anal. Calcd for $C_{11}H_{21}F_3O_2Si$: C, 48.87; H, 7.83; Si, 10.39. Found: C, 49.02; H, 7.93; Si, 10.19.

Cyclohexanone Reductions by Di-*tert*-butylmethylsilane. Product Analyses. Reductions of 4-*tert*-butylcyclohexanone and 4-methylcyclohexanone were run as previously described.[2] Alkene, alcohol, trifluoroacetate, and silyl ether products were identified by ^1H NMR and GLC methods through comparison with authentic samples. For the reduction of 4-*tert*-butylcyclohexanone in the presence of *trans*-4-methylcyclohexanol, ketone (3.0 mmol), di-*tert*-butylmethylsilane (3.2 mmol), and alcohol (2.5 mmol) were weighed into a round-bottom flask and 8.7 mmol of trifluoroacetic acid was added. The homogeneous solution was stirred at room temperature, and aliquots were removed at various times over a 3-hr period. Concurrently, 4-methylcyclohexanone (2.8 mmol) was reduced by di-*tert*-butylmethylsilane (3.2 mmol) in trifluoroacetic acid (8.7 mmol), and aliquots were removed at reaction times comparable to those for the 4-*tert*-butylcyclohexanone reduction. The isomeric 4-methylcyclohexyl di-*tert*-butylsilyl ethers were identified by ^1H NMR (δ 3.95 and 3.35 for the methine hydrogen of the cis and trans isomers, respectively) and GLC methods. No trace of the 4-methylcyclohexyl silyl ethers (<0.5% of the 4-*tert*-butylcyclohexyl silyl ether) was observed during the 3-hr reaction period for the reduction of 4-*tert*-butylcyclohexanone. Although *trans*-4-methylcyclohexanol was slowly converted to the corresponding trifluoroacetate, the amount of this alcohol present during the reduction of 4-*tert*-butylcyclohexanone was always greater than that of 4-*tert*-butylcyclohexanol.

Registry No.—*cis*-ROSiMe(*t*-Bu)$_2$, 56889-82-8; *trans*-ROSiMe(*t*-Bu)$_2$, 56889-83-9; *cis*-RO_2CCF_3, 7556-86-7; *trans*-RO_2CCF_3, 7600-15-9; di-*tert*-butylmethylsilanol, 56889-84-0; di-*tert*-butylmethylsilyl trifluoroacetate, 56889-85-1.

References and Notes

(1) (a) Part V: M. P. Doyle and C. T. West, *J. Org. Chem.*, preceding paper in this issue. (b) Support for this work from the Research Corporation is gratefully acknowledged. (c) Camille and Henry Dreyfus Foundation Teacher-Scholar Grant Awardee, 1973–1978.

(2) Part IV: M. P. Doyle and C. T. West, *J. Org. Chem.*, accompanying paper in this issue.

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Benzospirans Bearing Basic Substitution. I. Spiro[cyclohexane-1,2′-indans]

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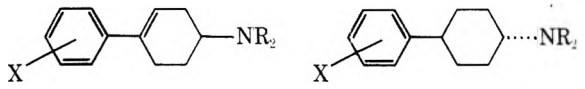
The carbanion obtained from the ethylene ketal of 4-carbomethoxycyclohexanone (LDA) was treated with benzyl chloride to give the corresponding 4-benzylated derivative. Protecting groups were removed and the resulting keto acid cyclized to spiro[cyclohexane-1,2′-indan]-1′,4-dione. This was converted in several steps to spiro[cyclohexane-1,2′-indan]-4-one. Preparation of analogues substituted by methoxyl in the aromatic ring is described. The ketone was transformed to the primary amine in several steps. Preparation of derivatives of the amines including the *p*-fluorobutyrophenones is described. Analogues containing hydroxy and exomethylene substituents in the five-membered ring were prepared by a modification of the synthesis. The stereochemistry of the *exo*-methylene compound is discussed.

We have reported earlier on the preparation and CNS activity of a series of derivatives of 4-arylcyclohex-3-enylamines (1)[1] and 4-arylcyclohexylamines (2).[2] The observation that the ortho-substituted derivatives (**1a,b, 2a,b**) in



1a, X = *o*-CH_3
b, X = *o*-OCH_3

2a, X = *o*-CH_3
b, X = *o*-OCH_3

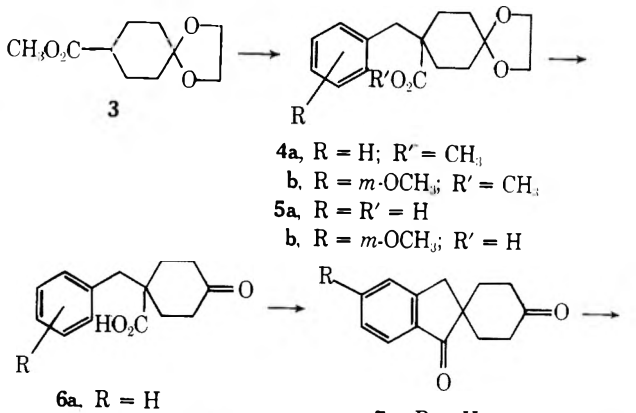
each series showed considerable biological activity was considered of particular interest; interaction of the ortho substituent with the equatorial proton on the adjacent alicyclic ring make it likely that the preferred conformation of these molecules is one in which the two rings are in some skewed arrangement. We thus decided to prepare analogues of those compounds in which those rings would be actually locked orthogonal to each other. The classic means for achieving this—at the cost of a slight increase in the ring to ring distance—lies in the preparation of the corresponding benzospirans.

The key to entry to the desired carbon skeleton was provided by the recently developed strong nonnucleophilic base, lithium diisopropylamide (LDA). Thus, treatment of the ethylene ketal (**3**) obtained from 4-carbomethoxycyclohexanone[3] with LDA followed by benzyl chloride afforded the alkylation product (**4a**) in good yield (Scheme I).

The highly hindered ester grouping of **4**, not surprisingly, proved refractory to saponification; the transformation was, however, achieved in good yield by means of sodium hydroxide in refluxing ethylene glycol. Deketalization of the crude acidic product (dilute hydrochloric acid in acetone) afforded the keto acid **6a**. Cyclization to the benzospiran skeleton (**7a**) was effected in modest yield by means of liquid hydrogen fluoride. The parent compound (**7a**) was accompanied by a trace of a product whose mass spectrum and elemental analysis suggested that the carbonyl group of the cyclohexane had reacted to form the corresponding difluoro derivative (**10**), an unusual reaction under the mild conditions employed.

Treatment of the diketone **7a** with 1 equiv of ethylene glycol under the usual conditions for ketalization went in straightforward manner to afford the monoketal **8a**; the ir spectrum of the product (ν_{max} 1690 cm^{-1}) confirms that the more reactive cyclohexanone carbonyl has in fact undergone reaction. Reduction of the free carbonyl group was then achieved by means of the Huang-Minlon modification of the Wolff–Kishner reaction. The amazingly simple NMR spectrum of the product, **9a**, which consists of but four singlets (ArH, δ 7.12, 4 H; ketal δ 4.0, 4 H; $ArCH_2$, δ 2.8, 4 H;

Scheme I



3

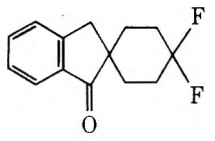
4a, R = H; R′ = CH_3
b, R = *m*-OCH_3; R′ = CH_3
5a, R = R′ = H
b, R = *m*-OCH_3; R′ = H

6a, R = H
b, R = *m*-OCH_3

7a, R = H
b, R = OCH_3

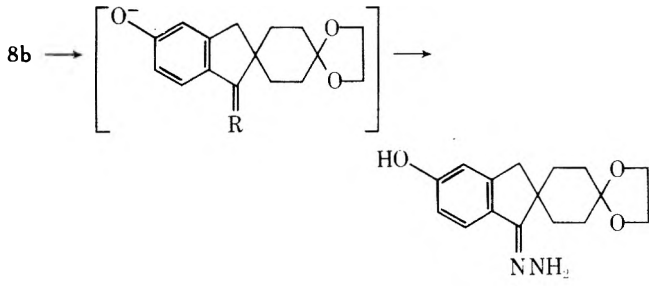
8a, R = H
b, R = OCH_3

9a, R = H
b, R = OCH_3



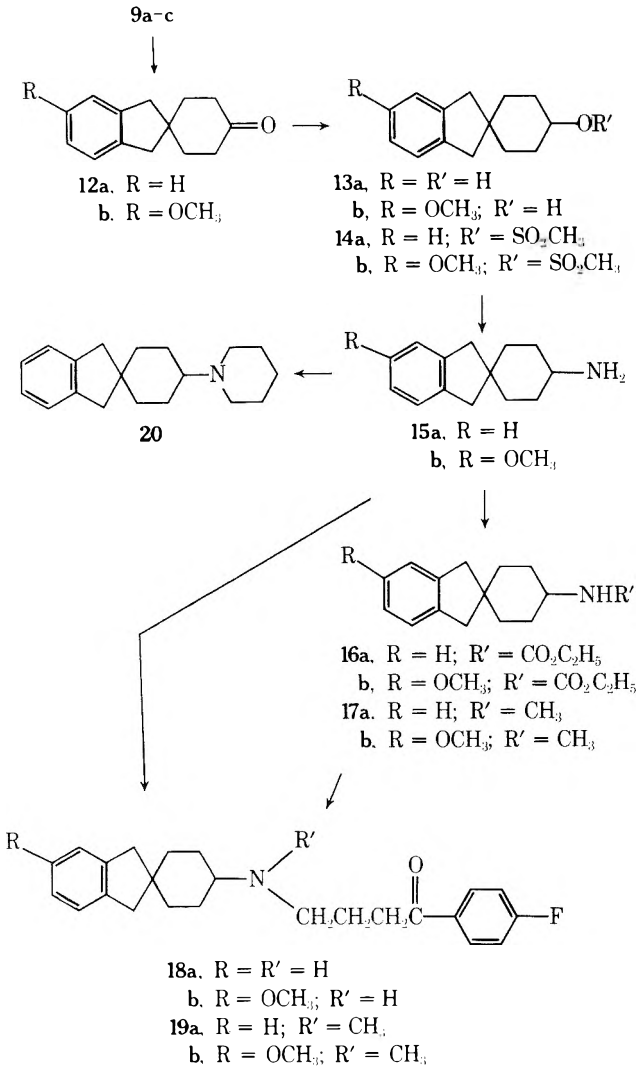
10

cyclohexane CH_2, δ 1.67, 8 H), at the same time confirms the structure of the product and attests to the high degree of symmetry of the molecule. The corresponding analogue substituted by methoxyl (**9b**) group was prepared in the same manner by using the meta-substituted benzyl chlorides in the initial alkylation step. Wolff–Kishner reaction of the methoxy analogue (**8b**) afforded the phenolic hydra-



11

Scheme II

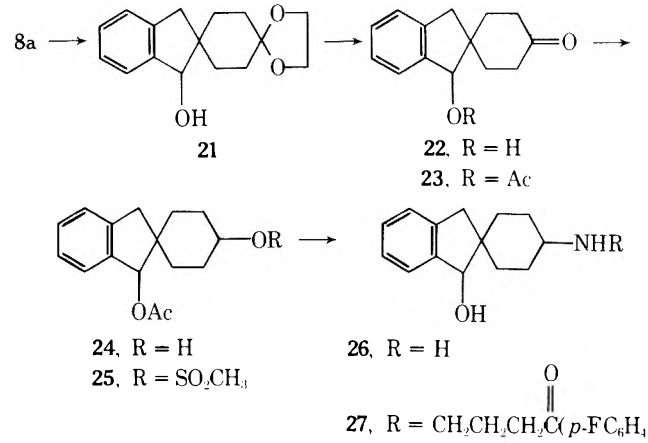


zone 11 in significant amounts. It is considered likely that some portion of the starting material or its hydrazone may undergo base-catalyzed ether cleavage under the strongly basic conditions;[4] the presence of the negative charge on the phenoxide may then inhibit formation of the hydrazine anion required for completion of the reduction.

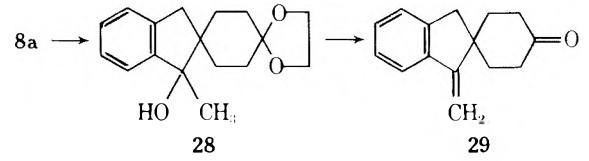
Removal of the ethylene ketal by means of dilute aqueous acid in acetone followed by reduction of the resulting ketones (**12a,b**) by means of sodium borohydride afforded the corresponding alcohols (**13a,b**) (Scheme II). These last were converted to the primary amines (**15a,b**) by a convenient three-step sequence which consists of conversion of the alcohol to its mesylate, displacement of the leaving group by means of sodium azide in DMF, and finally reduction of the crude azide with lithium aluminum hydride. Reaction of the parent amine **15a** with 1,5-diiodopentane gave the corresponding piperidine **20.**

Each of the primary amines was then converted to its carbamate by means of ethyl chloroformate. Reduction of these acylated products with lithium aluminum hydride gave the N-methylated analogues (**17a,b**). It has been frequently shown that central nervous system activity of amines is maximized by conversion of these to the *p*-fluorobutyrophenone derivatives.[5] Both primary and secondary amines were thus alkylated with the neopentyl glycol ketal of 4-chloro-*p*-fluorobutyrophenone. Brief exposure of the alkylation product to aqueous methanolic acid afforded the butyrophenone derivatives (**18a,b, 19a,b**).

Turning our attention to the functionality present in the five-membered ring in one of the intermediates, we found the carbonyl group of **8a** to be surprisingly inert toward sodium borohydride. Reduction by means of lithium aluminum hydride afforded an oily alcohol, which was characterized as its crystalline acetate **23.** Reduction of the cyclohexanone obtained on deketalization (**23**) again afforded an oily product; both NMR and TLC suggested that this consisted largely of one of the two possible hydroxy acetates (syn and anti OH and OAc). Isolation of a homogeneous crystalline mesylate in 65% yield from treatment of the mixture with methanesulfonyl chloride in pyridine confirms the predominance of one isomer. It is, however, hazardous to assign configurations in this case without both isomers in hand.[6] The mesylate **25** was then taken on to the amine **26** by the azide displacement scheme. Alkylation as above afforded the *p*-fluorobutyrophenone **27.**

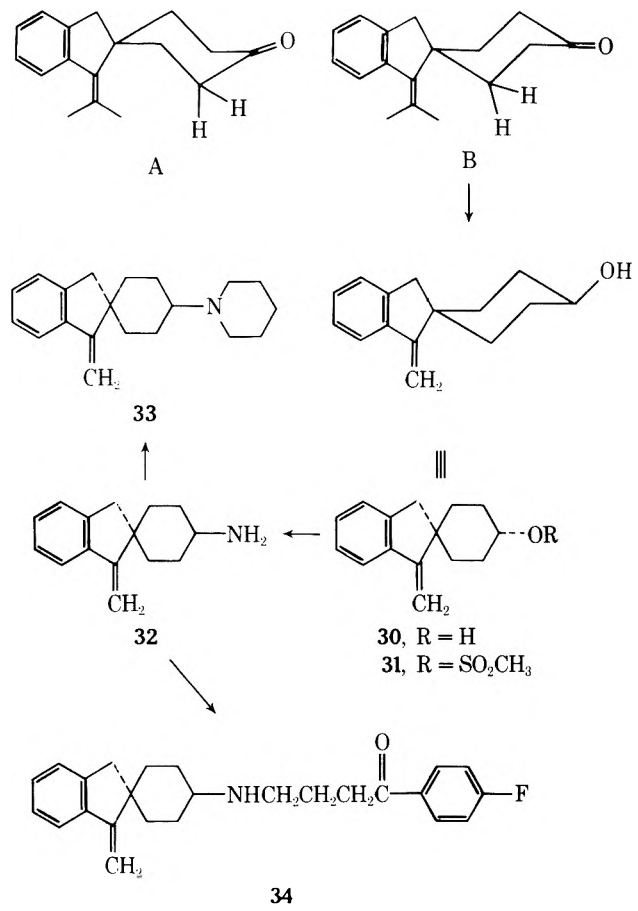


Reaction of ketone **8a** with methylmagnesium bromide proceeds uneventfully to afford the tertiary alcohol **28.** An attempt to deketalize this compound under the usual mild conditions, surprisingly resulted in dehydration of the alcohol to afford the *exo*-methylene ketone **29.** The ketone was

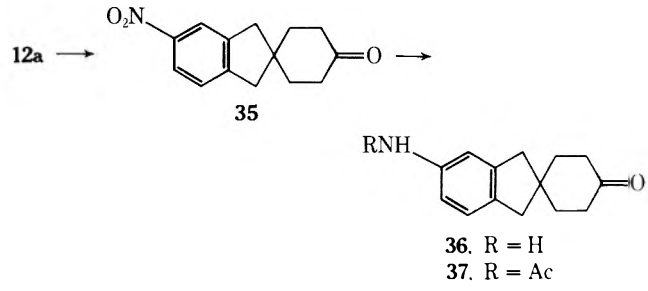


then reduced by means of sodium borohydride. Careful chromatography of the product afforded first a trace of an alcohol whose NMR spectrum was consistent with an axial hydroxyl group; the bulk of the product had an NMR consistent with an equatorial group. Examination of molecular models of the starting ketone reveals two conformations which contain a chair cyclohexane (A, B). Of these, B is perhaps slightly favored since it does not contain the interaction of the exomethylene group with the axial protons on the 3 positions on the cyclohexane. Granting this assumption, the equatorial alcohol obtained from this conformer would be formulated as in **30.** Formation of the mesylate gave **31.** This is of course inverted in the azide displacement step; the amine obtained by reduction of the azide is thus tentatively formulated as **32.** Alkylation of this last product with 1,5-diiodopentane affords the piperidine **33;** reaction with the neopentyl glycol ketal of 4-chloro-*p*-fluorobutyrophenone followed by hydrolysis gives butyrophenone **34.**

Finally, nitrogen was introduced as an attachment to the aromatic ring. Treatment of a solution of the ketone **12a** in trifluoroacetic acid in the cold with a limited amount of nitric acid gave the corresponding nitro compound in modest yield. Reduction of **35** was accomplished by catalytic hy-



drogenation. Since the free amine proved rather unstable, the compound was characterized as its acetamide (**37**).



Experimental Section[7]

4-Carbomethoxycyclohexanone Cyclic Ethylene Acetal (3). A mixture of 17.41 g (0.11 mol) of 4-carbomethoxycyclohexanone,[3] 6.25 ml of ethylene glycol, and 0.25 g of *p*-toluenesulfonic acid in 200 ml of benzene was heated at reflux under a Dean-Stark trap for 5 hr. The mixture was allowed to cool, washed in turn with saturated aqueous sodium bicarbonate, water, and brine, and taken to dryness. The residual oil was distilled at 0.5 mm to afford 20.0 g (91%) of product: bp 96–100°; ir 2960, 1735, 1195, 1170, 1135, 1105, and 925 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 60.15; H, 8.45.

4-Benzyl-4-carbomethoxy-1-cyclohexanone Cyclic Ethylene Acetal (4a). To a solution of 5.0 g (0.05 mol) of diisopropylamine in 50 ml of THF cooled in ice–MeOH there was added over 5 min 32 ml of 1.57 *N* BuLi in pentane. There was then added in turn 10.0 g (0.05 mol) of 4-carbomethoxy-1-cyclohexanone cyclic ethylene acetal in 50 ml of THF (15 min) and 8.50 g (0.05 mol) of α-bromotoluene in 15 ml of THF (5 min). The clear solution was stirred at room temperature for 1 hr, cooled in ice again, and treated with 50 ml of saturated NH_4Cl. The organic layer was separated, diluted with C_6H_6, and washed in turn with H_2O, ice-cold 1 *N* HCl, $NaHCO_3$, and brine. The oil which remained when the organic layer was taken to dryness was distilled at 0.25 mm to afford 13.57 g (93.5%) of product as a viscous oil: bp 155–156°; NMR δ 1.7 (m, 8, CH_2), 2.8 (s, 2, $ArCH_2$), 3.58 (s, 3, OCH_3), 3.93 (s, 4, ketal), 7.18 (m, 5, ArH); ir 2950, 1725, 1210, 1190, 1150, 1105, and 705 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 69.94; H, 7.60.

4-(*m*-Methoxybenzyl)-4-carbomethoxy-1-cyclohexanone Cyclic Ethylene Acetal (4b). The ester (19.6 g, 0.0995 mol) was alkylated as above with 15.3 g of *m*-methoxybenzyl chloride to give 22.32 g (70%) of ester acetal: bp 159–165° (0.2 mm); ir 2950, 1725, 1260, 1205, 1190, 1155, and 1105 cm^{-1}.

Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.71; H, 7.81.

1-Benzyl-4-cyclohexanone-1-carboxylic Acid (6a). A mixture of 16.64 g (0.057 mol) of the ester ketal and 2.5 g of KOH in 100 ml of ethylene glycol was stirred at reflux overnight. The mixture was then allowed to cool and diluted with H_2O. The solution was washed once with H_2O and then made strongly acidic with concentrated HCl. The precipitated gum was extracted with Et_2O and this solution washed in turn with H_2O and brine and taken to dryness. A solution of the residue and 13 ml of 2.5 *N* HCl in 130 ml of Me_2CO was stirred at room temperature for 20 hr. The bulk of the solvent was then removed under vacuum and the residue dissolved in ether. The organic layer was washed with water and brine and taken to dryness. The residual gum was chromatographed on 800 ml of acid-washed silica gel (elution with 4% AcOH in CH_2Cl_2). The crystalline fractions were combined and recrystallized twice from CH_2Cl_2–cyclohexane. There was obtained 5.62 g (42%) of the keto acid: mp 120–123°; ir 3160, 1730, 1690, 1220, 1180, and 705 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.24; H, 6.86.

4-(*m*-Methoxybenzyl)-1-cyclohexanone-1-carboxylic Acid (6b). Ester ketal **4b** (24.3 g, 0.076 mol) was saponified and isolated as above. The resulting solid was recrystallized twice from Et_2O–Skellysolve B (SSB)[8] to give 7.8 g (36%) of the desired keto acid, mp 109–112.5°, and a second crop of 3.82 g (19%) of product: mp 109–111°; ir 3040, 1730, 1690, 1260, 1185, 1155, and 1050 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.30; H, 6.92.

Spiro[cyclohexane-1,2′-indan]-1′,4-dione (7a). To 100 ml of freshly distilled hydrogen fluoride there was added 14.63 g (0.063 mol) of the keto acid. The solution was allowed to stand at room temperature for 18 hr and then poured cautiously into saturated $NaHCO_3$. The precipitated gum was extracted with C_6H_6. The organic layer was washed with H_2O, $NaHCO_3$, and brine and taken to dryness. The residue was chromatographed over 1.5 l. of silica gel (elution with 20% Me_2CO in SSB). There was obtained first a small amount of by-product followed by 10.50 g (78%) of spiro diketone, mp 70.5–72°. A small sample from another run was obtained as polymorph to mp 61–64°; ir 1705, 1600. 1285, and 740 cm^{-1}.

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.43; H, 6.59.

The less polar by-product was recrystallized from petroleum ether to give 0.28 g of product (**10**): mp 77–78°; ir 1705, 1290, 1270, 1115, 1065, 1000, 915, and 730 cm^{-1}.

Anal. Calcd for $C_{14}H_{14}F_2O$: C, 71.17; H, 5.97; mol wt, 236. Found: C, 71.18; H, 6.01; mol wt, 236.

5′-Methoxyspiro[cyclohexane-1,2′-indan]-1′,4-dione (7b). A suspension of 15.63 g (0.060 mol) of keto acid and 12.5 g of PCl_5 in 190 ml of C_6H_5Cl was stirred mechanically under reflux for 1.5 hr and at room temperature for 1.5 hr. The mixture was then cooled in ice and treated with 6.85 ml of $SnCl_4$. Following 0.5 hr of stirring in the cold and 18 hr at room temperature there was added 96 ml of 2.5 *N* HCl over 10 min. Following an additional 1 hr of stirring, the organic layer was separated, washed with H_2O, $NaHCO_3$, and brine, and taken to dryness. The residue was chromatographed on 1.2 l. of silica gel (elution with 10% EtOAc in CH_2Cl_2). The crystalline fractions were combined to give 7.51 g (51%) of product: mp 105–107°; ir 1710, 1685, 1600, 1275, 1250, and 1095 cm^{-1}.

The analytical sample melted at 110–112°.

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60; mol wt, 244. Found: C, 73.75; H, 6.65; mol wt, 244.

Spiro[cyclohexane-1,2′-indan]-1′,4-dione Cyclic 4-(Ethylene Acetal) (8a). A mixture of 1.77 g (0.0083 mol) of the diketone, 0.51 g (0.46 ml, 0.0082 mol) of ethylene glycol, and 0.10 g of *p*-TSA in 50 ml of C_6H_6 was heated at reflux under a Dean-Stark trap for 4 hr. The mixture was allowed to cool, washed in turn with $NaHCO_3$, H_2O, and brine, and taken to dryness. The residual solid was recrystallized from cyclohexane to afford 1.67 g (75%) of monoacetal: mp 158–160.5°; NMR δ 1.90 (m, 8, CH_2), 3.05 (s, 2,

$ArCH_2$), 4.0 (s, 4, ketal) 7.5 (m, 4, ArH); ir 1700, 1295, 1115, 1075, 935, 890, and 735 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02; mol wt, 258. Found: C, 73.99; H, 6.98; mol wt, 258.

5'-Methoxyspiro[cyclohexane-1,2'-indan]-1',4-dione Cyclic 4-(Ethylene Acetal) (8b). The diketone (4.89 g, 0.0196 mol) was ketalized as above to yield 4.13 g (73%) of monoacetal: mp 142–144°; ir 1695, 1600, 1280, 1255, 1100, and 1080 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 71.06; H, 7.19.

Spiro[cyclohexane-1,2'-indan]-4-one Cyclic Ethylene Acetal (9a). A mixture of 5.0 g (0.0194 mol) of the ketone, 2.6 ml of $N_2H_4 \cdot H_2O$, and 3.76 g of KOH in 50 ml of ethylene glycol was heated at reflux for 1.5 hr. Material was then removed by distillation to bring the pot temperature to 200°. At the end of an additional 5 hr heating at reflux, the mixture was allowed to cool and diluted with H_2O. The precipitated solid was collected on a filter, dried, and recrystallized from petroleum ether. There was obtained 4.00 g (85%) of reduced product: mp 70–74°; ir 1100, 1065, 1040, 755, and 735 cm^{-1}.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.39; H, 8.19.

5'-Methoxyspiro[cyclohexane-1,2'-indan]-4-one Cyclic Ethylene Acetal (9b) and 5'-Hydroxyspiro[cyclohexane-1,2'-indan]-1',4-dione Cyclic 4-(Ethylene Acetal) 1'-Hydrazone (11). A mixture of 4.57 g (0.0158 mol) of ketone, 2.45 g of $N_2H_4 \cdot H_2O$, and 3.15 g of KOH in 40 ml of ethylene glycol was heated at reflux for 1 hr. Solvent was removed by distillation to bring the reaction mixture to 200°. Following 1.5 hr at this temperature the mixture was poured into H_2O, and this was extracted well with Et_2O. The organic fractions were combined and taken to dryness. The residue was chromatographed on 250 ml of silica gel (elution with 10% Me_2CO in SSB). There was obtained 2.07 g (48%) of product, mp 59–61°. The analytical sample from an earlier run melted at 65–66.5°; ir 1495, 1265, 1100, 1030, and 820 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.22; H, 8.08. Found: C, 74.57; H, 8.24.

The aqueous portion above was "acidified" with solid CO_2. The precipitated solid was collected on a filter and recrystallized from MeOH. There was obtained 0.51 g of by-product: mp 243–246°, 285–290°; ir 3340, 1605, 1595, and 1275 cm^{-1}.

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.69; H, 6.99; N, 9.71; mol wt, 288. Found: C, 66.16; H, 7.14; N, 9.96; mol wt, 288.

Spiro[cyclohexane-1,2'-indan]-4-ol (13a). A mixture of 4.0 g (0.016 mol) of acetal and 8 ml of 2.5 *N* HCl in 80 ml of Me_2CO was heated at reflux for 4 hr. The bulk of the solvent was removed under vacuum and Et_2O was added. The organic layer was separated, washed with H_2O and brine, and taken to dryness. The residue was chromatographed on 350 ml of silica gel (elution with CH_2Cl_2). Those fractions similar by TLC were combined to afford the ketone as an amorphous gum: NMR δ 2.18 (A_2B_2, 8, CH_2), 2.95 (s, 4, $ArCH_2$), 7.18 (s, 4, ArH).

To a solution of 8.33 g (0.042 mol) of the crude oily ketone in 85 ml of EtOH there was added 1.60 g of $NaBH_4$. Following 6 hr stirring at room temperature the bulk of the solvent was removed under vacuum. The residue was taken up in Et_2O and H_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residue was chromatographed on 800 ml of silica gel (elution with 1% Me_2CO in CH_2Cl_2). The crystalline fractions were combined and recrystallized from petroleum ether to give 5.52 g (66%) of product: mp 76–78°; ir 3270, 1080, 1050, and 735 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.33; H, 8.92.

5'-Methoxyspiro[cyclohexane-1,2'-indan]-4-ol (13b). The acetal (2.87 g, 0.0105 mol) was hydrolyzed as above to give 1.95 g (81%) of ketone: mp 89–91°; ir 1715, 1495, 1290, 1245, and 1030 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 77.96; H, 7.96.

This was reduced ($NaBH_4$) to give the alcohol as an oil.

Spiro[cyclohexane-1,2'-indan]-4-ol Methanesulfonate (14a). A mixture of 5.52 g (0.027 mol) of the alcohol in 50 ml of ice-cold pyridine was treated with 5.5 ml of CH_3SO_2Cl. Following 7 hr standing in the cold the mixture was diluted with ice–H_2O. The precipitated solid was recrystallized from Me_2CO–SSB to give 7.15 g (93%) of mesylate: mp 100–102°; ir 1355, 1345, 1340, 1330, 1185, 1160, 920, and 905 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}O_3S$: C, 64.25; H, 7.19. Found: C, 63.87; H, 7.50.

5'-Methoxyspiro[cyclohexane-1,2'-indan]-4-ol Methanesulfonate (14b). The alcohol (1.86 g, 0.0080 mol) was acylated as above to give 2.10 g (85%) of mesylate: mp 63–67; ir 1490, 1350, 1245, 1170, 950, and 855 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.14. Found: C, 61.80; H, 7.14.

Spiro[cyclohexane-1,2'-indan]-4-amine Hydrochloride (15a). A mixture of 7.15 g (0.0256 mol) of the mesylate and 7.0 g of sodium azide in 70 ml of DMF was stirred in an oil bath at 90° for 17 hr. The solvent was then removed under vacuum and the residue dissolved in C_6H_6 and H_2O. The organic layer was washed with H_2O and brine and taken to dryness.

A solution of the crude azide in 75 ml of THF was added to a well-stirred suspension of 1.0 g of $LiAlH_4$ in 25 ml of THF. Following 5 hr of stirring at room temperature, the mixture was cooled in ice and treated in turn with 1 ml of H_2O, 1 ml of 15% NaOH, and 3 ml of H_2O. The inorganic gel was removed by filtration and the filtrate taken to dryness. The residue was dissolved in Et_2O and this treated with 5 *N* HCl in Et_2O. The precipitated solid was recrystallized from MeOH–EtOAc to give 4.58 g (76%) of amine: mp 280–282°; ir 3000, 1500, 1485, 755, and 740 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}ClN$: C, 70.71; H, 8.48; N, 5.89. Found: C, 70.68; H, 8.55; N, 5.69.

5'-Methoxyspiro[cyclohexane-1,2'-indan]-4-amine Hydrochloride (15b). The mesylate (2.10 g, 0.0068 mol) was converted to the azide and this reduced as above to give 0.69 g (38%) of product: mp 274–277°; ir 3130, 1580, 1495, 1290, 1250, and 1035 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}ClNO$: C, 67.27; H, 8.28; N, 5.23. Found: C, 67.25; H, 8.18; N, 4.98.

Concentration of the mother liquors afforded 0.43 g (23%) of an apparently polymorphic form of the product, mp 246–248°.

Anal. Found: C, 66.98; H, 8.50; N, 4.87; *m/e* 231.

4'-Fluoro-4-(spiro[cyclohexane-1,2'-indan]-4-yl)amine Butyrophenone Hydrochloride (18a). To a solution of 1.12 g (0.0047 mol) of the amine hydrochloride in 30 ml of DMF there was added 0.22 g of NaH. Following 1 hr of stirring at room temperature there was added 0.81 g of KI, 1.32 g of K_2CO_3, and 1.14 g of 4-chloro-*p*-fluorobutyrophenone 2,2-dimethylpropylene acetal. The mixture was then stirred overnight in an oil bath at 90°. The solvent was removed under vacuum and the residue dissolved in C_6H_6 and H_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residue was then stirred with 15 ml of MeOH and 7.5 ml of 2.5 *N* HCl for 2 hr. The bulk of the MeOH was removed under vacuum and the solid collected on a filter. Two recrystallizations from CH_2Cl_2–EtOAc afforded 0.84 g (46%) of product: mp 195–198°; ir 2760, 2500, 1680, 1595, 1155, 835, and 770 cm^{-1}.

Anal. Calcd for $C_{24}H_{29}ClFNO$: C, 71.71; H, 7.27. Found: C, 71.68; H, 7.14.

4'-Fluoro-4-[5'-methoxyspiro[cyclohexane-1,2'-indan]-4-yl)aminobutyrophenone Hydrochloride (18b). The amine hydrochloride (0.69 g, 0.0026 mol) was alkylated and the product isolated as above to give 0.52 g (46%) of product: mp 190–193°; ir 2760, 1680, 1600, 1495, 1290, 1275, and 1240 cm^{-1}.

Anal. Calcd for $C_{25}H_{31}ClFNO_2$: C, 69.51; H, 7.23; N, 3.24. Found: C, 69.62; H, 7.20; N, 3.11.

Spiro[cyclohexane-1,2'-indan]-4-methylamine Hydrochloride (17a). A suspension of 3.03 g (0.0128 mol) of the salt in CH_2Cl_2 was shaken with 1 *N* NaOH until the solid had all dissolved. The organic layer was separated and taken to dryness. To an ice-cooled solution of the residue in 25 ml of pyridine there was added dropwise 2 ml of $ClCO_2C_2H_5$. At the end of 5 hr in the cold the mixture was poured onto ice–H_2O. The precipitated solid was recrystallized from SSB to give 2.90 g (83%) of carbamate, mp 70–73°.

A solution of 2.90 g (0.0106 mol) of the carbamate in 50 ml of THF was added to a well-stirred suspension of 0.50 g of $LiAlH_4$ in 25 ml of THF. The mixture was heated at reflux for 6 hr and then cooled in ice. There was added in turn 0.5 ml of H_2O, 0.5 ml of 15% NaOH, and 1.5 ml of H_2O. The inorganic gel was collected on a filter and the filtrate taken to dryness. A solution of the residue in Et_2O was treated with 6 *N* HCl in Et_2O. The precipitate was recrystallized from CH_2Cl_2–MeOH–EtOAc to give 1.80 g (66%) of product, mp 251–254°.

Anal. Calcd for $C_{15}H_{22}ClN \cdot \frac{1}{3}H_2O$: C, 69.88; H, 9.22; N, 5.43. Found: C, 69.99; H, 8.55; N, 5.25.

5'-Methoxyspiro[cyclohexane-1,2'-indan]-4-methylamine Hydrochloride (17b). Reduction of the waxy carbamate, prepared as above, afforded on work-up a 35.1% yield of the secondary amine hydrochloride, mp 225–229°.

Anal. Calcd for $C_{16}H_{24}ClNO \cdot \frac{1}{2}CH_3OH$: C, 66.53; H, 8.80; N, 4.70. Found: C, 66.74; H, 8.54; N, 4.82.

4'-Fluoro-4-[methyl(spiro[cyclohexane-1,2'-indan]-4-yl)-amino]butyrophenone Hydrochloride (19a). Alkylation of the secondary amine (1.0 g, 0.0040 mol) with the neopentyl glycol acetal of 4-chloro-*p*-fluorobutyrophenone followed by hydrolysis and work-up afforded 0.77 g (45%) of product: mp 195–197°; ir 2450, 1675, 1595, 1225, 1150, 830, and 730 cm^{-1}.

Anal. Calcd for $C_{25}H_{31}ClFNO$: C, 70.65; H, 7.35; N, 3.29. Found: C, 71.10; H, 7.44; N, 3.20.

4'-Fluoro-4-[methyl(5'-methoxyspiro[cyclohexane-1,2'-indan]-4-yl)amino]butyrophenone, Hydrochloride (19b). Proceeding exactly as above, alkylation of the amine (0.84 g, 3.0 mmol) with 4-chloro-*p*-fluorobutyrophenone-2,2-dimethylpropylene acetal followed by hydrolysis afforded 0.45 g (33.6%) of the butyrophenone as an amorphous foam.

1-Spiro[cyclohexane-1,2'-indan]-4-yl Piperidine Hydrochloride (20). To a suspension of 1.53 g (0.0065 mol) of the amine hydrochloride in 30 ml of EtOH there was added 1.58 ml of 4.2 *N* NaOMe in MeOH. Following 1 hr of stirring 1.62 g of K_2CO_3 and 0.97 ml of 1,5-diiodopentane were added and the mixture brought to reflux. At the end of 18 hr the mixture was allowed to cool and the bulk of the solvent removed under vacuum. The residue was partitioned between Et_2O and H_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residual solid was dissolved in Et_2O and this treated with 5 *N* HCl in Et_2O. The resulting precipitate was recrystallized from CH_2Cl_2–EtOAc to afford 1.53 g (77%) of product: mp 282–286°; ir 2620, 2520, 1038, 755, and 730 cm^{-1}.

Anal. Calcd for $C_{19}H_{28}ClN$: C, 74.60; H, 9.23; N, 4.58. Found: C, 74.33; H, 9.27; N, 4.71.

1'-Hydroxyspiro[cyclohexane-1,2'-indan]-4-one Cyclic Ethylene Acetal (21). A solution of 2.60 g (0.010 mol) of the ketone in 50 ml of THF was added to a well-stirred suspension of 0.50 g of $LiAlH_4$ in 10 ml of THF. The mixture was stirred at room temperature for 5 hr, cooled in ice, and treated in turn with 0.5 ml of H_2O, 0.5 ml of 15% NaOH, and 1.5 ml of H_2O. The inorganic gel was removed by filtration and the filtrate taken to dryness. The residue was recrystallized from cyclohexane to give 2.45 g (95%) of product: mp 125–128°; ir 3450, 1090, 1035, 1025, 755, and 725 cm^{-1}.

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.48; H, 7.78.

1'-Acetoxy(cyclohexane-1,2'-indan)-4-one (23). A solution of 2.45 g (0.0094 mol) of the ketal and 5 ml of 2.5 *N* HCl in 50 ml of Me_2CO was allowed to stand overnight at room temperature. The bulk of the solvent was then removed under vacuum and the residue dissolved in H_2O and Et_2O. The organic layer was washed with H_2O and brine and taken to dryness to afford the product as a gum, ν_{max} 3500, 1705 cm^{-1}.

A solution of the gum and 4 ml of Ac_2O in 16 ml of pyridine was allowed to stand at room temperature for 7 hr and then poured onto ice–H_2O. The precipitate was extracted with Et_2O. This extract was washed in turn with H_2O, ice-cold 2.5 *N* HCl, H_2O, and saturated $NaHCO_3$ and taken to dryness. The residual solid was recrystallized from SSB to give 1.82 g (75%) of acetoxy ketone: mp 87–89°; NMR δ 2.05 (s, 3, $COCH_3$), 2.10 (m, 9), 3.0 (s, 2, ArCH), 3.10 (s, 1, ArCH), 7.25 (s, 4, ArH); ir 1725, 1240, 1210, 1020, 975, 770, and 755 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 73.99; H, 6.95.

1'-Acetoxy(cyclohexane-1,2'-indan)-4-ol Methanesulfonate (25). To a solution of 1.82 g (0.0071 mol) of acetoxy ketone in 25 ml of 95% *i*-PrOH there was added 0.32 g of $NaBH_4$. Following 1 hr stirring at room temperature the bulk of the solvent was removed under vacuum. The residue was dissolved in Et_2O and H_2O; the organic layer was washed with H_2O and brine and taken to dryness.

The residual gum was dissolved in 15 ml of pyridine. This solution was cooled in ice and treated with 1.7 ml of CH_3SO_2Cl. Following 17 hr of standing in the cold the mixture was poured onto ice–H_2O. The precipitated gum was extracted with Et_2O. The organic layer was washed in turn with H_2O, 2.5 *N* HCl, H_2O, and brine and taken to dryness. The residue was recrystallized twice from Et_2O–petroleum ether to give 1.54 g (65%) of mesylate: mp 97–100°; ir 1725, 1350, 1345, 1245, 1180, 1170, and 905 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}O_5S$: C, 60.69; H, 5.99; mol wt, 338. Found: C, 60.60; H, 6.58; mol wt, 338.

1'-Hydroxyspiro[cyclohexane-1,2'-indan]-4-amine (26). The mesylate (5.0 g, 0.015 mol) was converted to the azide and this reduced ($LiAlH_4$) exactly as above. The product was recrystallized from a small amount of EtOAc to afford 1.71 g (53%) of amino alcohol, mp 156–160°; the analytical sample melted at 158–161°.

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 76.98; H, 8.79; N, 6.41. Ir 3340, 3270, 2710, 1600, 1035, 770, 750, and 720 cm^{-1}.

4'-Fluoro-4-[(1'-hydroxyspiro[cyclohexane-1,2'-indan]-4-yl)amino]butyrophenone Hydrochloride. The amino alcohol (1.71 g, 0.0079 mol) was alkylated with the neopentyl glycol acetal of 4-chloro-*p*-fluorobutyrophenone as above. There was obtained 1.03 g (33%) of product, mp 190–193°.

Anal. Calcd for $C_{24}H_{29}ClFNO_2$: C, 68.97; H, 6.99; N, 3.35. Found: C, 69.37; H, 7.77; H, 3.11.

1'-Hydroxy-1'-methylspiro[cyclohexane-1,2'-indan]-4-one Cyclic Ethylene Acetal (28). A solution of 5.0 g (0.019 mol) of the ketone in 60 ml of THF was added to 67 ml of 3 *M* CH_3MgBr in Et_2O. Following 17 hr standing at room temperature, the mixture was cooled in ice and treated cautiously with 50 ml of saturated NH_4Cl. The organic layer was separated, diluted with C_6H_6, and washed in turn with H_2O and brine. The solid which remained when the solution was taken to dryness was recrystallized from CH_2Cl_2–cyclohexane to give 3.70 g (71%) of product: mp 140–143°; NMR δ 1.48 (s, 3, CH_3), 1.78 (m, 8, CH_2), 2.95 (d, 2, $ArCH_2$), 4.0 (s, 4, ketal), 7.4 (m, 4, ArH); ir 3490, 1215, 1115, 1095, and 775 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.47; H, 8.08. Found: C, 74.21; H, 8.09.

1'-*exo*-Methylenespiro[cyclohexane-1,2'-indan]-4-one (29). A solution of 9.82 g (0.036 mol) of the acetal and 25 ml of 2.5 *N* HCl in 250 ml of Me_2CO was stirred at room temperature overnight. The solvent was then removed under vacuum and the residue dissolved in Et_2O and H_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residue was recrystallized from petroleum ether to give 5.12 g (67%) of solid: mp 60–62°; NMR δ 2.18 (A_2B_2, 8, CH_2), 3.17 (s, 2, $ArCH_2$), 4.88 (s, 1, vinyl), 5.42 (s, 1, vinyl), 7.28 (m, 4, ArH).

Anal. Calcd for $C_{15}H_{16}O$: C, 84.86; H, 7.60. Found: C, 84.46; H, 7.97.

1'-*exo*-Methylenespiro[cyclohexane-1,2'-indan]-3-ol (30). A mixture of 2.17 g (0.010 mol) of the ketone and 0.75 g of $NaBH_4$ in 40 ml of *i*-PrOH was stirred at room temperature for 6 hr. The solvent was removed under vacuum and the residue dissolved in H_2O and Et_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residue was chromatographed on 250 ml of silica gel (elution with 20% Me_2CO–SSB). There was obtained first 0.08 g of solid: mp 65–69°; NMR δ 1.84 (m, 8, CH_2), 2.90 (s, 2, $ArCH_2$), 4.10 (m, $W_{1/2}$ = 10 Hz, 1, CHOH), 5.10 (s, 1, vinyl), 5.50 (s, 1, vinyl), 7.28 (m, 4, ArH). This was followed by a gum which crystallized only in the presence of H_2O: 1.71 g (78%); mp 57–61°; NMR δ 1.72 (m, 8, CH_2), 2.90 (s, 2, $ArCH_2$), 3.70 (m, $W_{1/2}$ = 20 Hz, 1, CHOH), 4.92 (s, 1, vinyl), 5.50 (s, 1, vinyl), 7.22 (m, 4, ArH). No satisfactory analysis could be obtained for this material.

1'-*exo*-Methylenespiro[cyclohexane-1,2'-indan]-4-ol Methanesulfonate (31). The major alcohol (4.26 g, 0.020 mol) was converted to the mesylate in the usual way. There was obtained 4.82 g (83%) of solid: mp 72–74°; ir 1350, 1335, 1175, 970, 935, 870, and 790 cm^{-1}.

Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.72; H, 6.89; mol wt, 292. Found: C, 65.32; H, 7.12; mol wt, 292.

1'-*exo*-Methylenespiro[cyclohexane-1,2'-indan]-4-amine Hydrochloride (32). The mesylate (5.65 g, 0.019 mol) was taken on to the amine via the azide as above. There was obtained 3.08 g (61%) of product: mp 250–253°; ir 3000, 1640, 1600, 1510, 875, 775, 735, and 720 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}ClN \cdot H_2O$: C, 67.29; H, 8.28; N, 5.23. Found: C, 67.50; H, 7.92; H, 5.21.

1'-exo-Methylenespiro[cyclohexane-1,2'-indan]piperidine (33). The amine prepared from 1.41 g (0.0056 mol) of the hydrochloride, 1.81 g of 1,5-diiodopentane, and 1.55 g of K_2CO_3 in 15 ml of EtOH was stirred at reflux for 18 hr. The mixture was allowed to cool and diluted with water and the solid was collected on a filter. This was recrystallized from MeOH to give 1.05 g (67%) of solid: mp 93–95°; ir 1630, 985, 865, 775, and 730 cm^{-1}.

Anal. Calcd for $C_{20}H_{27}N$: C, 85.35; H, 9.67; N, 4.90. Found: C, 85.58; H, 9.99; N, 5.24.

4'-Fluoro-4-[(1'-methylenespiro[cyclohexane-1,2'-indan]-4-yl)amino]butyrophenone Hydrochloride (34). The amine hydrochloride (2.0 g, 0.0080 mol) was converted to the butyrophenone as above. There was obtained 0.95 g (29%) of product: mp 208–211°; ir 2780, 1680, 1600, 1230, and 735 cm^{-1}.

Anal. Calcd for $C_{25}H_{29}ClFNO$: C, 72.53; H, 7.06; N, 3.38. Found: C, 72.20; H, 7.19; N, 3.68.

3'-Nitrospiro[cyclohexane-1,2'-indan]-4-one (35). To an ice-

cooled solution of 9.04 g (0.045 mol) of the ketone in 45 ml of TFA there was added 9 ml of HNO_3. At the end of 2 hr reaction in the cold, the solution was poured onto ice–H_2O. The precipitated solid was chromatographed on 1 l. of silica gel (elution with 25% Me_2CO–SSB). The crystalline fractions were combined and recrystallized from Me_2CO–SSB. There was obtained 7.23 g (65%) of product, mp 124–128°. The analytical sample melted at 126–127.5°; ir 1710, 1515, 1345, 1330, 825, and 740 cm^{-1}.

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.38; H, 6.24; N, 5.95.

3'-Acetamidospiro[cyclohexane-1,2'-indan]-4-one (37). A suspension of 0.50 g of 10% Pd/C in a solution of 7.89 g (0.032 mol) of nitro ketone in 150 ml of EtOAc was shaken under H_2. At the end of 3 hr an additional 0.50 g of catalyst was added and shaking resumed. When the theoretical uptake had been observed the catalyst was removed by filtration and a solution of 6.1 g of *p*-TSA in a small amount of MeOH added. The solvent was removed under vacuum and an attempt made to recrystallize the residue from MeOH–Me_2CO. On standing in the cold over the weekend extensive decomposition occurred. The material was then reconverted to the free base. A solution of this in 40 ml of pyridine was treated with 10 ml of Ac_2O. At the end of 5 hr the mixture was poured onto ice–H_2O. The precipitate was extracted with CH_2Cl_2. This solution was washed with H_2O, 2.5 *N* HCl, H_2O, and brine and taken to dryness. The residue was chromatographed on 700 ml of silica gel (elution with 25% Me_2CO–CH_2Cl_2). The crystalline fractions were combined and recrystallized from MeOH. There was obtained 3.15 g (38%) of product: mp 169–171°; ir 3340, 1695, 1680, 1600, 1540, 1490, and 1290 cm^{-1}.

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44; mol wt, 257. Found: C, 74.36; H, 7.54; N, 5.48; mol wt, 257.

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Registry No.—**3**, 26845-47-6; **4a**, 56868-10-1; **4b**, 56868-11-2; **6a**, 56868-12-3; **6b**, 56868-13-4; **7a**, 56868-14-5; **7b**, 56868-15-6; **8a**, 56908-37-3; **8b**, 56868-16-7; **9a**, 56868-17-8; **9b**, 56868-18-9; **10**, 56868-19-0; **11**, 56868-20-3; **12a**, 56868-21-4; **12b**, 56868-22-5; **13a**, 56868-23-6; **13b**, 56868-24-7; **14a**, 56868-25-8; **14b**, 56868-26-9; **15a**, 56868-27-0; **15b**, 56858-28-1; **16a**, 56868-29-2; **16b**, 56868-30-5; **17a**, 56868-31-6; **17b**, 56908-38-4; **18a**, 56868-32-7; **18b**, 56868-33-8; **19a**, 56868-34-9; **19b**, 56868-35-0; **20**, 56868-37-2; **21**, 56868-38-3; **23**, 56868-39-4; **25**, 56868-40-7; **26**, 56868-41-8; **27**, 56868-42-9; **28**, 56868-43-0; **29**, 56868-44-1; **30**, 56868-45-2; **31**, 56868-46-3; **32**, 56868-47-4; **33**, 56868-48-5; **34**, 56868-36-1; **35**, 56868-49-6; **37**, 56868-50-9; 4-carbomethoxycyclohexanone, 6297-22-9; ethylene glycol, 107-21-1; *m*-methoxybenzyl chloride, 824-98-6; 4-chloro-*p*-fluorobutyrophenone 2,2-dimethylpropylene acetal, 36714-65-5; carbonochloridic acid ethyl ester, 541-41-3.

References and Notes

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(4) See, for example, J. J. Eisch, *J. Org. Chem.*, **28**, 707 (1962).
(5) P. A. J. Janssen, C. J. E. Niemegeers, and K. L. H. Schellekens, *Arzneim.-Forsch.*, **15**, 104 (1965).
(6) Applying the same argument as in the case of the exo-methylene compound **29** would suggest that the two oxygen atoms in **24** occupy an anti relationship.
(7) All melting points are uncorrected and recorded as observed on a Thomas-Hoover capillary melting point apparatus. NMR spectra were determined in deuteriochloroform on a Varian A-60D NMR spectrometer. Infrared spectra were obtained on either a Perkin-Elmer Model 421 or on a Digilab Model 14D spectrophotometer. Solids were prepared as mineral oil mulls while liquids were prepared neat between sodium chloride plates. Mass spectra were obtained with an Atlas MAT CH4 instrument. The authors are indebted to the Department of Physical and Analytical Chemistry of The Upjohn Co. for elemental analyses.
(8) A petroleum fraction, bp 60–70°, sold by the Skelly Oil Co.

Benzospirans Bearing Basic Substitution. II. Amines Derived from 3',4'-Dihydrospiro[cyclohexane-1,2'(1'*H*)-naphthalen]-4-one and 3',4'-Dihydro[cyclohexane-1,1'(2'*H*)-naphthalen]-4-one

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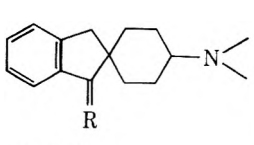
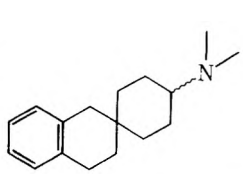
The cyclic ethylene acetal of 4-benzyl-4-carbethoxycyclohexan-1-one was homologated to the corresponding acetic acid via the nitrile. Removal of the acetal followed by cyclization gave spiro[cyclohexane-1,2'(1'*H*)-naphthalene]-4,4'(3'*H*)-dione. Taking advantage of the differing reactivities of the two carbonyl groups that compound was converted in several steps to 3',4'-dihydrospiro[cyclohexane-1,2'(1'*H*)-naphthalen]-4-one. The two isomeric amines were prepared from the ketone. The configuration of these products was assigned the basis of NMR. Double homologation via Wittig reaction on 4-oxo-1-phenylcyclohexanecarboxaldehyde 4-cyclic ethylene acetal followed by reduction gave the corresponding propionic acid. This was taken in a series of steps analogous to those above to 3',4'-dihydrospiro[cyclohexane-1,1'(2'*H*)-naphthalen]-4-one. The ketone was converted to the corresponding amine via the mesylate. The configuration of these amines is discussed as well.

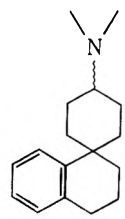
The subtle stereochemical effects observed in the course of the preparation of the spirocyclohexylindans (**1**),[1] particularly when those compounds bore substitution on the benzylic carbon (**2**), encouraged us to examine the corresponding spirocyclohexyltetralins (**3, 4**).



1, R, H_2
2, R, CH_2; R, H, OH



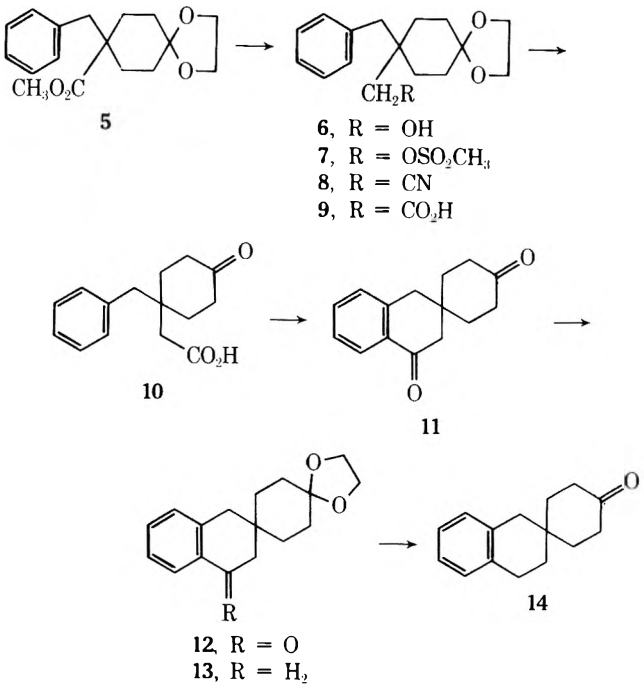
3



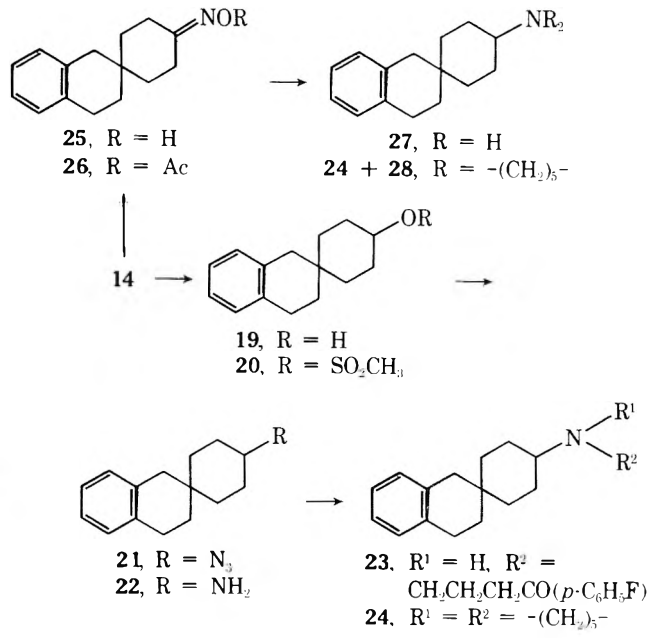
4

Derivatives of 3',4'-Dihydrospiro[cyclohexane-1,-2'(1'*H*)naphthalen]-4-one. Preparation of the spiran containing the cyclohexyl group attached to the 2 position of the tetralin **3** is rendered easier by the fact that this carbon skeleton differs from that of **1**, which we had prepared earlier, only by the interposition of a methylene group. The first task thus consisted in the preparation of a homologue of the acid used to prepare the spiro indan (Scheme I). Reduction of the ester **5** used as source of the carbon skeleton in the earlier work by means of lithium aluminum hydride smoothly gave the corresponding alcohol **6**; this was converted to its methanesulfonate by conventional means. Initial attempts to effect displacement of the mesylate with cyanide ion under a variety of conditions bore evidence for

Scheme I



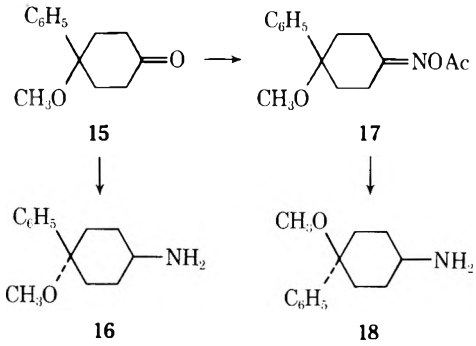
Scheme II



the highly hindered milieu of the reaction site. Starting material was thus recovered unchanged from treatment of **7** with potassium cyanide in DMF at 140°C. Simple substitution of hexamethylphosphoric triamide (HMPA) for DMF in this last reaction unexpectedly resulted in complete disappearance of starting material with the appearance of a single product. The oily nitrile **8** was isolated by chromatography; this material was saponified to the acid **9** without further characterization (potassium hydroxide in ethylene glycol). The high overall yield for the conversion of mesylate to acid (77%) attests to the efficacy of HMPA as solvent in this displacement. Removal of the ketal affords the desired homologated keto acid **10.**

Cyclization to the spiro diketone **11** was effected in workable yield by means of liquid hydrogen fluoride. The product was then converted to the monoketone **14** by first selective protection of the cyclohexanone as its ethylene ketal; reduction of the aromatic ketone by Wolff–Kishner reaction followed by deketalization afforded the desired product as an oil.

In earlier work on the preparation of cyclohexylamines containing geminal substituents at the 4 position we had developed stereoselective schemes for the preparation of the isomeric compounds.[2] Thus, conversion of cyclohexanone **15** to its oxime acetate followed by reduction with diborane afforded the isomer containing the cis amine and ether groups (**18**). Reduction of the ketone by means of sodium borohydride affords largely the alcohol with the same stereochemistry as the amine. This was then taken on to the epimeric amine **16** by conversion to the mesylate, inversion by displacement with azide, and finally reduction.



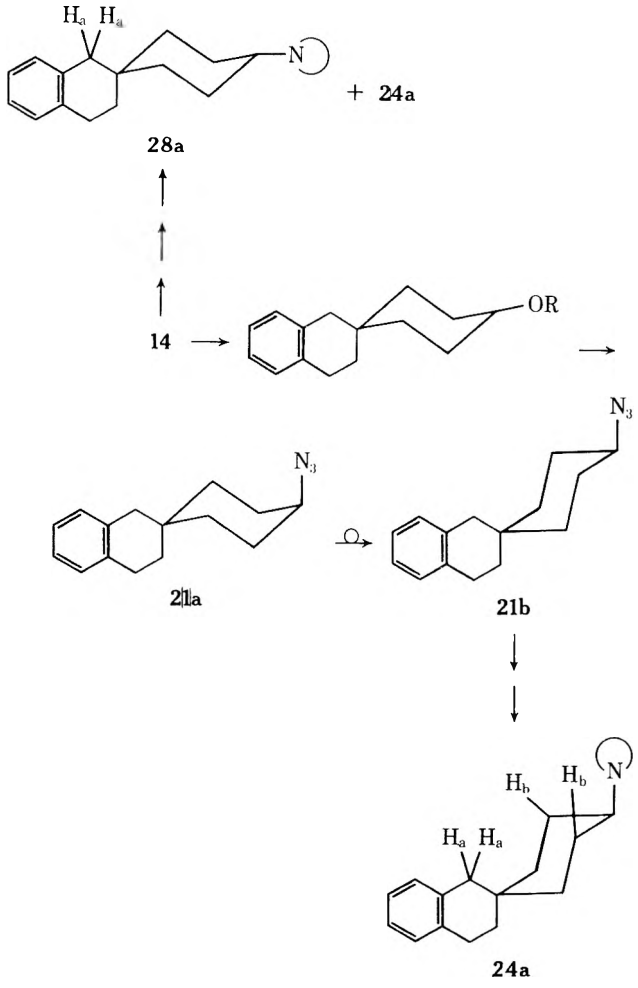
We thus anticipated that application of analogous schemes to ketone **14** would lead to the isomeric amines (Scheme II). Treatment of the spiro ketone with sodium borohydride followed by chromatography of the product afforded alcohol **19** as a crystalline solid. The NMR spectrum of this product showed the carbinyl proton as a broad band ($W_{1/2}$ = 15 Hz) centered at δ 3.55, suggestive of an equatorial hydroxyl group. This assignment must remain tentative in view of our failure to isolate any of the axial isomer for purpose of comparison. The mesylate **20** showed a similar signal in the NMR though now displaced to δ 4.7. Contrary to our expectations, the corresponding proton in the azide **21,** obtained by treatment of the mesylate with sodium azide, also seemed to have the equatorial configuration. The 100-MHz NMR spectrum of that compound resolved that band (δ 3.25) into a seven-line pattern characteristic of axial protons on cyclohexanes.[3] Setting this puzzle aside for the moment, the azide was reduced to the corresponding amine **22** by means of lithium aluminum hydride. Alkylation by means of the neopentyl glycol ketal of 4-chloro-*p*-fluorobutyrophenone followed by hydrolysis afforded the derivative **23.** Treatment of the primary amine with 1,5-diiodopentane afforded the corresponding piperidine **24,** mp 293°C; the 100-MHz NMR spectrum of this last again shows a signal for the proton on carbon bearing nitrogen (δ 2.25) with a multiplicity suggesting an axial hydrogen.

In the scheme intended to obtain the isomeric amine, the ketone **14** was converted to its oxime (**25**) in high yield. Acetylation (**26**) followed by reduction of the total crude acetate by means of diborane in THF afforded on work-up a modest yield of a mixture of isomeric amines which resisted attempts at separation by conventional means. This mixture was thus converted to the corresponding piperidines by alkylation with 1,5-diiodopentane. Fractional crystallization of the hydrochloride salt afforded first a compound which proved identical with the piperidine, mp 293°C, obtained by the azide route (**24**). There was obtained in addition a second piperidine, mp 263°C, whose 100-MHz spectrum also showed a signal (δ 2.25) with multiplicity suggestive of an equatorial piperidine group.

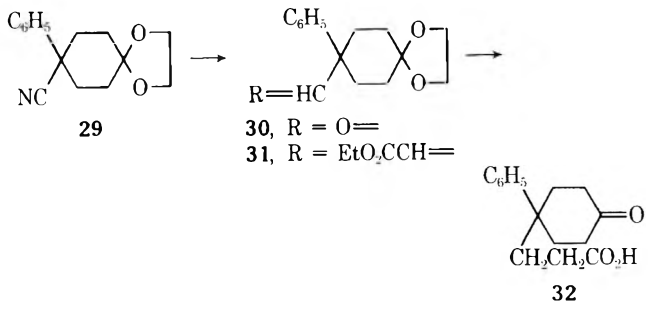
More detailed examination of the 100-MHz NMR spec-

tra of the isomeric piperidines shows the signal for protons on the one carbon benzyl bridge (H_a) in the high-melting isomer to occur as a singlet at δ 2.62; the signal for the corresponding protons in the low-melting isomer is observed as a singlet at δ 2.46. An examination of Dreiding models reveals that there exist two isomeric amines for the gross structure (**24, 28**) each of which carries the piperidine group in the equatorial position. Structure **24a** shows significant interaction between H_a and the axial protons on the 3 position of the cyclohexane (H_b); **28a** is free of this interaction. It has been recently shown that such steric compression is often expressed in a downfield shift for the signal of the affected protons.[4] On this basis it is thus possible to assign structure **24a** to that isomer which shows the lower field benzyl signal. Some confirmation for this assignment comes from the observation that H_a of **24** shows a barely significant downfield shift (0.05 ppm) displacement on treatment with $Eu(thd)_3$; the isomer **28** shows no effect whatever.

We rationalize these findings by the assumption that both the alcohol **19** and the mesylate **20** can be represented as equatorial isomers derived from the apparently preferred conformer of the spiran. Displacement by azide does indeed initially afford the inverted axial isomer **21a;** this then apparently undergoes a flip to the equatorial isomer **21b.** The remaining steps to **24a** do not affect the stereochemical outcome. Diborane reduction of the oxime acetate apparently affords both axial and equatorial isomers of the amine. The former can by a simple flip go to the amine **22;** the equatorial isomer goes on unchanged to the amine which affords finally the low-melting piperidine hydrochloride. No ready explanation occurs for the lack of stereoselectivity for the diborane reduction.[5]



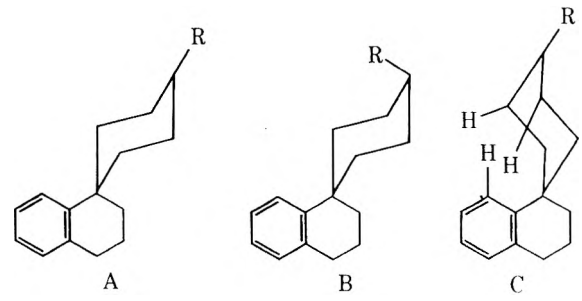
Scheme III



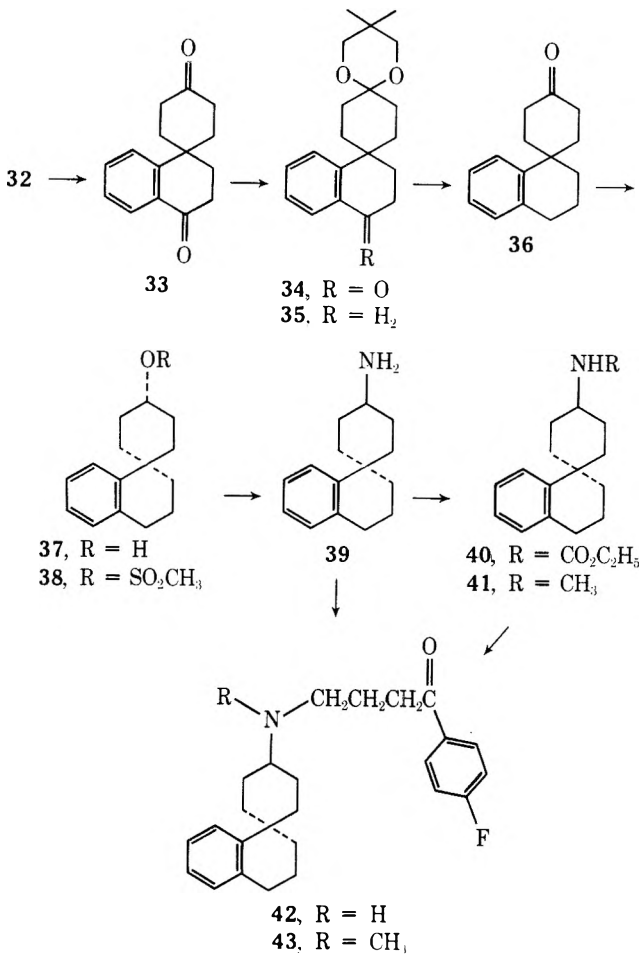
Derivatives of 3′,4′-Dihydrospiro[cyclohexane-1,-1′(2*H*′)-naphthalen]-4-one. The route chosen for the preparation of the remaining spirotetralincyclohexanone is conceptually quite similar to that described above. We required, however, a keto acid in which, at least in principle, a methylene group was transferred from the benzylic position to the acid side chain (Scheme III). Though announced quite some time ago,[6] the partial reduction of nitriles to aldehydes by means of lithium aluminum hydride has in fact only recently proven of synthetic value, and then mainly for highly hindered nitriles.[7] Thus treatment of the nitrile ketal **29**[8] with 0.5 molar equiv of that hydride at room temperature followed by carefully controlled hydrolysis of the intermediate imine afforded aldehyde **30** admixed with small amounts of starting material and amine. Though the aldehyde was isolated for characterization, in practice the crude product was used for further elaboration. Condensation of that crude aldehyde with the ylide obtained from triethyl phosphonoacetate (sodium hydride) afforded the acrilic ester **31** as an oil whose NMR spectrum suggested that this consisted of a single isomer of the desired product. This intermediate was then subjected in turn to catalytic reduction, saponification, and deketalization to give the desired keto acid **32** as a crystalline compound. The intermediates were all characterized by spectral means.

Cyclization of the keto acid **32** to the spiro diketone **33** was again accomplished by means of liquid hydrogen fluoride (Scheme IV). Treatment of that diketone with 1 equiv of neopentyl glycol under conditions for ketal formation resulted in selective reaction at the alicyclic ketone to afford **34** (ν_{max} 1680 cm^{-1}). This last was then converted to the monoketone **36** by first reduction under Wolff–Kishner conditions and the removal of the protecting group. Reduction of the ketone by means of sodium borohydride in this case afforded a mixture of the isomeric alcohols. The stereochemistry in this series can thus be assigned in relatively straightforward manner. Chromatographic separation gave first 6.0% of the axial alcohol (NMR δ 4.1, $W_{1/2}$ = 7 Hz) followed by 75.6% of the equatorial isomer (NMR δ 3.85, $W_{1/2}$ = 14 Hz).

Examination of Dreiding models reveals conformers A (and B) to be relatively free of nonbonding hydrogen–hydrogen interactions; conformer C, on the other hand, shows



Scheme IV



serious interaction between the proton on the peri position of the teralin with the axial hydrogens at the 3 position of the cyclohexane ring. These considerations lead us to assign the structure A (R = OH) to the major alcohol. The alcohol was then taken on to the amine **39** via its mesylate (**38**) and azide. The inversion which accompanies the displacement step will, of course, cause that amine and its derivatives to have the stereochemistry depicted by B. Even in the event that these compounds would undergo a flip interconversion of the type described above, the *relative* stereochemistry remains unchanged. The primary amine was then converted to its carbamate **40** by means of ethyl chloroformate; reduction of the urethane with lithium aluminum hydride afforded the *N*-methyl derivative **41**. Both the primary and secondary amines were then converted to the butyrophenone derivatives (**42, 43**) exactly as in the case of **22**.

Experimental Section[9]

4-Benzyl-4-hydroxymethylcyclohexan-1-one Cyclic Ethylene Acetal (6). A solution of 22.3 g (0.077 mol) of methyl 4-benzyl-4-carbomethoxycyclohexanone ethylene acetal in 220 ml of THF was added to 3.0 g of $LiAlH_4$ in 30 ml of THF. The mixture was stirred at reflux for 5.5 hr and then cooled in ice. There was added in turn 3 ml of H_2O, 3 ml of 15% NaOH, and 9 ml of H_2O. The inorganic gel was collected on a filter and the filtrate taken to dryness. The residue was recrystallized from CH_2Cl_2–Skellysolve B (SSB) to give 18.8 g (93%) of the alcohol: mp 76–78°; NMR δ 1.6 (m, 8, CH_2), 2.68 (s, 2, $ArCH_2$), 3.32 (d, J = 5 Hz, 2, CHOH), 3.90 (s, 4, ketal), 7.25 (s, 5, ArH).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: 73.08; H, 8.65.

4-Benzyl-4-hydroxymethylcyclohexan-1-one Cyclic Ethylene Acetal Methanesulfonate (7). To an ice-cold solution of 18.8 g (0.072 mol) of the alcohol in 100 ml of pyridine there was added 19 ml of CH_3SO_2Cl. Following 5.5 hr of standing in the cold, the mixture was poured onto ice–H_2O. The precipitated gum was extracted with Et_2O. The organic layer was washed with H_2O, ice-cold 2.5 *N* HCl, H_2O, saturated $NaHCO_3$, and brine. The residual solid was recrystallized from CH_2Cl_2–SSB to give 21.1 g (86%) of mesylate: mp 94–97°; NMR δ 1.60 (m, 8, CH_2), 2.68 (s, 2, $ArCH_2$), 2.95 (s, 3, SO_2CH_3), 2.83 (s, 2, $-CH_2OSO_2$), 2.85 (s, 4, ketal), 7.20 (s, 5, ArH).

Anal. Calcd for $C_{17}H_{24}O_5S$: C, 59.97; H, 7.11. Found: C, 60.00; H, 7.17.

1-Benzyl-4-oxocyclohexaneacetic Acid Cyclic Ethylene Acetal (9). A mixture of 18.6 g (0.055 mol) of the mesylate and 18 g of KCN was heated in 200 ml of HMPA overnight in an oil bath at 145°. The resulting gel was then allowed to cool, diluted to 800 ml with H_2O, and extracted with C_6H_6. The organic layer was washed with H_2O and brine and taken to dryness. The residue was chromatographed on 1 l. of silica gel (elution with 25% EtOAc in SSB). Those fractions which were similar by TLC were combined and heated overnight with 14.5 g of KOH in 105 ml of ethylene glycol. The mixture was then allowed to cool, diluted with H_2O, and washed once with Et_2O. The aqueous layer was then covered with Et_2O and cautiously acidified. The organic layer was separated, washed with brine, and taken to dryness. The residue was recrystallized from cyclohexane to give 12.3 g (77%) of acid, mp 116–118°. The analytical sample melted at 118–120°: NMR δ 1.65 (s, 8, CH_2), 2.26 (s, 2, CH_2CO_2H), 2.80 (s, 2, $ArCH_2$), 4.0 (s, 4, ketal), 7.31 (s, 5, ArH).

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.50; H, 7.83.

1-Benzyl-4-oxocyclohexaneacetic ACID (10). A solution of 12.3 g (0.042 mol) of the ketal and 18 ml of 2.5 *N* HCl in 180 ml of Me_2CO was stirred at room temperature for 62 hr. The bulk of the solvent was removed under vacuum and the residue dissolved in Et_2O and H_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residue was recrystallized from Et_2O–SSB to give 7.94 g (76%) of product: mp 85–87°; analytical sample, mp 91–92°; ir 1720, 1680, 1270, 1230, and 1175 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.01; H, 7.58.

Spiro[cyclohexane-1,2′(1′*H*)-naphthalene]-4,4′(3′*H*)-dione (11). Hydrogen fluoride (200 ml) was added from an inverted cylinder to 34.58 g (0.14 mol) of the keto acid. Following 48 hr standing at room temperature the residual syrup was poured into saturated aqueous $NaHCO_3$. Sufficient solid $NaHCO_3$ was then added to neutralize the mixture. The precipitated gum was extracted with methylene chloride. These extracts were washed in turn with water and brine and taken to dryness. The residue was chromatographed over 4 l. of silica gel (elution with 20% acetone in SSB) to afford 19.19 g (60%) of product, mp 157–159°.

A small sample was recrystallized from acetone–SSB to afford diketone: mp 158–160°; NMR δ A_2B_2 pattern centered at 2.12 (8, cyclohexanone), 2.72 (s, 2, $ArCH_2$), 3.10 (s, 2, $COCH_2Ar$), 7.48 (m, 3, ArH), 8.05 (m, 1, ArH); ir 1710, 1675, 1595, 1285, and 775 cm^{-1}.

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06; mol wt, 228. Found: C, 78.69; H, 7.31; mol wt, 228.

Spiro[cyclohexane-1,2′(1′*H*)-naphthalene]-4,4′(3′*H*)-dione Cyclic 4-(Ethylene Acetal) (12). A mixture of 2.65 g (0.012 mol) of diketone, 0.72 g (0.65 ml) of ethylene glycol, and 0.20 g of *p*-TSA in 100 ml of C_6H_6 was heated at reflux under a Dean-Stark trap for 4.5 hr. The mixture was allowed to cool, washed with $NaHCO_3$ and brine, and taken to dryness. The residue was chromatographed on 300 ml of silica gel (elution with 25% EtOAc–SSB). The crystalline fractions were combined and recrystallized from Et_2O–SSB. There was obtained 2.20 g (70%) of monoketal: mp 90–91.5°; ir 1685, 1290, 1115, 1100, and 770 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.00; H, 7.66.

3′,4′-Dihydrospiro[cyclohexane-1,2′(1′*H*)-naphthalen]-4-one Cyclic Ethylene Acetal (13). A mixture of 2.20 g (0.0081 mol) of the ketone, 1.2 ml of $N_2H_4 \cdot H_2O$, and 1.6 g of KOH in 20 ml of ethylene glycol was heated at reflux for 1 hr. Solvent was then removed by distillation to bring the temperature to 200°, and reflux continued for 17 hr. The mixture was then poured into H_2O and this was extracted with Et_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residue was recrystallized from petroleum ether to give 1.86 g (88%) of product: mp 79–81°; NMR δ 2.60 (m, 10, CH_2), 2.62 (s, 2, $ArCH_2$), ~2.78 (m, 2, $ArCH_2CH_2$), 4.0 (s, 4, ketal), 7.08 (s, 4, ArH).

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.59. Found: C, 79.14; H, 8.72.

3',4'-Dihydrospiro[cyclohexane-1,2'(1'*H*)-naphthalen]-4-ol (19). A mixture of 1.86 g (0.0072 mol) of the ketal and 2 ml of 2.5 *N* HCl in 40 ml of Me_2CO was heated at reflux overnight. The bulk of the solvent was removed under vacuum and the residue dissolved in H_2O and Et_2O. The organic layer was washed with H_2O and brine and taken to dryness to afford the ketone as an oil whose NMR spectrum was in accord with the structure.

A solution of the residue in 50 ml of 95% *i*-PrOH was treated with 1.0 g of $NaBH_4$. At the end of 5 hr the solvent was removed under vacuum and the residue worked up as above. The crude product was chromatographed on 170 ml of silica gel (elution with CH_2Cl_2). There was obtained first 0.24 g of recovered ketal. The product fractions were combined and recrystallized from SSB to give 0.65 g (42%) of alcohol: mp 78–82°; NMR δ 1.5 (m, 10, CH_2), 2.6 (m, 4, $ArCH_2$), 3.56 (seven-line pattern, 1, CHOH), 7.0 (s, 4, ArH).

Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32; mol wt, 216. Found: C, 83.37; H, 9.43; mol wt, 216.

3',4'-Dihydrospiro[cyclohexane-1,2'(1'*H*)-naphthalen]-4-ol Methanesulfonate (20). To an ice-cold solution of 2.16 g (0.01 mol) of the alcohol in 10 ml of pyridine there was added 2 ml of CH_3SO_2Cl. Following 4 hr in the cold the mixture was poured onto ice–H_2O. The solid was collected on a filter and recrystallized from Et_2O–petroleum ether. There was obtained 2.52 g (86%) of mesylate: mp 66–69°; NMR δ 1.7 (m, 10, CH_2), 2.7 (m, 4, $ArCH_2$), 3.0 (s, 3, SO_2CH_3), 4.70 (seven-line pattern, 2, CHO), 7.05 (s, 4, Ar H).

Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.27; H, 7.53. Found: C, 65.38; H, 7.54.

3',4'-Dihydrospiro[cyclohexane-1,2'(1'*H*)-naphthalen]-4-amine Hydrochloride (22). A mixture of 2.52 g (0.0085 mol) of the mesylate and 2.5 g of NaN_3 in 25 ml of DMF was heated overnight in an oil bath at 90°. The solvent was then removed under vacuum and the residue taken up in H_2O and C_6H_6. The organic layer was washed with H_2O and brine and taken to dryness. A solution of the residue in 60 ml of THF was added to 0.35 g of $LiAlH_4$ in 10 ml of THF. Following 4 hr of stirring at room temperature, the mixture was cooled in ice and treated with 0.35 ml of H_2O, 0.35 ml of 15% NaOH, and 1.05 ml of H_2O. The inorganic gel was collected on a filter and the filtrate was taken to dryness. A solution of the residue in Et_2O was treated with 6 *N* HCl in Et_2O. The resulting solid was recrystallized from CH_2Cl_2–EtOAc to give 1.65 g (77%) of product: mp 208–211°; ir ca. 2950 br, 1615, 1495, 1035, and 760 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}ClN$: C, 71.75; H, 8.83; N, 5.58. Found: C, 71.52; H, 8.79; N, 5.54.

4'-Fluoro-4-[(3',4'-dihydrospiro[cyclohexane-1,2'(1'*H*)-naphthalen]-4-yl)amino]butyrophenone Hydrochloride (23). The free base from 1.65 g (0.0066 mol) of the amine hydrochloride, 1.34 g of KI, 2.06 g of K_2CO_3, and 1.90 g of the neopentyl glycol acetal of 4-chloro-*p*-fluorobutyrophenone in 35 ml of DMF was heated in an oil bath at 90°. At the end of 18 hr the bulk of the solvent was removed under vacuum. The residue was dissolved in C_6H_6 and H_2O. The organic layer was washed with H_2O and brine and taken to dryness.

A mixture of the residue and 10 ml of 2.5 *N* HCl in 20 ml of MeOH was stirred at room temperature for 4 hr. The MeOH was then removed under vacuum and the solid collected on a filter. This was recrystallized twice from CH_2Cl_2–EtOAc to afford 1.07 g (39%) of the butyrophenone: mp 182–184°; ir 2760, 1690, 1600, 1245, 1160, 835, and 755 cm^{-1}.

Anal. Calcd for $C_{25}H_{31}ClFNO$: C, 72.18; H, 7.51; N, 3.37; mol wt, 379. Found: C, 72.20; H, 7.53; N, 3.47; mol wt, 379.

(3',4'-Dihydrospiro[cyclohexane-1,2'(1'*H*)-naphthalen]-4-yl)piperidine Hydrochloride. Isomer A (24). A mixture of the free base prepared from 1.81 g (0.0072 mol) of the free base **22**, 2.34 g of 1,5-diiodopentane, and 2.0 g of potassium carbonate in 20 ml of ethanol was heated at reflux for 17 hr. The solvent was then removed under vacuum and the residue partitioned between water and ether. The organic layer was washed with water and brine and taken to dryness. The residue was dissolved in a small amount of ether and treated with excess 3 *N* ethereal hydrogen chloride. The precipitated solid was recrystallized twice from methanol–ethyl acetate to afford 0.78 g (34%) of product: mp 290–293°; ir 2640, 2500, 2420, 1495, 745, and 735 cm^{-1}.

Anal. Calcd for $C_{20}H_{30}ClN$: C, 75.08; H, 9.45; N, 4.38. Found: C, 75.07; H, 9.56; N, 4.23.

3',4'-Dihydrospiro[cyclohexane-1,2'(1'*H*)-naphthalen]-4-one Oxime (25). A mixture of 8.33 g (0.039 mol) of the ketone, 5.40 g of hydroxylamine hydrochloride, and 10.7 g of K_2CO_3 in 100 ml of methanol was heated at reflux for 6 hr. The solvent was then removed under vacuum and the residue partitioned between methylene chloride and water. The organic layer was washed with water and brine and taken to dryness. The residue was recrystallized from methylene chloride–Skellysolve B to give 8.52 g (95%) of product, mp 105–106.5°.

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.36; H, 8.31; N, 6.05.

(3',4'-Dihydrospiro[cyclohexane-1,2'(1'*H*)-naphthalen]-4-yl)amine Hydrochloride. Isomeric Mixture (27). To a solution of 2.50 g (0.011 mol) of the oxime in 12.5 ml of pyridine there was added 2.5 ml of acetic anhydride. At the end of 6 hr the solution was poured into ice water. The precipitated gum was extracted with ether and the organic layer washed in turn with water, 2.5 *N* hydrochloric acid, aqueous sodium bicarbonate, and brine. The extract was then taken to dryness to afford the product as a viscous gum whose NMR spectrum is in accord with the structure.

An ice-cold solution of the crude oxime acetate in 60 ml of THF was treated with 12 ml of *N*-diborane in THF. At the end of 6 hr there was added 1 ml of water; as soon as effervescence ceased, the bulk of the solvent was removed under vacuum. A mixture of the residue and a small amount of ether was stirred with 50 ml of 2.5 *N* hydrochloric acid for 17 hr, and then made strongly basic. The mixture was extracted with ether; the organic layer was washed with water and brine and taken to dryness. A solution of the residue in ether was treated with a solution of 2.2 g of *p*-toluenesulfonic acid in the same solvent. The gummy precipitate was recrystallized several times from methylene chloride–ethyl acetate to give 1.58 g (34%) of product, mp 203–207°.

Anal. Calcd for $C_{22}H_{29}NO_3S$: C, 68.19; H, 7.54; N, 3.62. Found: C, 67.81; H, 7.43; N, 3.39.

(3',4'-Dihydrospiro[cyclohexane-1,2'(1'*H*)-naphthalen]-4-yl)piperidine Hydrochloride (24, 28). A mixture of the free base from 1.58 g (0.0042 mol) of the tosylate, 1.36 g of 1,5-diiodopentane, and 1.16 g of potassium carbonate in 10 ml of ethanol was heated at reflux for 17 hr. The solvent was removed under vacuum and the residue partitioned between water and ether. The organic layer was washed with water and brine and taken to dryness. A solution of the residue in ether was treated with excess 3 *N* ethereal hydrogen chloride.

The precipitated solid was recrystallized twice from methanol–ethyl acetate to give 0.40 g (30%) of isomer A, mp 290–293°, mmp with authentic material 290–293°.

The solid which was obtained on taking the mother liquors to dryness was recrystallized several times from methylene chloride–ethyl acetate to give 0.37 g (28%) of isomer B: mp 260–263°; ir 2640, 2610, 2490, 2410, 1495, 1485, and 750 cm^{-1}; mmp with isomer A 255–258°.

Anal. Calcd for $C_{20}H_{30}ClN$: C, 75.08; H, 9.45; N, 4.38. Found: C, 75.02; H, 9.66; N, 4.71.

4-Oxo-1-phenylcyclohexanecarboxaldehyde Cyclic 4-(Ethylene Acetal) (30). To a suspension of 0.16 g (0.0041 mol) of $LiAlH_4$ in 10 ml of THF was added 2.0 g (0.0082 mol) of cyano ketal in 100 ml of THF over 15 min. The mixture was stirred at room temperature for 1.75 hr and cooled in an ice bath. There was added in turn 0.16 ml of H_2O, 0.16 ml of 15% NaOH, and 0.48 ml of H_2O. The inorganic gel was collected on a filter and rinsed with Et_2O and the combined filtrates taken to dryness.

The residue in 30 ml of THF and 3 ml of 2.5 *N* HCl was stirred at room temperature for 15 min, treated with 1.0 g of $NaHCO_3$, and taken to dryness under vacuum. Et_2O was added to the residue, and the organic fraction was separated and taken to dryness. This material proved suitable for use in the next step.

The residue was chromatographed on silica gel (elution with 1% EtOAc–CH_2Cl_2) and the more polar crystalline fractions combined to yield 0.87 g (86.4%) of aldehyde: mp 59–64°; ir 1710, 1110, 1030, 825, and 700 cm^{-1}.

The analytical sample melted at 68.5–71°.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.43; H, 7.56.

4-Oxo-1-phenylcyclohexanepropionic Acid (32). To a solution of 4.74 g (0.021 mol) of triethyl phosphonoacetate in 60 ml of THF was added 0.89 g of 57% NaH. Following 10 min stirring at room temperature there was added a solution of 5.20 g (0.021 mol) of the aldehyde in 60 ml of THF. The solution was stirred at reflux for 4 hr and at room temperature for 18 hr. The bulk of the solvent was removed under vacuum, and the residue was dissolved in Et_2O and H_2O. The organic fraction was washed with H_2O and brine

and taken to dryness. The residue was chromatographed over 700 ml of silica gel (elution with 1600 ml of SSB, then 4 l. of 5% Me_2CO–SSB). Those uv-absorbing fractions alike by TLC were combined to yield 6.38 g (96%) of acrylic ester as a gum.

A mixture of 6.38 g (0.020 mol) of the ester obtained above, 0.63 g of 10% Pd/C, and 150 ml of EtOAc was shaken under an atmosphere of H_2 until the theoretical amount was consumed. The catalyst was collected on a filter and the filtrate taken to dryness to yield 6.38 g (~100%) of product as an oil.

A solution of 6.38 g (0.020 mol) of the reduced product and 8.0 ml of 50% NaOH in 80 ml of MeOH was heated at reflux for 20 hr. The bulk of the MeOH was removed under vacuum, H_2O was added to the residue, and the latter was washed with Et_2O. The aqueous fraction was then made strongly acidic. The precipitated material was extracted with Et_2O and the combined extracts washed with brine and taken to dryness.

The residue was dissolved in 50 ml of Me_2CO and 5.0 ml of 2.5 *N* HCl and allowed to stand at room temperature for 48 hr. The solution was taken to near dryness under vacuum and the residue dissolved in H_2O and Et_2O. The organic fraction was washed with H_2O and brine and taken to dryness. The residue was recrystallized from CH_2Cl_2–SSB to yield 1.70 g (34.5%) of keto acid: mp 143–144.5°; ir 1708, 1698, 1230, and 780 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.04; H, 7.40.

Spiro[cyclohexane-1,1′(2′*H*)-naphthalene]-4,4′(3′*H*)-dione (33). HF (5.0 ml) was distilled onto 5.0 g (0.0203 mol) of the keto acid and the resulting solution allowed to stand at room temperature for 20 hr. The residue was dissolved in Et_2O, washed with H_2O, saturated aqueous $NaHCO_3$, and brine, and taken to dryness. The residue was recrystallized from Et_2O to give 1.13 g (28%) of spiro diketone: mp 145.5–148°; ir 1705, 1685, 1595, 1290, 1275, and 780 cm^{-1}.

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.23; H, 7.88. Found: C, 78.39; H, 7.18.

Spiro[cyclohexane-1,1′(2′*H*)-naphthalene]-4,4′(3′*H*)-dione 4-2,2-Dimethylpropylene Acetal (34). A solution of 3.19 g (0.014 mol) of the spiro diketone, 1.45 g (0.014 mol) of 2,2-dimethylpropanediol, and 0.06 g of *p*-TSA in 57 ml of benzene was heated at reflux under a Dean-Stark trap for 5.5 hr. The solution was washed with saturated aqueous $NaHCO_3$ and brine and taken to dryness. The residue was chromatographed over 400 ml of Florisil (elution with 7.5% EtOAc–SSB). The crystalline fractions were combined to yield 3.29 g (75%) of product, mp 136–138°. An analytical sample from an earlier run recrystallized from Et_2O–SSB melted at 138.5–142°; ir 1690, 1295, 1115, 930, 870, and 780 cm^{-1}.

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.49; H, 8.38.

3′,4′-Dihydrospiro[cyclohexane-1,1′(2′*H*)-naphthalen]-4-one 2,2′-Dimethylpropylene Acetal (35). A solution of 3.63 g (0.0115 mol) of ketone, 1.54 ml of hydrazine hydrate, and 2.23 g of KOH in 28 ml of ethylene glycol was heated at reflux. Distillate was collected until the pot temperature rose to 200° and reflux was continued for 18 hr. The mixture was poured into H_2O and a precipitated material extracted with Et_2O. The combined extracts were washed with H_2O and brine and taken to dryness. The residue was recrystallized from petroleum ether to yield 2.39 g (69.5%) of product: mp 109–111°; ir 1110, 1020, 910, 860, 760, and 755 cm^{-1}.

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.95; H, 9.51.

3′,4′-Dihydrospiro[cyclohexane-1,1′(2′*H*)-naphthalen]-4-one (36). A mixture of 2.39 g (0.008 mol) of ketal and 2.4 ml of 2.5 *N* HCl in 24 ml of Me_2CO was stirred at room temperature for 6 hr. H_2O (15 ml) was added and the bulk of the Me_2CO was removed under vacuum. Et_2O was added to the residue, and the organic fraction was washed with H_2O, saturated aqueous $NaHCO_3$, and brine and taken to dryness. The residue was recrystallized from petroleum ether to yield 1.19 g (70%) of ketone, mp 115–120°. An analytical sample from a previous run melted at 120.5–123°; ir 1710, 1495, 1160, 765, and 735 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.83; H, 8.48.

3′,4′-Dihydrospiro[cyclohexane-1,1′(2′*H*)-naphthalen]-4-ol (37). To a partial solution of 5.10 g (0.024 mol) of ketone in 105 ml of 95% EtOH was added 2.59 g of $NaBH_4$ and the mixture was stirred at room temperature for 4 hr. The bulk of the solvent was removed under vacuum and H_2O added to the residue. A precipitated material was extracted with Et_2O and the combined extracts washed with H_2O and brine and taken to dryness. The residue was recrystallized once from SSB and then chromatographed over 500 ml of silica gel (elution with 10% Me_2CO–SSB). On the basis of TLC the less polar fractions were combined and recrystallized from C_6H_6–cyclohexane to give 0.31 g (6.0%) of product: mp 144.5–146°; NMR δ 4.1 (*m*, $W_{1/2}$ = 7 Hz, 1, CHOH).

Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.53; H, 9.61.

On the basis of melting point the polar fractions were combined and recrystallized from SSB to give 3.89 g (74.9%) of product: mp 80–83°; NMR δ 3.85 (m, $W_{1/2}$ = 12 Hz, 1, CHOH).

Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.47; H, 9.55.

3′,4′-Dihydrospiro[cyclohexane-1,1′(2′*H*)-naphthalen]-4-ol Methanesulfonate (38). To an ice-cooled solution of 3.89 g (0.018 mol) of the alcohol in 40 ml of pyridine was added 4.0 ml of methanesulfonyl chloride. The mixture was allowed to stand in the cold for 6 hr and then diluted with H_2O. A precipitated material was extracted with Et_2O and the combined extracts washed with ice-cold 2.5 *N* HCl, H_2O, saturated aqueous $NaHCO_3$, and brine and taken to dryness. The residue was recrystallized from cyclohexane to yield 5.0 g (94.3%) of mesylate: mp 118–120°; ir 1345, 1170, 980, 935, 865, and 760 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.27; H, 7.53; S, 10.89. Found: C, 65.17; H, 7.61; S, 10.70.

3′,4′-Dihydrospiro[cyclohexane-1,1′(2′*H*)-naphthalen]-4-ylamine Hydrochloride (39). A mixture of 5.0 g (0.017 mol) of the mesylate and 5.0 g of NaN_3 in 50 ml of DMF was heated in an oil bath at 90° for 20 hr. The bulk of the solvent was removed at vacuum pump pressure and the residue dissolved in H_2O and C_6H_6. The organic fraction was washed with H_2O and brine and taken to dryness to yield the crude azide as an oil.

A solution of the above in 75 ml of THF was added to a suspension of 0.65 g of $LiAlH_4$ in 8 ml of THF, stirred at room temperature for 5.5 hr, and cooled in an ice bath. There was added in turn 0.65 ml of H_2O, 0.65 ml of 15% NaOH, and 1.95 ml of H_2O. The resulting gel was collected on a filter and washed with Et_2O, and filtrates were taken to dryness. The residue was dissolved in a small amount of Et_2O and an excess of 6.4 *N* HCl in Et_2O added. The precipitate was collected on a filter and recrystallized from MeOH–EtOAc to yield 1.76 g (40.5%) of amine salt: mp 271–273°; ir 3000, 1590, 1505, 1490, 755, and 725 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}ClN \cdot \frac{1}{4}H_2O$: C, 70.29; H, 8.85; N, 5.47. Found: C, 70.48; H, 8.78; N, 5.55.

Ethyl Spiro[cyclohexane-1,1′(2′*H*)-naphthalene]-4-carbamate (40). To an ice-cooled solution of the amine free base [prepared from 1.53 g (6.1 mmol) of the amine salt] in 12 ml of pyridine was added 0.95 ml of ethyl chloroformate. The mixture stood in the cold for 5 hr and then was poured into ice–H_2O. A solid precipitate was collected on a filter and recrystallized from CH_2Cl_2–C_6H_{12} to yield 1.36 g (77.7%) of the carbamate: mp 163.5–165°; ir 3270, 1695, 1335, 1090, and 760 cm^{-1}.

Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: 74.91; H, 8.77; N, 4.83.

3′,4′-Dihydrospiro[cyclohexane-1,1′(2′*H*)-naphthalen]-4-yl-*N*-methylamine Hydrochloride (41). To a suspension of 0.22 g (5.8 mmol) of $LiAlH_4$ in 10 ml of THF was added a solution of 1.30 g (4.5 mmol) of the carbamate. The mixture was stirred at reflux for 6 hr and at room temperature for 18 hr, and then cooled in an ice bath. There was added in turn 0.22 ml of H_2O, 0.22 ml of 15% NaOH, and 0.66 ml of H_2O. The resulting inorganic gel was collected on a filter and rinsed with Et_2O and the filtrates were taken to dryness. The residue was dissolved in a small amount of Et_2O and treated with an excess of 6.4 *N* HCl in Et_2O. The resulting precipitate was collected on a filter and recrystallized from MeOH–EtOAc to yield 0.81 g (52.7%) of the secondary amine, mp 285–286°.

Anal. Calcd for $C_{16}H_{24}ClN$: C, 72.29; H, 9.10; N, 5.25. Found: C, 72.60; H, 9.16; N, 5.35.

4′-Fluoro-4-(3′,4′-dihydrospiro[cyclohexane-1,1′(2′*H*)-naphthalen]-4-ylamino)butyrophenone Hydrochloride (42). A mixture of the free base [prepared from 1.0 g (3.97 mmol) of the amine salt], 0.81 g of KI, 1.24 g of K_2CO_3, and 1.14 g of 4-chloro-*p*-fluorobutyrophenone 2,2-dimethylpropylene acetal in 20 ml of DMF was heated together in an oil bath at 90° for 20 hr. The solvent was removed under vacuum and the residue dissolved in H_2O and C_6H_6. The organic layer was washed with H_2O and brine and taken to dryness.

A mixture of the residue, 8.0 ml of 2.5 *N* HCl, and 16 ml of

MeOH was stirred at room temperature for 2 hr and the bulk of the MeOH removed under vacuum. A residual suspended solid was collected on a filter, washed with Et_2O, and recrystallized from MeOH–EtOAc to give 0.65 g (39.5%) of the butyrophenone: mp 194–197°; ir 2760, 2720, 1685, 1600, 835, and 770 cm^{-1}.

Anal. Calcd for $C_{25}H_{31}ClFNO$: C, 72.18; H, 7.51; N, 3.37. Found: C, 72.42; H, 7.66; H, 3.14.

4'-Fluoro-4-(3',4'-dihydrospiro[cyclohexane-1,1'(2'*H*)-naphthalen]-4-yl-*N*-methylamino)butyrophenone Hydrochloride (43). A mixture of the amine free base [prepared from 0.81 g (3.06 mmol) of the amine salt], 0.63 g of KI, 0.96 g of K_2CO_3, and 0.87 g of 4-chloro-*p*-fluorobutyrophenone 2,2-dimethylpropylene acetal in 15 ml of DMF was heated together in an oil bath at 90° for 20 hr. The solvent was removed under vacuum and the residue dissolved in H_2O and C_6H_6. The organic layer was washed with H_2O and brine and taken to dryness.

A mixture of the residue, 6.0 ml of 2.5 *N* HCl, and 12 ml of MeOH was stirred at room temperature for 1.5 hr and the bulk of the MeOH was removed under vacuum. A residual suspended solid was collected on a filter, washed with Et_2O, and recrystallized from MeOH–EtOAc to yield 0.59 g (44.8%) of the butyrophenone: mp 204–205.5°; ir 2660, 1675, 1225, 1210, 1150, and 755 cm^{-1}.

Anal. Calcd for $C_{26}H_{33}ClFNO$: C, 72.62; H, 7.74; N, 3.26. Found: C, 72.69; H, 7.93; N, 3.03.

Registry No.—**5**, 56868-61-2; **6**, 56868-62-3; **7**, 56868-63-4; **9**, 56868-64-5; **10**, 56868-65-6; **11**, 56868-66-7; **12**, 56868-67-8; **13**, 56868-68-9; **19**, 56868-69-0; **20**, 56868-70-3; **22**, 56868-71-4; **23**, 56868-72-5; **24**, 56868-73-6; **25**, 56868-74-7; *cis*-**27** tosylate, 56868-76-9; *trans*-**27** tosylate, 56868-78-1; **28**, 56868-79-2; **29**, 51509-98-9; **30**, 56327-24-3; **32**, 2572-26-1; **33**, 56868-88-3; **34**, 56868-89-4; **35**, 56868-90-7; **36**, 56868-91-8; *cis*-**37**, 56868-80-5; *trans*-**37**, 56868-81-6; **38**, 56868-82-7; **39**, 56868-83-8; **40**, 56868-84-9; **41**, 56868-85-0; **42**, 56868-86-1; **43**, 56868-87-2; 4-chloro-*p*-fluorobutyrophenone neopentyl glycol acetal, 36714-65-5; 2,2-dimethylpropanediol, 126-30-7.

References and Notes

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Acid-Catalyzed Rearrangements of Polymethylnaphthalenes

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α,β-Methyl migrations were found to occur smoothly in trifluoroacetic acid in seven polymethylnaphthalenes with methyl substituents in peri positions and with at least one adjacent β position unsubstituted. For example, 1,2,3,4,5,8-Me_6-naphthalene gave the 1,2,3,4,5,7 isomer, which, in turn, gave the 1,2,3,4,6,7 isomer; 1,4,5,8-Me_4-naphthalene gave the 1,3,5,8 isomer, which further gave a mixture (10:1) of 1,3,5,7 and 1,4,6,7 isomers. In naphthalenes without peri position methyl groups, little rearrangement occurred but, instead, intermolecular methyl and hydride transfer took place at slow rates; e.g., 1,2,3,4-Me_4-naphthalene in CF_3COOH gave 1,2,3-Me_3- and a Me_5-naphthalene as well as 1,2,3,4-tetrahydro-5,6,7,8-Me_4-naphthalene; Me_8-naphthalene, though with peri position methyl groups, gave 1,2,3,4,5,6,7-Me_7- and 1,2,3,5,6,7-Me_6-naphthalene. The basicity of polymethylnaphthalenes, structures of naphthalenium ions, and methyl migrating forces were discussed in terms of peri dimethyl interaction. A kinetic study of the rates of rearrangement for seven naphthalenes showed that the rates do not always follow a first-order rate equation.

It has been well known that introduction of two bulky groups in the peri position of a naphthalene causes steric crowding (so-called peri interaction)[1] as most evident in the crystal structure of octamethyl- and octachloronaphthalene.[2] Hart and one of the authors (A.O.)[3] observed the formation of stable naphthalenium ions of octamethylnaphthalene and 1,2,3,4,5,8- and 1,2,3,4,5,6-hexamethylnaphthalene by NMR in trifluoroacetic acid (CF_3COOH), and suggested that the observed increase in basicity is characteristic of naphthalenes with methyl substituents in peri positions and that the primary force to increase the stability of carbocations must be the relief of steric strain in peri interaction. In the present study, we have found that a smooth migration of peri methyl groups can be induced from naphthalenium ions where the β position adjacent to the protonated peri position is unsubstituted. On the assumption that the peri interaction not only increases the basicity of a naphthalene but also accelerates the migration of peri substituents, we have carried out the experiments reported here in order to clarify the characteristics of this effect.

Protonation and rearrangements in carbocyclic systems promoted by the accompanying relief of steric strain have often been encountered.[4] Additionally, methyl migration in methylbenzenes as well as in mono- and dimethylnaphthalenes has been known to occur at a slow rate measurable only in such strong acids as $HF–BF_3$ or superacids.[5] Our work, however, found a significant difference in the ease of methyl migration between polymethylnaphthalenes with and without methyl substituents in peri positions; for example, the former naphthalenes undergo methyl rearrangement readily in such relatively weak acids as CF_3COOH or HCl, but the latter do not. It was also found even among peri-substituted naphthalenes that the rate of rearrangement depends markedly upon the number and position of methyl substituents. Therefore, with the purpose of reveal-

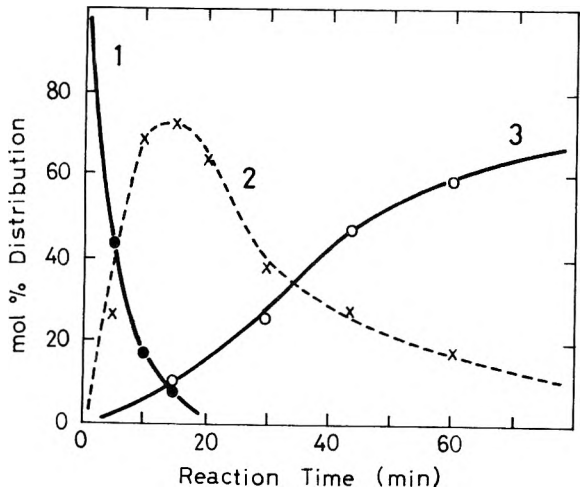


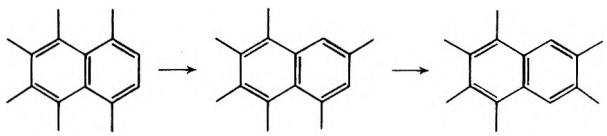
Figure 1. Rearrangement of 1,2,3,4,5,8-Me_6-naphthalene in CF_3COOH at 77°: **1**, 1,2,3,4,5,8-Me_6; **2**, 1,2,3,4,5,7-Me_6-; **3**, 1,2,3,4,6,7-Me_6-naphthalene.

ing the interrelationship between the existence of peri methyls and the substituent effect of other methyl groups, a kinetic study has been conducted.

The rearrangement reported here provides simple methods for the preparation of some polymethylnaphthalenes—1,2,3,4,5,7- and 1,2,3,4,6,7-Me_6-naphthalene, 1,2,3,4,6-Me_5-naphthalene, 1,3,5,8-, 1,3,5,7-, 1,4,6,7-, and 1,3,6,7-Me_4-naphthalene, and 1,7-Me_2-naphthalene—starting from those whose efficient preparative routes have been known.

Results

When 1,2,3,4,5,8-Me_6-naphthalene (**1**) was heated in boiling CF_3COOH (0.34 mol/l.) for 1 hr, 1,2,3,4,6,7-Me_6-naphthalene (**3**) was obtained (70%) as the final rearranged



product besides some by-products.[6] Analogous treatment at 25° gave an intervening isomer, 1,2,3,4,5,7-Me_6-naphthalene (**2**), which, isolated, proved to be the precursor of **3**. Figure 1 shows the change in naphthalene distribution in this rearrangement. Thus, the optimum preparation of **2** was attained (72%) in 15 min at 77°.

The composition of by-products was complex. It was found by GLC–mass spectroscopy that they consisted of three Me_5- (*m/e* 198) and two Me_7-naphthalenes (*m/e* 226), dihydro- and tetrahydro-Me_6-naphthalenes (*m/e* 214 and 216, respectively), and a polymeric product. Their formation, however, was suppressed by dilution. There are only two possible structures for Me_7 isomers, i.e., 1,2,3,4,5,6,7- (**19**) and 1,2,3,4,5,6,8-Me_7-naphthalene (**38**). As for Me_5 isomers, two of them were identified with **12** and 1,2,3,5,7-Me_5-naphthalene (**40**) by comparison with the authentic compound and the reported data.[7]

Other acidic media than CF_3COOH were also examined for the rearrangement (see Table I). Hydrogen chloride was found to induce the rearrangement with relatively low yields of by-products in acetic acid and more effectively by the addition of Lewis acid [$AlCl_3$, BF_3, $Zn(CN)_2$[8]]. However, they are still not so effective as CF_3COOH with regard to yields, reaction time, and simplicity of products.

1,4,5,8-Me_4-Naphthalene (**4**) gave 1,3,5,7 (**6**, 87%) and 1,4,6,7 (**7**, 8%) isomers as the final rearrangement products

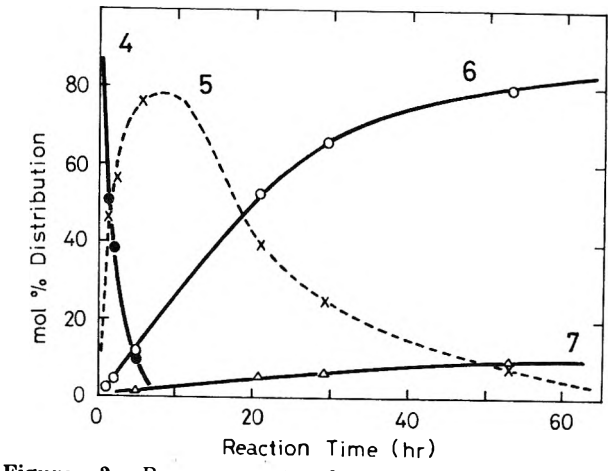


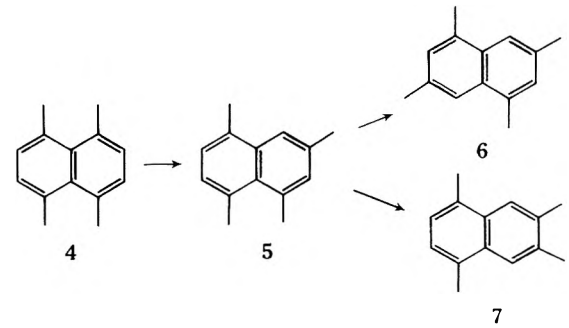
Figure 2. Rearrangement of 1,4,5,8-Me_4-naphthalene in CF_3COOH at 77°: **4**, 1,4,5,8-Me_4-; **5**, 1,3,5,8-Me_4-; **6**, 1,3,5,7-Me_4-; **7**, 1,4,6,7-Me_4-naphthalene.

Table I
Rearrangement of 1,2,3,4,5,8-Hexamethylnaphthalene in Various Acids (1.4 mmol/10 g acid)

Run	Acid	Temp, °C	Time, hr	Product ratio[c,d] 1	2	3
1	AcOH, HCl[a]	115	4	100	0	0
2	AcOH, HCl	115	4	75	25	0
3	AcOH, H_2SO_4 (10%)	115	1	15	82	3
4		115	2	0	75	25
5	AcOH, HCl, $AlCl_3$[b]	80	20	39	61	1
6	AcOH, HCl, BF_3·Et_2O[b]	80	20	56	44	0
7	Cl–AcOH	135	3	19	78	3
8	CF_3COOH	77	0.25	4	86	10
9		77	1	0	25	75

[a] HCl was passed through the solution at 115° in run 1, saturated at 0° and sealed in other runs. [b] Lewis acid; 0.86 mol/l. [c] Based on 1 + 2 + 3 = 100%, determined after removing polymeric products, which weighed 15–20% in runs 3 and 4, less than 5% in other runs. [d] 1, 1,2,3,4,5,8-Me_6-; 2, 1,2,3,4,5,7-Me_6-; 3, 1,2,3,4,6,7-Me_6-naphthalene.

after heating in CF_3COOH for 60 hr (0.42 mol/l.). A GLC analysis of the reaction proved that 1,3,5,8-Me_4-naphthalene (**5**), isolated, was an intervening precursor of both **6** and **7**. Although the rate was slower than that of **1**, the total



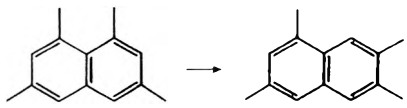
yield of **6** plus **7** was over 90% unless the reaction was carried out at high concentrations. Figure 2 shows the change in product distribution in this rearrangement and the optimum preparation of **5** (76%) was attained in 5 hr at 77°. The main by-products were two tetrahydro-Me_4-naphthalenes (*m/e* 188), three Me_3-naphthalenes (*m/e* 170), and a Me_5-naphthalene (*m/e* 198), as analyzed by GLC–mass spectroscopy.

Treatment of 1,3,6,8-Me_4-naphthalene (**8**) in boiling CF_3COOH (0.172 mol/l.) for 110 hr gave 1,3,6,7-Me_4-naphthalene (**9**) in 90% yield. Under the above conditions, fur-

Table II
Rates of Rearrangement of Polymethylnaphthalenes in CF_3COOH Calculated from the First-Order Rate Equation

Rearrangement[b]	$[A_0]$, mmol/l.	$k_1 \times 10^5$ sec^{-1} 40°	50°	60°	70°	E_a[a]	ln A
1 → 2	15.1	6.20	18.6	52.3	114	20.9	23.9
2 → 3	15.1	1.60	3.94	9.46	19.5	17.9	17.7
4 → 5	16.8	3.50	10.4	27.5	74.6	21.7	24.7
5 → 6	14.8	0.245	0.786	2.40	6.20	23.2	24.3
5 → 7	14.8	0.0205	0.0687	0.222	0.501	24.1	23.4
8 → 9	16.9			0.217			
10 → 11	96	0.0028	0.0102	0.0275	0.0718	22.1	22.7
12 → 13	84				3.20		
21 → 1,3-Me_2					$<10^{-4}$		

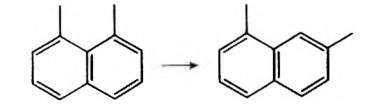
[a] ±0.2–0.5 kcal/mol. [b] 1, 1,2,3,4,5,8-Me_6-; 2, 1,2,3,4,5,7-Me_6-; 3, 1,2,3,4,6,7-Me_6-; 4, 1,4,5,8-Me_4-; 5, 1,3,5,8-Me_4-; 6, 1,3,5,7-Me_4-; 7, 1,4,6,7-Me_4-; 8, 1,3,6,8-Me_4-; 9, 1,3,6,7-Me_4-; 10, 1,8-Me_2-; 11, 1,7-Me_2-; 12, 1,2,3,4,5-Me_5-; 13, 1,2,3,4,6-Me_5-; 21, 1,4-Me_2-naphthalene.



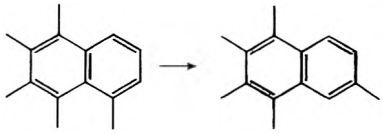
8 9

ther rearrangement of **9** did not occur but, instead, a trace amount of by-product (methyl disproportionation and reduction products) was formed (<2%).

Although at a very slow rate, 1,8-Me_2-naphthalene (**10**) rearranged into the 1,7 isomer (**11**) without forming by-products. Similarly, despite structural similarity to **1**, 1,2,3,4,5-Me_5-naphthalene (**12**) rearranged into the 1,2,3,4,6 isomer (**13**) more slowly than **1** or **4** (see Table II).



10 11

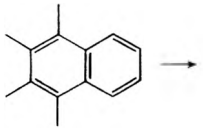


12 13

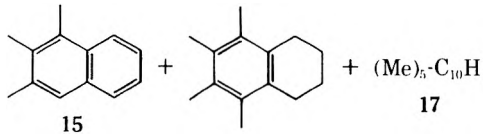
However, **13** was the only product not accompanied by an appreciable amount of by-products.

It was independently confirmed that the rearrangements mentioned above were irreversible processes.

In all the naphthalenes examined above, α,β-methyl migration was the main reaction. However, the formation of some anomalous products, though in low yields, necessitated the examination of such naphthalenes as 1,2,3,4-Me_4- (**14**) and Me_8-naphthalene (**18**). In **14**, essentially no rearrangement was observed as predicted from the lack of peri strain. However, treatment of **14** in boiling CF_3COOH over 1100 hr gave a mixture of 1,2,3-Me_3-naphthalene (**15**, 13%), 1,2,3,4-tetrahydro-5,6,7,8-Me_4-naphthalene (**16**, 4%), and a Me_5-naphthalene (**17**, 1%) besides unreacted **14** (80%).



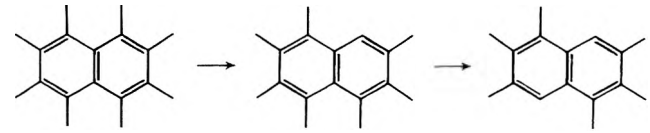
14



15 16 17

These products were isolated and their structures were determined by the comparison of their NMR and mass spectra and melting point of picrates with those reported.[9]

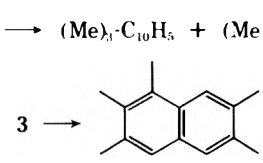
When a CF_3COOH solution of Me_8-naphthalene (**18**, 0.05 mol/l.) was heated for 72 hr, a Me_6-naphthalene (**20**, 20%) and a Me_7-naphthalene (**19**, 2%), whose precursory role to the formation of **20** was confirmed independently, were obtained besides unreacted **18** (38%) and polymeric



18 19 20

materials (40%). Both **19** and **20** were isolated and their structures determined as 1,2,3,4,5,6,7-Me_7- and 1,2,3,5,6,7-Me_6-naphthalene for **19** and **20**, respectively, by spectroscopy joined with a rational mechanistic account.[10]

Analogously, the main reaction of the following naphthalenes, none of which has any methyl substituents in peri positions, was the dealkylation. Thus, 1,4- (**21**, 0.254 mol/l.) and 2,3-Me_2-naphthalene (**22**, 0.190 mol/l.) in CF_3COOH produced a very small amount of Me_1-naphthalene (1- and 2-Me, respectively) in less than 0.1% yield after heating for 720 hr.[11] 1,4,6,7-Me_4- (**7**, 0.08 mol/l.) and 1,3,5,7-Me_4-naphthalene (**6**, 0.09 mol/l.), after heating for 720 hr, produced methyl disproportionation products (Me_3- and Me_5-naphthalenes, *m/e* 170 and 198, respectively) in relatively high yields (12.7% from **7**, 8% from **6**, and ratios Me_5/Me_3 slightly lower than unity in both cases). Similarly, **3** gave a Me_5-naphthalene (*m/e* 198, 4%). Its structure is assumed to be



1,2,3,6,7-Me_5, since it is not identical with **13** and the possibility of 1,2,4,6,7-Me_5 seems unlikely when compared with the result from **14**.

In order to estimate a quantitative character of peri dimethyl interaction as well as substituent effects of other methyl groups participating in the rearrangement, the rates of rearrangement of seven polymethylnaphthalenes, i.e., **1**, **2**, **4**, **5**, **8**, **10**, and **12**, were measured in CF_3COOH. All rearrangements were carried out in diluted solutions (<20 mmol/l.) to suppress the formation of by-products. In fact, **1**, which is most susceptible to side reactions, did not form an appreciable amount of by-products under this condition. Thus, neglecting side reactions, we assumed that

Table III
Rate Constants Recalculated from the Rate Equation $d[B]/dt = k_n[A]^n$ ($n < 1$)

Rearrangement[a]	Reaction order, n	$k_n \times 10^5$, (l./mol)$^{1-n}$ sec^{-1}				E_a, kcal/mol	ln A
		40°	50°	60°	70°		
2 → 3	0.82	0.866	1.85	4.08	8.17	15.8 ± 0.3	14.0
4 → 5	0.70	0.84	2.48	7.50	23.7	22.6 ± 0.5	24.5
5 → 6	0.86	0.132	0.437	1.31	3.04	21.3 ± 0.3	19.7
5 → 7	0.86	0.0111	0.0382	0.121	0.291	22.1 ± 1.5	20.8

[a] 2, 1,2,3,4,5,7-Me_6-; 3, 1,2,3,4,6,7-Me_6-; 4, 1,4,5,8-Me_4-; 5, 1,3,5,8-Me_4-; 6, 1,3,5,7-Me_4-; 7, 1,4,6,7-Me_4-naphthalene.

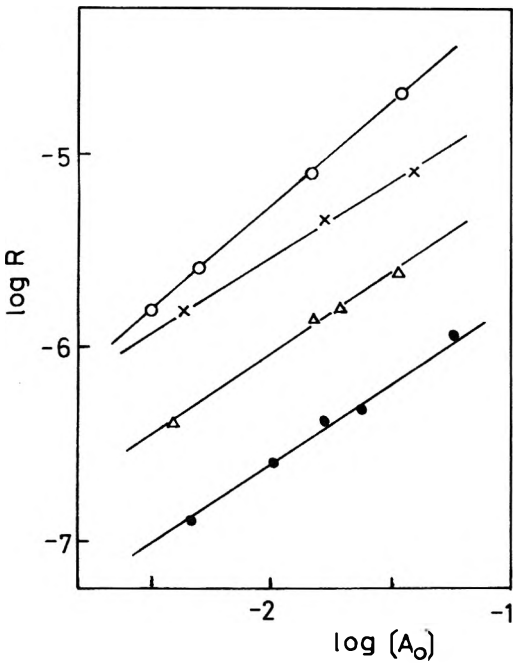


Figure 3. Plots of log R ($R = k_1[A_0]$) for the rearrangements of 1,2,3,4,5,8-Me_6- (○), 1,2,3,4,5,7-Me_6- (△), 1,4,5,8-Me_4- (×), and 1,3,5,8-Me_4-naphthalene (●) at 60° in CF_3COOH. $[A_0]$ is initial substrate concentration.

the total molar amount of substrates was unchanged throughout the treatment. Results are listed in Table II, where rate constants K_1 are calculated based on the first-order rate equation

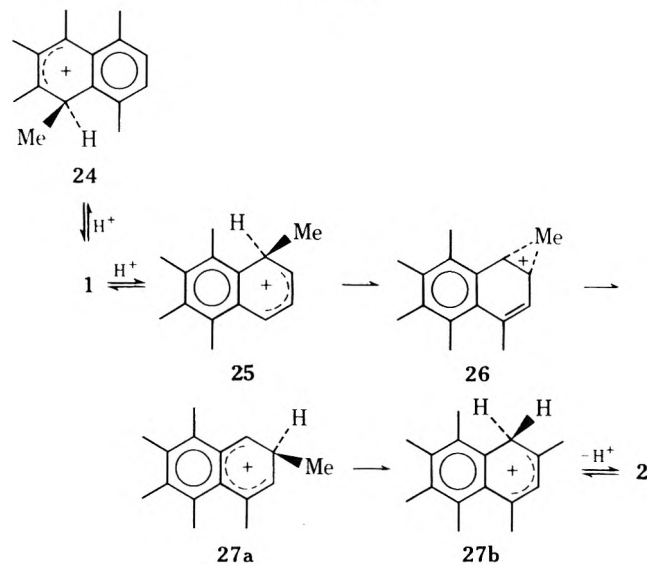
$$d[\text{product}]/dt = k_1[\text{starting naphthalene}] \quad (1)$$

However, careful examination of k_1 values at 60° resulting from changes in the initial substrate concentration showed that they were not constant in the cases of **2, 4, 5,** and 8, as long as they were calculated from eq 1. For example, as to the rearrangement of **2** → **3**, k_1 values were 1.08×10^{-4}, 7.37×10^{-5}, and 6.83×10^{-5} sec^{-1}, for 3.97×10^{-3}, 2.03×10^{-2}, and 3.40×10^{-2} mol/l. concentrations, respectively. In contrast, k_1 for **1** → **2** remained unchanged over various concentrations. Therefore, kinetic orders, n, were calculated for five rearrangements (**1** → **2**, **2** → **3**, **4** → **5**, **5** → **6**, **5** → **7**) according to the rate equation $R = d[B]/dt = k_n[A]^n$, for the reaction A → B. By plotting log R against log $[A_0]$ (see Figure 3), the n values were found: 1.05 ± 0.02 (**1** → **2**), 0.82 ± 0.07 (**2** → **3**), 0.70 ± 0.06 (**4** → **5**), 0.86 ± 0.05 (**5** → **6, 7**). The rearrangements, except **1** → **2**, seem to follow the equation where $n = 0.8$ on the average. The calculated rate constants k_n, which remained almost constant over various concentrations, are listed in Table III.

Discussion

Rearrangement. It has been known that the general-acid-catalyzed α,β-alkyl shifts in naphthalene systems are caused by protonation on an α position though the kinetically controlled first σ protonation may not necessarily be on the same α position but may be on the other unsubstituted position as indicated by the NMR study of methylarenes.[12,5] On the other hand, the first kinetically controlled σ protonation seems to occur on the substituted α position in such naphthalenes as **18**, **1**, and 1,2,3,4,5,6-Me_6-naphthalene (**50**) according to the NMR observation of their corresponding stable arenium ions, e.g., **24** from **1**.[3] However, the observed intramolecular rearrangement of **1** indicates that another naphthalenium ion, **25**, which alone can give rise to the formation of **2**, must be involved in the protonation equilibrium (Scheme I), although its stability must be relatively lower than that of **24**. The higher basicity of the peri carbons of **1** than that of other naphthalenes, such as **3**, which do not have any methyl substituents in peri positions, can reasonably be attributed to the strain release of peri interaction as the result of protonation.[13,14] Between the two peri positions in **1**, the basicity of C-1 (or C-4) is higher than that of C-5 (C-8), which is caused mainly by differences in hyperconjugative and inductive effects of methyl groups and, secondly, by differences in the extent of strain release between naphthalenium ions **24** and **25**.[15]

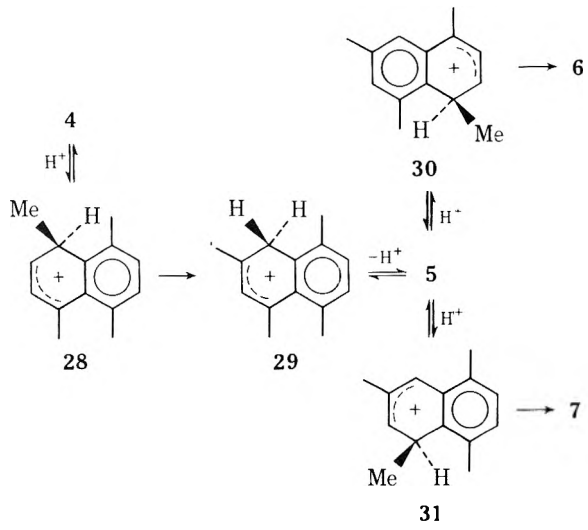
Scheme I



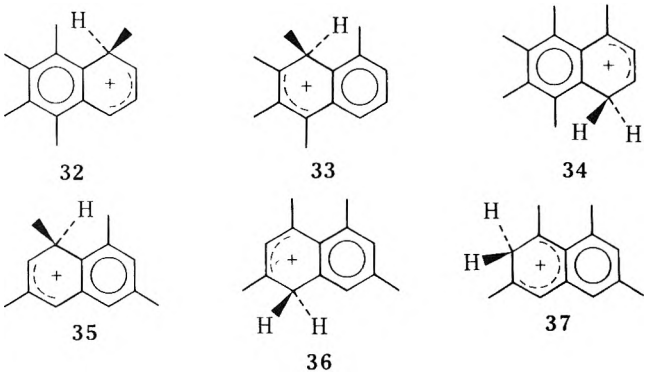
With this logic, protonation and rearrangement of **4** can be explained in terms of peri interaction. In the first step (Scheme II), naphthalenium ion **28** seems to be the sole protonated species but the basicity of **4** is not high enough to enable NMR observation of **28** in CF_3COOH. Protonation of **5** can take place on either C-1 or C-8. The predominant formation of **6** over **7** ($k_{5\to7}/k_{5\to6} = 0.105$) indicates that naphthalenium ion **30** predominates over the alternative **31**. This is because, though the peri interactions in both **30** and **31** are essentially the same, the basicity of C-8 is higher than that of C-1 because of the difference in the position of methyl substitution.

The unexpectedly slow rate of rearrangement of **12** indi-

Scheme II



cates another substituent effect. Naphthalenium ion **32**, which must be the rearrangement precursor but may not be as major a carbocation as **33** (or **34**), has no methyl group in



the C-8 position but four methyl groups on the A ring. If the A ring contributes significantly to delocalize the positive charge, then the rate would not be remarkably slower than that of **1**. However, the observed slow rate, even slower than that of **4**, implies that this is not the case and that the presence of methyl substituent in the para position to the reacting site, together with the peri interaction, is a requirement for increasing basicity. This is in accord with the reported effect for monomethylnaphthalenes.[12]

The rate of rearrangement of **8** was as slow as that of **5** → **7** owing to the structural similarity of **35** to **31**. Naphthalene **8** could also give rise to the formation of other ions **36** and **37** judging from the report of thermodynamically favored 2,4-dimethyl-1-hydronaphthalenium ion from **21**.[5] However, we have not yet obtained information enough to predict the priority among these three cations.

In relation to this argument, the apparent lack of migrating power in **6**, **7**, **9**, and **21** (their rates of rearrangement were more than 10^{-2} times slower than that of **10**) will partly enable us to differentiate carbocation stability and methyl migrating force: that is, the migrating force mainly derives from the strain release of peri interaction, and the carbocation stability from both the strain release and the electronic effects of methyl substitution.

On the above assumption as well as taking into account the positive charge being delocalized mainly in the protonated ring, the rate of **4** → **5** would be comparable to that of **1** → **2**. In fact, this speculation seems supported by the observation that the rate of **4** is slightly lower than that of **1** (see Table II). The slight difference in rate may be attributed to the difference in the way the unprotonated ring participates partially in sharing the positive charge. In addition, the difference can be explained by referring to the crystal structure of **18** where both α and β methyl (as well as ring carbons) are largely displaced from the mean plane.[2] Analogous to **18**, the strength of nonbonded peri interaction in **1** must be higher than in **4** where β positions are unsubstituted, and this difference in strain will be reflected in the basicity; and the secondary peri interaction which still remains around the protonated sp^3 carbon of naphthalenium ions[15] must be greater in **25** than in **28**, being reflected in the methyl migrating rate.

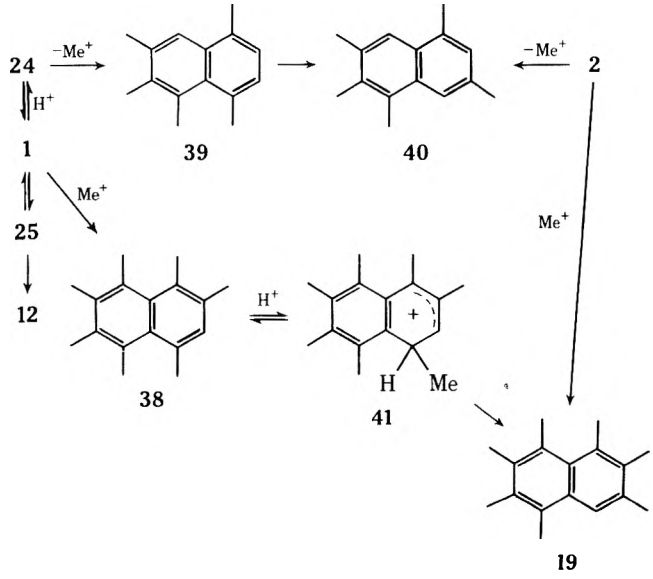
The formation of polymeric products was not negligible in **1**, **4**, and **18**, whose peri positions are all substituted by methyl groups, and was promoted by increasing the substrate concentration as well as by lowering the temperature. The sequence most rationally accounting for this intermolecular reaction with a low activation energy seems to involve the formation of ArH^+Ar complex[16] in which a pair of peri strains are relieved simultaneously without the molecule's undergoing the high energy rearrangement; and, consequently, a telomerization is induced.

Methyl Disproportionation and Reduction. As most typically illustrated by the behavior of 1,2,3,4-Me_4-naphthalene (**14**), polymethylnaphthalenes undergo methyl disproportionation (dealkylation and alkylation) and reduction. These side reactions became major for **21**, **6**, **7**, and **9** and the α,β-methyl migrations were negligible.

Intermolecular alkyl shifts for arenes have been widely reported[17,18] in the cases of *tert*-butyl, isopropyl, ethyl, and their homologues as the migrating groups, but the methyl group has been known to hardly migrate intermolecularly. Roberts proposed that the disproportionation of primary alkylarenes proceeds by the chain mechanism via benzyl-type carbocations.[19] This sequence, however, seems not applicable to the peri-substituted polymethylnaphthalenes and, instead, the methyl migration via ArH^+Ar complexes resulting in the strain relief seems most likely.[20] According to this sequence, α-methyl was eliminated much faster than β-methyl in **18** to give **19**, which in turn gave **20**.

The ratio of two heptamethylnaphthalenes formed from **1** was time dependent. In the light of the argument for the relief of peri strain, the increasing isomer must be **19**, which was identical with the product formed from **18**, and the decreasing isomer must be **38**. The formation of **12** indicates that naphthalenium ion **25** undergoes demethylation as well, and the formation of **40** suggests the existence

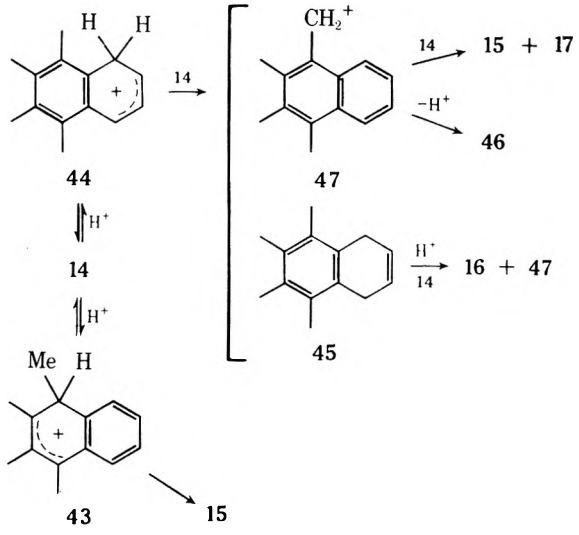
Scheme III



of its precursor **39** whose rate of rearrangement must be similar to that of **1** (see Scheme III).

The isolation of **16** from **14** as well as the detection of dihydro- and tetrahydronaphthalenes in the product mixture of **1**, **4**, and **18** demonstrates that the reduction of naphthalene nuclei took place almost with the same ease as the methyl disproportionation. Although some examples of the reduction of alkenes by the hydride transfer from alkylarenes have been known,[21] very few have been reported for the reduction of arene nuclei.[32] The reaction proceeds via the intermolecular hydride shift (Scheme IV) where methyl

Scheme IV

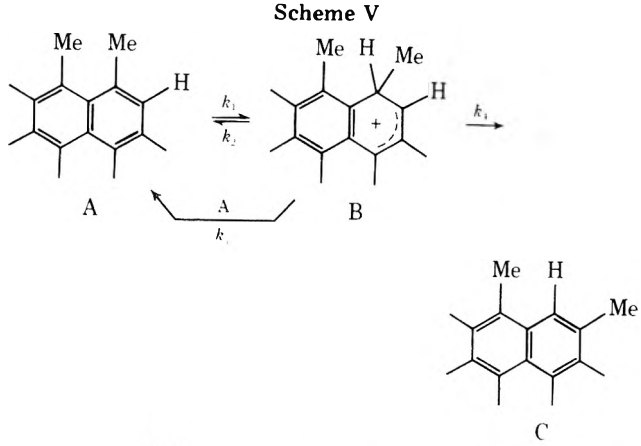


groups are the hydride donor, thus resulting in the formation of hydronaphthalenes and naphthylcarbinyl cation **47** (which can be the precursor of methyl disproportionation[19]). It is also interesting that **14** undergoes reduction preferentially on the ring that has no methyl substituent. Presumably, hydride transfer occurs through the ArH^+Ar complex where the sterically less crowded transition state may be favored.[16]

Kinetics. The rate of reaction for the present type of rearrangement, seemingly accountable in terms of an unimolecular protonation–deprotonation mechanism, is supposed to be proportional to the first order of substrate concentration. In order to interpret the smaller order of the reaction observed in the cases of **2**, **4**, and **5**, we postulate a sequence in which the basic naphthalene molecule participates in both the deprotonation (reversible) and irreversible side reactions (Scheme V); that is, the rate of deprotonation depends upon both first- and second-order terms of substrates as expressed in eq 2. Then, by the method of stationary state approximation, eq 3 is derived from eq 2 for the rate of formation of the product C. This equation obviously indicates that the observed rate constant depends on [A]; as [A] increases the apparent rate constant decreases and vice versa. Consequently, it can be re-formulated with approximation into eq 4. Thus, in the cases of **2**, **4**, and **5**, n appeared between 0.7 and 0.86 since [A] must be considerably higher than [B]. However, in **1**, n = 1.0, since [A] must be much lower than [B] or almost negligible owing to the extraordinarily higher basicity in C-1 positions, as evidenced by the NMR observation of **24** in CF_3COOH.[3]

Results in either Table II or III lead to the following sequence for decreasing rate of rearrangement: **1** > **4** > **2** > **5** → **6** > **12** > **5** → **7** > **10** > **21**. Since the rate depends not on the total basicity of a naphthalene molecule but mainly on the basicity of the peri carbon on which protonation can induce the rearrangement, we can estimate the factors necessary and/or facilitating the reaction: (a) existence of at least a pair of peri dimethyl substituents; (b) the position ortho to the protonated peri carbon being unsubstituted; (c) existence of a methyl group in the position para to the protonated site; (d) the unprotonated ring of a cation possessing many methyl groups. Usually, protonated species that satisfy the above conditions are not observed by NMR in CF_3COOH and a predominant species in a protonated equilibrium is not necessarily the one that causes rearrangements.

Scheme V



$$\frac{d[B]}{dt} = k_1[A] - (k_2 + k_4)[B] - k_3[A][B] \quad (2)$$

$$\frac{d[C]}{dt} = k_4[B] = \frac{k_1k_4}{k_2 + k_4 + k_3[A]}[A] \quad (3)$$

$$\frac{d[C]}{dt} = k_n[A]^n \ (n < 1) \quad (4)$$

Activation parameters, E_a and A, were obtained by fitting rate constants to the Arrhenius equation (Tables II and III). The average value of E_a (21–23 kcal/mol) is almost the same as that reported for methylbenzenium ions.[31] However, since the present calculation is based on the consumption and formation of naphthalenes but not on the concentration of arenium ions, the values for the methyl migration in ions would be lower than those in the tables.

Preparative Utilization. Although relatively easy preparations of C_2-symmetric polymethylnaphthalenes have been known,[22] the procedures hitherto known for unsymmetric homologues[23] seem troublesome. Instead, the present rearrangement can be used as a simple method to prepare such unsymmetrical polymethylnaphthalenes as **2**, **5**, **6**, **9**, and **13** from the corresponding isomers whose preparations are easy. The isolation and purification of products can be achieved by column chromatography and recrystallization.

Experimental Section

General. All melting points are uncorrected. Mass spectra were taken on a Hitachi Model RMU-6L spectrometer, which was connected to a Hitachi Model 063 gas chromatograph equipped with a single column of Apiezon Grease L, 5%, 3 mm × 4 m. NMR spectra (60 and 100 MHz) were recorded on either a Varian T-60A or a Jeol 4H-100 spectrometer in carbon tetrachloride solution, unless otherwise stated. All chemical shifts are given in τ units. Uv and ir spectra were taken on a Hitachi Model 124 and a Jasco Model IRA-I spectrometer, respectively.

Polymethylnaphthalenes. 1,2,3,4,5,8-Me_6- (**1**), 1,2,3,4,6,7-Me_6- (**3**), 1,2,3,4,5,6-Me_6- (**50**), 1,2,3,4,5-Me_5- (**12**), 1,2,3,4-Me_4- (**14**), and Me_8-naphthalene (**18**) were prepared from hexamethyl-2,4-cyclohexadienone (**53**)[24] and methylbenzynes according to the procedure reported.[22] 1,4,5,8-Me_4- (**4**), 1,4,6,7-Me_4- (**7**), and 1,4-Me_2-naphthalene (**21**) were prepared according to Mosby's procedure,[25] 1,3,6,8-Me_4-naphthalene (**8**) from 3,5-dimethylbenzyl bromide and diethyl allylmalonate,[26] and 1,8-Me_2-naphthalene (**10**) from

naphthalic anhydride.[27] Preparative procedures for **12** and **50** will be described in this section.

A General Procedure for the Rearrangement. Commercially available CF_3COOH of guaranteed grade with the same batch number was used in all treatments. A CF_3COOH solution of a polymethylnaphthalene was heated under solvent reflux (77°) for a certain period. After cooling, the reaction mixture was poured into an excess amount of cold 5% aqueous sodium carbonate and the precipitate separated was extracted with diethyl ether three times. The ethereal solution was again washed with aqueous sodium bicarbonate and then with water three times. After drying over anhydrous $MgSO_4$, ether was removed in vacuo and the residue was dissolved in cyclohexane and chromatographed through a silica gel column (Merck silica gel 60, 70–230 mesh) by using cyclohexane as eluent to remove polymeric by-products. The eluted substance was dissolved in benzene and then analyzed by GLC (using a 3 mm × 3 m column packed with Apiezon Grease L, 10%, on Chromosorb W).

Kinetics. Rates of rearrangement of seven polymethylnaphthalenes, **1**, **2**, **4**, **5** (at 40, 50, 60, and 70°), and **8**, **10**, **12** (at 70°), in CF_3COOH were measured by GLC analysis of the reaction mixtures whose initial substrate concentrations were kept as low as indicated below to suppress the formation of by-products; **1** and **2** (15.1 mmol/l.), **4** (16.8–17.1), **5** (14.8–17.4), **8** (16.9), **10** (96), **12** (84). In all analyses, molar change of substrates vs. reaction time was measured by the method of calibration curves. The number of sample collections per reaction at a temperature was more than six in all cases. Work-up procedure for the collected samples was the same as the above-mentioned general procedure for the rearrangement. The 0.8-order rate constants $k_{0.8}$, for example, were calculated according to eq 5, which can be derived by integrating eq 4.

$$1 - ([A]/[A_0])^{0.2} = k_{0.8}t/5[A_0]^{0.2} \quad (5)$$

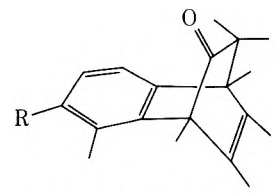
Rearrangement of 1,2,3,4,5,8-Me_6-naphthalene (1). A solution of **1** (0.51 g, 2.4 mmol) dissolved in 7 ml of CF_3COOH was heated under reflux for 10 min. After work-up, about 20% of the initial weight was lost by column chromatography. The substance which was trapped in the column was then extracted with benzene to give a resinous material,[28] whose NMR spectrum showed a complex pattern between 7.0 and 8.5 ppm. The eluted substance consisted of **1** (17%), **2** (69%), and **3** (5%) besides a small amount of by-products. Column chromatography followed by recrystallization from methanol afforded **2**,[29] mp 79.5–81.0°, NMR (all singlet) Me at 7.74, 7.71, 7.64, 7.53, 7.43, and 7.29, 1 H at 3.16 and 2.59. When the solution was heated for 1 hr, the obtained column eluate consisted of **2** (19%) and **3** (58%) and the latter was identified with the authentic sample. As to the composition of by-products, see the results in the text.

Rearrangement of 1,4,5,8-Me_4-naphthalene (4). A solution of **4** (1.56 g, 8.5 mmol) in 19 ml of CF_3COOH was heated at 77° for 5 hr. After work-up, the product mixture was chromatographed (ca. 10% was trapped in the column) and the eluate was analyzed by GLC to find that it consisted of unreacted **4** (9.5%), **5** (75.6%), **6** (12.4%), and **7** (1.2%). Column chromatography (or a preparative GLC) of the mixture afforded **5**, whose melting point (57°) and uv were identical with those reported. NMR of **5**: 7.59 (Me, s), 7.49 (Me, s), 7.20 (2 Me, br s), 3.06 (3 H, br s), and 2.51 ppm (H, s). When the same solution of **4** was heated for 100 hr, the obtained product mixture (93% of the initially charged weight of **4**) consisted of **6** (88.2%) with a small amount of **7** (9%) which was removed by recrystallization from methanol. The melting point and other spectral data of **6** were identical with those reported.[26]

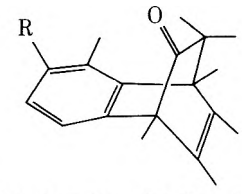
Rearrangement of 1,3,6,8-Me_4-naphthalene (8). A solution of **8** (0.41 g/15 ml CF_3COOH) was heated for 110 hr. The product mixture consisted of **9** (93%) and **8** (7%). **9**: mp 46–47°; λ_{max} (ethanol) 283 nm (ϵ 5200); NMR 7.59 (3 Me, s), 7.41 (Me, s), 3.03 (H, s), 2.73 (H, s), 2.63 (H, s), 2.44 ppm (H, s).

Rearrangement of 1,8-Me_2-naphthalene (10). A solution of **10** (0.50 g/20 ml CF_3COOH) was heated for 24 hr. The product mixture consisted of unreacted **10** (85%) and **11** (15%), whose melting point and NMR were identical with those reported.[7]

Preparation of 1,2,3,4,5-Me_5-naphthalene (12). A stirred mixture of **53** (62 mmol), propylene oxide (0.25 mol), 3-methylbenzenediazonium 2-carboxylate hydrochloride (62 mmol), and 1,2-dichloroethane (150 ml) was heated under reflux for 30 min. After work-up in the same manner as reported before,[3] a mixture of two isomers of 1,3,3,4,7,8-hexamethyl-5,6-(methylbenzo)bicyclo[2.2.2]octa-5,7-dien-2-one (**51** and **52**) was obtained, ν (C=O) 1705 cm^{-1}. NMR chemical shifts corresponding to each isomer are obtained by comparing spectrum intensity on the basis that is applied in distinguishing two isomers **54** and **55** in the following paragraph. **51**: *gem*-Me at 9.46 and 8.96, Ar-Me 7.53, other Me 8.2–8.45, ArH 3.0–3.25 ppm. **52**: *gem*-Me 9.39 and 9.02, ArMe 7.49, other Me 8.2–8.45, ArH 3.0–3.25 ppm. **51**/**52** = 1.75. The above mixture of **51** and **52** (not separated) was treated with a Me_2SO solution of dimsyl sodium[30] to give **12** (4.2 g, 35%) in white crystals, mp 75–76°. Further purification was done by column chromatography.



51, R = H **54**, R = Me



52, R = H **55**, R = Me

Rearrangement of 1,2,3,4,5-Me_5-naphthalene (12). A solution of **12** (0.5 g/20 ml CF_3COOH) was heated for 5 hr. The product mixture consisted of **13** (88%) and **12** (12%). **13**: mp 85°;[10] NMR 7.70 (2 Me, s), 7.54 (Me, s), 7.50 (2 Me, s), 2.85–3.0 (H), 2.2–2.4 ppm (2 H).

Preparation of 1,2,3,4,5,6-Me_6-naphthalene (50). A mixture of two structural isomers of 1,3,3,4,7,8-hexamethyl-5,6-(dimethylbenzo)bicyclo[2.2.2]octa-5,7-dien-2-one (**54** and **55**) was obtained according to the previous report.[3] Separation of the isomers was possible by recrystallization from methanol. With varying amount of Eu(fod)$_3$ in carbon tetrachloride, one of the isomers exhibited a more sensitive separation of two aromatic hydrogens (which appeared equivalent without the shift reagent) than the other isomer. Therefore, this was assigned to **55** where the aromatic hydrogens are placed closer to the carbonyl group than in **54**. **54**: mp 154–156.5; NMR *gem*-Me at 9.44 and 9.00, allylic Me 8.27, bridgehead Me 8.48 and 8.20, ArMe 7.79 and 7.63, ArH 3.17 ppm, with relative areas 3:3:6:3:3:3:3:2; ν (C=O) 1710 cm^{-1} (for both isomers). **55**: mp 127–130°, NMR *gem*-Me 9.38 and 9.03, allylic Me 8.33 and 8.23, bridgehead Me 8.48 and 8.16, ArMe 7.77 and 7.59, ArH 3.19 ppm, with relative areas 3:3:3:3:3:3:3:2. Isomer ratio **54**/**55** = 1.71. Treatment of the above mixture, or separated isomer, with dimsyl sodium gave **50** (98%): mp 55.5–56.5°; NMR 7.69 (Me, s), 7.68 (Me, s), 7.66 (Me, s), 7.49 (3 Me, brs), 2.98 and 2.44 (H for each, AB type, J = 9 Hz).

Rearrangement of 1 in Acetic Acid. In each of five tubes 10 g of acetic acid and 0.30 g (1.4 mmol) of **1** were placed. Three of them were saturated with dry HCl at 0°; the first of the three tubes was sealed without additives. To the second and third tubes were added $AlCl_3$ (1.0 g) and boron trifluoride etherate (1.1 g), respectively. Two remaining tubes were sealed after adding to each 1.0 g of H_2SO_4. Another tube containing chloroacetic acid and **1** was also prepared. Six tubes, thus prepared, were heated under the conditions cited in Table I.

Treatment of 1,2,3,4-Me_4-naphthalene (14) in CF_3COOH. A solution of **14** (0.584 g/11 ml CF_3COOH) was heated for 1100 hr. The originally colorless solution turned to dark blue during the above period. The reaction mixture, after work-up, was chromatographed through a silica gel column (cyclohexane). About 20% of the original weight was removed as a cyclohexane-insoluble material. The eluted mixture was then analyzed to find that it consisted of **15** (15%), **16** (4%), **17** (1%), and unreacted **14** (82%). A preparative GLC afforded **15** and **16**. **15**: mp 140.5–142° (picrate); NMR 7.65 (Me, s), 7.59 (Me, s), 7.42 (Me, s), 2.0–2.8 ppm (5 H, m); P^+ *m/e* 170. **16**: mp 77.5–78.5°;[9] NMR 8.27 (4 H, m), 7.92 (2 Me, s), 7.84 (2 Me, s), 7.41 ppm (4 H, m); P^+ *m/e* 188. **17**: P^+ *m/e* 198.

Treatment of Me_8-naphthalene (18) in CF_3COOH. A solution of **18** (0.52 g/30 ml CF_3COOH) was heated for 30 hr. By chromatographing the reaction mixture through a silica gel column (cyclohexane), about 40% of the original weight was removed as polymeric materials. The eluted mixture consisted of several components in which **20** and **19** (2 and 20%, respectively) were the main products. **20**: P^+ *m/e* 226; mp 133–136°; NMR 7.68 (3 Me, br s), 7.61 (Me, s), 7.48 (3 Me, s), 2.54 (H, s). **19**: P^+ *m/e* 212; mp 176–177°;[10] λ_{max} (ethanol) 274 nm (ϵ 6450), 284 (6080); NMR 7.67 (2 Me, s), 7.58 (2 Me, s), 7.46 (2 Me, s), 2.49 ppm (2 H, s). When the heating was stopped after 8 hr, a mixture of **20** (4%) and **19** (14%) was obtained.

Treatment of Other Polymethylnaphthalenes in CF_3COOH. Solutions of **3**, **6**, **7**, **21**, and **22** (0.08–0.25 mol/l.) in CF_3COOH were heated for 720 hr. After work-up and column chromatography, the product mixtures were analyzed by GLC–mass spectroscopy as well as by GLC. Results are shown in the text.

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Registry No.—**1**, 36230-30-5; **2**, 56908-77-1; **3**, 17384-76-8; **4**, 2717-39-7; **5**, 14558-12-4; **6**, 7383-94-0; **7**, 13764-18-6; **8**, 14558-14-6; **9**, 7435-50-9; **10**, 569-41-5; **11**, 575-37-1; **12**, 56908-78-2; **13**, 56908-79-3; **14**, 3031-15-0; **15**, 879-12-9; **15** picrate, 56908-80-6; **16**, 19063-11-7; **17**, 56908-81-7; **18**, 18623-61-5; **19**, 56908-82-8; **20**, 51958-57-7; **21**, 571-58-4; **22**, 581-40-8; **50**, 56908-83-9; **51**, 56908-84-0; **52**, 56908-85-1; **54**, 56908-86-2; **55**, 56908-87-3; 3,5-dimethylbenzyl bromide, 56908-88-4; diethyl allylmalonate, 2049-80-1; naphthalic anhydride, 81-84-5; dimsyl sodium, 15590-23-5; 1,3-dimethylnaphthalene, 575-41-7.

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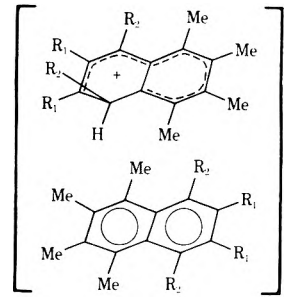
(16) One of the tentative models for the hypothetical complex ArH⁺Ar is illustrated below as an overlapping double-layered form. (1) Telomerization may take place via σ complex resulting in the strain relief at the position para to the protonated carbon; (2) hydrogen transfer may take place via π complex from the Me substituents of the basic Ar to the protonated ring most favorably when $R_1 = R_2 = H$.



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Ion Radicals. XXXV. Reactions of Thianthrene and Phenoxathiin Cation Radicals with Ketones. Formation and Reactions of β-Ketosulfonium Perchlorates and Ylides[1,2]

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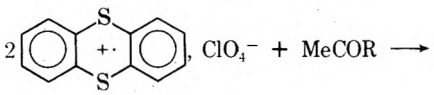
Thianthrene cation radical perchlorate (**1**) and phenoxathiin cation radical perchlorate (**3**) react with ketones to give, in most cases, a β-ketoalkylsulfonium perchlorate and the parent heterocycle (thianthrene or phenoxathiin) in equimolar amounts. Reaction with diketones or β-keto esters leads, in some cases, directly to a sulfur ylide. Some of the β-ketosulfonium perchlorates were themselves easily converted into sulfur ylides by treatment with base. Reaction of selected β-ketosulfonium perchlorates with nucleophiles led easily, also, to displacement of the parent heterocycle and formation of an α-substituted ketone bearing the nucleophile at the α-carbon atom.

Several methods of preparing β-ketosulfonium salts are to be found in the literature. Most common among these is the reaction of a dialkyl or alkyl aryl sulfide with an α-halogeno ketone or ester. Phenacyl bromide[3-6] and α-bromo esters[5,7] are often used. This method is quite old, having been used years ago by Clarke in measuring the reactivities of some dialkyl and cyclic sulfides,[8] but in those cases the salts were not isolated. Alternatively, in another common method, a β-ketoalkyl sulfide is alkylated. Methylation is most common, dimethyl sulfate,[9] methyl tosylate,[9] and trimethyloxonium fluoroborate[10,11] having been used.

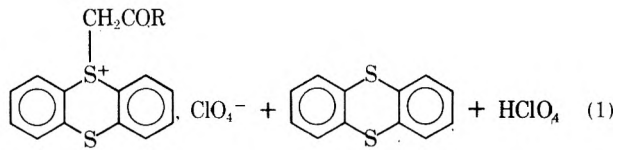
Carbonyl-stabilized sulfur ylides are not as long known. In fact, until 1965–1966 these ylides appear to have been unknown as isolable compounds,[12-14] having been prepared and used until then only in situ.[15,16] Isolable carbonyl-stabilized sulfur ylides are prepared usually by the deprotonation of β-ketosulfonium ions with bases such as triethylamine.[17] This method, and direct ones, such as the reactions of Me_2SO and dicyclohexylcarbodiimide (DCC) with activated methylene groups (such as in 1,3-diketones), have been reviewed by Ratts.[18] More recently, reaction of carbonyl-containing carbenes with a sulfide, e.g., in the pho-

tolysis of $(MeCO)_2C{=}N^+{=}N^-$ in the presence of Me_2S, has given some varieties of β-carbonyl sulfur ylides.[19]

Recently we reported an entirely new and different method of preparing β-ketoalkylsulfonium salts of the thianthrene series by reaction of thianthrene cation radical perchlorate (1) with ketones in acetonitrile solution.[20] Reaction with acetone and methyl ketones, MeCOR, in which R does not have an α-H, followed the stoichiometry of eq 1.



1

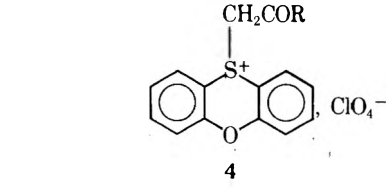


2

2a, R = Me; b, R = *t*-Bu; c, R = C_6H_5; d, R = 2-naphthyl

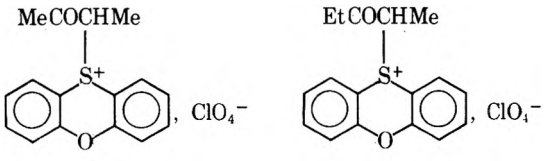
The products, 2, and thianthrene, were obtained in almost quantitative yields, the only other product being a small amount of thianthrene 5-oxide, formed presumably by the reaction of 1 with water in the solvent or liquid ketones. Reactions with butanone, tetralone-1, dimedone, and ethyl benzoylacetate were also described, the last two leading directly to ylides rather than the corresponding sulfonium salts.

We now report some further reactions of 1 with ketones, and analogous reactions of the recently isolated phenoxathiin cation radical perchlorate (3).[1a] Thus, reaction of 3 with a series of methyl ketones has given the sulfonium perchlorates 4a–d. Phenoxathiin was also formed (see eq 1). Reaction with butanone, 3-pentanone, cyclohexanone, cyclopentanone, and dibenzoylmethane gave the products 5, 6, 7, 8, and 9, respectively. Reaction with 1,3-pentanedione led directly to the ylide 10. Reactions of 1 with indanone and 4-*tert*-butylcyclohexanone gave the sulfonium salts 11 and 12. Reaction of 1 with cyclohexanone, cyclopentanone, diisopropyl ketone, and ethyl acetoacetate gave an oil in each case. The oils were not analyzed, but in the cases of diisopropyl ketone and ethyl acetoacetate the structures of the oils were deduced to be β-ketosulfonium perchlorates from their reactions with nucleophiles. These cases and the reactions of 2c and 2d with nucleophiles are discussed below.



4

a, R = Me; b, R = *t*-Bu; c, R = C_6H_5; d, R = 2-naphthyl



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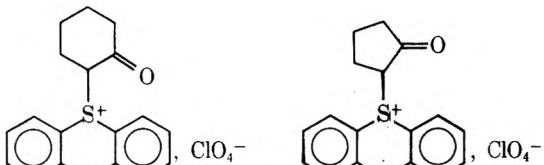

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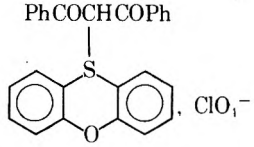

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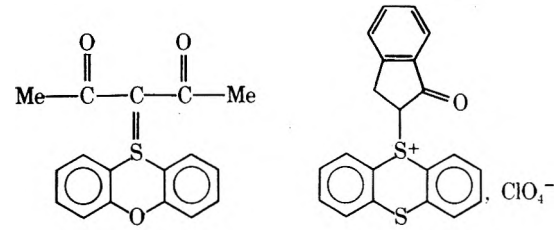
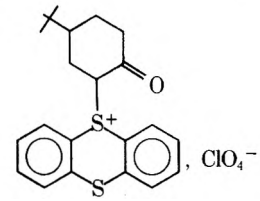


10 11



12

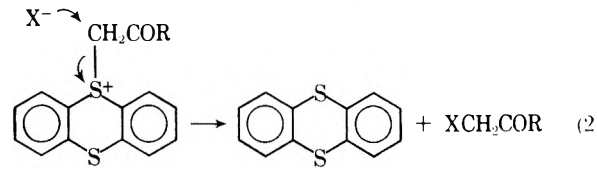
Discussion

As far as we are aware, prior to our first communication[20] the only report in the literature indicating that a cation radical may react with a ketone concerns the cyclization of the 6-β-ketopropionic ester side chain of a magnesium porphyrin derivative during oxidation by iodine. This reaction is thought to occur within the metalloporphyrin cation radical,[21] but whether or not the cation radical is involved has not been made certain. It is, in fact, uncommon also for organic carbocations of the usual type (i.e., nonradical) to react with ketones. Alkylation of ketones on the carbonyl oxygen occurs in reaction with trialkyloxonium salts. For example, triethyloxonium fluoroborate leads to salts of the type $R_2C{=}O^+Et\ BF_4^-$.[22] Corresponding ions, i.e., $Me_2C{=}OR^+$, have been implicated in certain solvolyses in acetone in which acetone is believed to behave as a nucleophile.[23,24]

In the cation radical reactions we have reported, we believe that the carbonyl compound behaves as a nucleophile also, but that reaction occurs at the α-carbon atom rather than at the carbonyl oxygen atom.

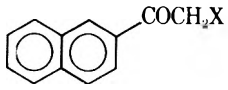
These reactions are viewed as electrophilic substitutions involving the enol, but a full discussion of mechanism must await the results of kinetic studies in progress.

Most of our reactions led to sulfonium salts. The sulfonium salts are nicely susceptible to reactions with strong nucleophiles. Displacement of the heterocycle occurs and an α-substituted carbonyl compound is formed (eq 2). We have carried out such reactions mostly with 2c and 2d.



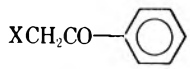
In most cases the products XCH_2COR which were obtained were already known, and we carried out the reactions to find how easily α-substituted carbonyl compounds

may be made by this method. In some cases, the products were new. That is, the ketones **13** and **14** were obtained



13

a, X = *p*-$MeC_6H_4SO_2$;

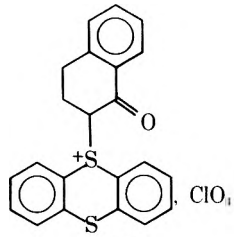


14

b, X = $EtOCS_2$

from reactions with sodium *p*-toluenesulfinate and potassium ethyl xanthate, and appear to be new. Ketone **14a** was made more easily by reaction of phenacyl bromide with sodium *p*-toluenesulfinate, but we were unable to obtain **14b** from reaction of phenacyl bromide with potassium ethyl xanthate. Our conclusion is that this displacement method (eq 2) may be useful for making α-substituted ketones which are not as readily accessible by more conventional routes.

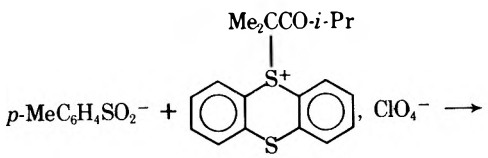
The displacement method may have wider implications, however, in reactions with conformationally stable ketoalkylsulfonium ions. The ^1H NMR spectra of **12** and **15** indi-



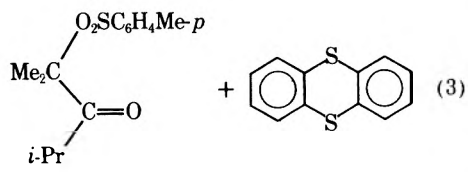
15

cate that the proton in the 2 position of each cyclohexyl ring is in the axial configuration. For **12** we obtain two well-resolved doublets centered at δ 5.42 with J = 7 and 13 Hz, while for **15** we obtain two very sharp doublets centered at δ 5.68 with J = 7 and 14 Hz. The peak-to-peak width of the doublets is 19 and 20 Hz, respectively, and the data are indicative of an axial 2 proton coupling with an adjacent axial–equatorial methylene group.[25] SN2 displacement reactions of **12** and **15** with nucleophiles, therefore, may give α-substituted ketones in which the nucleophile is in the axial and the 2 proton in the equatorial configuration, provided that epimerization does not occur after substitution. Exploration of these features of the displacement reaction is being undertaken.

The sulfonium salt (**16**) obtained by reaction of **1** with diisopropyl ketone was a solid which appeared to decompose during attempts at recrystallization. Elemental analysis was waived, therefore. ^1H NMR and infrared (ClO_4^- band) indicated that **16** had the anticipated structure, and this was confirmed by reaction with sodium *p*-toluenesulfinate. Thianthrene (103%) and the ketone **17** (33%) were obtained (eq 3).



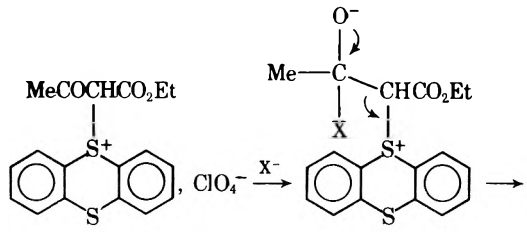
16



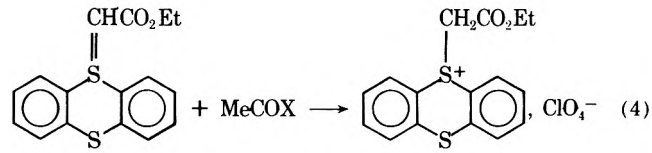
(3)

17

Ethyl acetoacetate reacted with **1** to give thianthrene and an oil (assumed to be **18**). The oil was treated with sodium *p*-toluenesulfinate and in this case thianthrene was not obtained; i.e., reaction did not follow eq 3. Instead, a sulfonium perchlorate was obtained which, from ^1H NMR and elemental analysis, appears to be **20.** Reaction of **18** with *p*-toluenesulfinate ion (X^-) appears to have followed the path in eq 4. Protonation of the ylide **19** in situ would



18

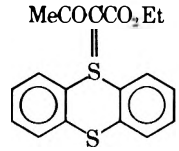


(4)

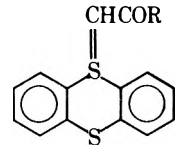
19 **20**

lead to the isolated product (**20**). Attempts to make **20** by direct reaction of **1** with ethyl acetate failed. A dimer of **1** was formed, instead, whose nature, and that of analogous dimers, will be discussed in a later publication. We failed also to obtain **20** by reaction of thianthrene with ethyl α-bromoacetate both in the absence and presence of silver perchlorate. Thianthrene was recovered quantitatively in each case.

Confirmation that **18** had been formed in reaction of **1** with ethyl acetoacetate was obtained by treating the oil produced with triethylamine, whereupon the ylide **21** was obtained.



21



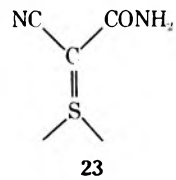
22

22b, R = *t*-Bu

d, R = 2-naphthyl

Ylides were obtained similarly from treating other sulfonium salts with triethylamine in ethanol; **2b** gave **22b,** and **2d** gave **22d.**

In view of the apparent scope of these ketone reactions, it is possible that the product of reaction of **1** with cyanoacetamide, formulated earlier as a sulfilimine derivative, namely 5-[(cyanoacetyl)imino]-5,5-dihydrothianthrene,[26] may be instead an ylide (**23**) analogous to **10.** This possibil-



23

ity and reactions with analogous activated amides is being investigated.

Experimental Section

Thianthrene cation radical perchlorate (**1**) was prepared as described earlier.[27] *Attention is called to the warning of explosive hazard.*[27] Phenoxathiin cation radical perchlorate was prepared by a modification of this procedure.[1a] Acetonitrile was Eastman anhydrous grade and was stored over molecular sieve in a septum-

capped bottle. Acetone, reagent grade, was boiled with $KMnO_4$ for 2 hr and distilled over 3 Å molecular sieve. All other carbonyl compounds were either distilled at atmospheric or reduced pressure as appropriate or recrystallized, except methyl 2-naphthyl ketone (J. T. Baker, photosensitizer grade, mp 53–54°) and dimedone (Aldrich, 99%), which were used without further treatment. Nucleophilic reactants were from standard sources except potassium ethyl xanthate, which was prepared by the standard route.[28] Sodium *p*-toluenesulfinate dihydrate was from Aldrich. Me_2SO was reagent grade (J. T. Baker) and hydriodic acid was Eastman, 50%.

Reactions of 1 and 3 with Carbonyl Compounds. General Procedure. Between 1 and 3 mmol of the cation radical perchlorate was dissolved in about 30 ml of acetonitrile and to this was added an excess of the carbonyl compound (50–200%). Stirring was continued for a variable period, since some reactions were rapid and others were quite slow as judged by the disappearance of the purple color of **1** and **3**. The solutions were usually colored at the end of the reaction. In the cases of reactions of **1** the colors varied from light purple to red, while in most reactions of **3** the final color of the solution was yellow. In most cases the solution was concentrated to small volume and placed on a column of silica gel (Merck No. 7733). In the cases of **1**, elution with benzene gave thianthrene, while elution next with ether gave thianthrene 5-oxide. The oxide was always formed in small amounts. Finally, elution with acetone gave the β-ketosulfonium perchlorate. The products of reactions of **3** were similarly separated by chromatography with the exception of some cases in which the β-ketosulfonium salt was precipitated before chromatographic separation of the phenoxathiin and phenoxathiin 5-oxide. Also, after use of benzene to remove phenoxathiin, the column was first treated with chloroform to begin the downward separation of phenoxathiin 5-oxide and this was then removed more quickly with ether. Data for individual reactions are given below.

Reaction of 1 with Indanone-1. Formation of 11. The sulfonium perchlorate (**11**) had mp 156–157° (ethanol–MeCN); λ_{max} (MeCN) (10^{-4} ϵ) 255 nm (4.13), 243 (2.50), and 291 br, (0.41); ^1H NMR (acetone-d_6) δ 7.9 (m, 12 H, aromatic), 5.2 (t, 1 H, J = 6 Hz, –CH–), and 3.1, 3.2 (2 d, 2 H, J = 6 Hz, $-CH_2-$).

Anal. Calcd for $C_{21}H_{15}S_2ClO_5$: C, 56.4; H, 3.38; S, 14.3; Cl, 7.93. Found: C, 56.6; H, 3.40; S, 14.6; Cl, 7.76.

Reaction of 1 with 4-*tert*-Butylcyclohexanone. Formation of 12. The sulfonium perchlorate (**12**) was isolated from the column as an oil. This was dissolved in a small amount of acetonitrile and diluted with a large volume of ether. An oil precipitated which solidified overnight in the refrigerator. Reprecipitation from acetonitrile with ether gave a white, crystalline solid: mp 122.5–123°; λ_{max} (MeCN) (10^{-4} ϵ) 225 nm (4.48), 255 (2.38), 290–312 br (0.95); ^1H NMR (CD_3CN) δ 7.98 (m, 8 H, aromatic), 5.42 (2 d, 1 H, C_2H), 2.48 (m, 2 H, $-CH_2-$), 1.60 (m, 5 H), 0.76, (9 H, *t*-Bu).

Anal. Calcd for $C_{22}H_{25}S_2ClO_5$: C, 56.3; H, 5.37; S, 13.7; Cl, 7.55. Found: C, 56.2; H, 5.46; S, 13.6; Cl, 7.57.

Reaction of 3 with Acetone. Formation of 4a. To a solution of 807 mg (2.69 mmol) of **3** in 30 ml of acetonitrile was added 2 ml of acetone. The purple color became brown after 1 hr of stirring. The solution was evaporated and the residue was dissolved in acetone, to which solution petroleum ether (bp 30–60°) was added to cause turbidity, and crude, white **4a** (444 mg, 1.24 mmol, 99%) crystallized out: mp 179–180° dec (aqueous Me_2SO); λ_{max} (MeCN) (10^{-3} ϵ) 235 nm (14.6), 287 (4.7); ^1H NMR (Me_2SO-d_6) δ 8.2–7.0 (m, 8 H, aromatic), 5.15 (s, 2 H, $-CH_2-$), and 2.15 (s, 3 H, Me).

Anal. Calcd for $C_{15}H_{13}SClO_6$: C, 50.5; H, 3.68; S, 8.97; Cl, 9.94. Found: C, 50.6; H, 3.66; S, 9.22; Cl, 9.99.

The filtrate from **4a** precipitation was concentrated and chromatographed to give 269 mg (1.35 mmol, 100%) of phenoxathiin and 21 mg (0.096 mmol, 7.1%) of phenoxathiin 5-oxide.

Reaction of 3 with Pinacolone. Formation of 4b. Reaction as above was carried out with 745 mg (2.48 mmol) of **3** and overnight stirring. After evaporation of the mixture and washing with water to remove excess of pinacolone, the residue was dissolved in a small amount of acetone and chromatographed, giving phenoxathiin (100%), phenoxathiin 5-oxide (7.8%), and 479 mg (1.21 mmol, 105%) of crude **4b:** mp 192–193° dec (acetone–ether); λ_{max} (MeCN) 287 nm (ϵ 4.85 × 10^3); ^1H NMR (Me_2SO-d_6) δ 7.4–8.3 (m, 8 H, aromatic), 5.45 (s, 2 H, $-CH_2-$), and 0.95 (s, 9 H, *t*-Bu).

Anal. Calcd for $C_{18}H_{19}SClO_6$: C, 54.2; H, 4.80; S, 8.04; Cl, 8.89. Found: C, 54.5; H, 4.97; S, 7.87; Cl, 8.99.

Reaction of 3 with Acetophenone. Formation of 4c. Reaction with 603 mg (2.01 mmol) of **3** for 3 hr and work-up as above (see **4b**), without water wash, gave 98% of phenoxathiin, 5.6% of phenoxathiin 5-oxide, and 410 mg (0.98 mmol, 103%) of crude **4c:** mp 165–166° dec (acetone–ether); λ_{max} (MeCN) (10^{-3} ϵ) 287 nm (6.26), 252 sh (37.9), and 241 (23.3); ^1H NMR (Me_2SO-d_6) δ 7.5–8.8 (m, 13 H, aromatic) and 5.1 (s, 2 H, $-CH_2-$).

Anal. Calcd for $C_{20}H_{15}SClO_6$: C, 57.4; H, 3.61; S, 7.66; Cl, 8.47. Found: C, 57.3; H, 3.67; S, 7.89; Cl, 8.49.

Reaction of 3 with 2-Acetonaphthone. Formation of 4d. Reaction of 1.05 g (3.5 mmol) of **3** for 30 min and work-up as above gave 100% of phenoxathiin, 4.3% of phenoxathiin 5-oxide, and 741 mg (1.58 mmol, 90%), of crude **4d:** mp 154–154.5° dec (ethanol); λ_{max} (MeCN) (10^{-3} ϵ) 292 nm (11.6), 252 sh (34.8), and 245 (39.7); ^1H NMR (Me_2SO-d_6) δ 8.5–7.0 (m, 15 H, aromatic), 5.9 (s, 2 H, $-CH_2-$).

Anal. Calcd for $C_{24}H_{17}SClO_6$: C, 61.5; H, 3.66; S, 6.84; Cl, 7.56. Found: C, 61.4; H, 3.90; S, 6.60; Cl, 7.24.

Reaction of 3 with Butanone. Formation of 5. After reaction of 1.12 g (3.73 mmol) of **3** for 20 min, ether was added to the medium to give a precipitate of crude **5**. The filtrate was evaporated and the residue was washed with water and chromatographed, giving 101% of phenoxathiin, 4% of phenoxathiin oxide, and a further portion of **5**, amounting to a total of 525 mg (1.42 mmol, 76%): mp 149° dec (acetone–ether); λ_{max} (MeCN) (10^{-3} ϵ) 289 nm (5.17) and 234 (18.4); ^1H NMR (Me_2SO-d_6) δ 6.9–8.1 (m, 8 H, aromatic), 5.05 (q, 1 H, –CH–), 2.2 (s, 3 H, Me), and 1.3 (d, 3 H, Me).

Anal. Calcd for $C_{16}H_{15}SClO_6$: C, 51.8; H, 4.08; S, 8.63; Cl, 9.56. Found: C, 51.6; H, 4.03; S, 8.53; Cl, 9.33.

Reaction of 3 with Pentan-3-one. Formation of 6. Reaction of 724 mg (2.41 mmol) of **3** for 1 hr was followed by evaporation to small volume and addition of ether. The precipitate of **6** was filtered and the filtrate was chromatographed to give 105% of phenoxathiin, 19% of phenoxathiin 5-oxide, and a further small amount of **6**. The combined portions of crude **6** amounted to 252 mg (0.66 mmol, 55%): mp 122° dec (acetone–ether); λ_{max} (MeCN) (10^{-3} ϵ) 291 nm (4.86) and 234 (19.9); ^1H NMR (Me_2SO-d_6) δ 6.95 (m, 8 H, aromatic), 5.1 (q, 1 H, –CH–), 1.35 (d, 3 H, Me), 0.91 (t, 3 H, Me). The $-CH_2-$ group signal was obscured by a solvent peak.

Anal. Calcd for $C_{17}H_{17}SClO_6$: C, 53.0; H, 4.46; S, 8.32; Cl, 9.22. Found: C, 52.8; H, 4.30; S, 8.27; Cl, 9.08.

Reaction of 3 with Cyclohexanone. Formation of 7. Reaction of 712 mg (2.37 mmol) of **3** for 5 min and addition of ether to the medium gave 277 mg of crude **7**. Chromatography gave 95% of phenoxathiin, 9.5% of phenoxathiin 5-oxide, and 83 mg of crude **7**, totaling 0.91 mmol (76%): mp 121–122° dec (acetone–ether); λ_{max} (MeCN) 291 nm (ϵ 5.05 × 10^3); ^1H NMR (Me_2SO-d_6) δ 6.8–8.1 (m, 8 H, aromatic), 5.1 (t, 1 H, α-CH), and 1.5 [br s, 8 H, $-(CH_2)_4-$].

Anal. Calcd for $C_{18}H_{17}SClO_6$: C, 54.5; H, 4.32; S, 8.08; Cl, 8.93. Found: C, 54.7; H, 4.30; S, 8.28; Cl, 8.89.

Reaction of 3 with Cyclopentanone. Formation of 8. Reaction of 762 mg (2.54 mmol) of **3** for 10 min and addition of ether gave 225 mg of crude **8**. Chromatography gave 91% of phenoxathiin, 11% of phenoxathiin 5-oxide, and 132 mg of crude **8**, totaling 0.95 mmol (75%), mp 96.0–96.5° (acetone–ether).

Anal. Calcd for $C_{17}H_{15}SClO_6$: C, 53.3; H, 3.95; S, 8.37; Cl, 9.26. Found: C, 53.3; H, 4.20; S, 8.50; Cl, 8.98.

Reaction of 3 with Dibenzoylmethane. Formation of 9. After reaction of 771 mg (2.57 mmol) of **3** for 15 min the solvent was removed and the residue was dissolved in a small amount of acetone. Addition of ether gave 556 mg (1.1 mmol, 85%) of crude **9:** mp 186° dec (acetone–ether); λ_{max} (MeCN) (10^{-3} ϵ) 319 nm (4.73), 277 (15.3), and 241 (40.5).

Anal. Calcd for $C_{27}H_{19}SClO_7$: C, 62.0; H, 3.66; S, 6.13; Cl, 6.78. Found: C, 61.7; H, 3.60; S, 6.09; Cl, 6.69.

Reaction of 3 with 2,4-Pentanedione. Formation of Ylide 10. After reaction of 843 mg (2.8 mmol) of **3** for 15 min the solvent was removed and the residue was washed with water to remove excess of ketone. The residue was treated as above (see **9**) to give 309 mg of crude **10:** mp 236° (acetone); λ_{max} (MeCN) (10^{-3} ϵ) 301 (5.73), 256 (19.7), and 227 (32.4); ^1H NMR ($CDCl_3$) δ 7.3 (m, 8 H, aromatic), 2.45 (s, 6 H, Me).

Anal. Calcd for $C_{17}H_{14}SO_3$: C, 68.4; H, 4.73; S, 10.75. Found: C, 68.2; H, 4.81; S, 11.0.

Reactions of 2d with Nucleophiles. Formation of α-Substituted Methyl 2-Naphthyl Ketones (13). Approximately 150–250 mg (0.3–0.5 mmol) of **2d** was dissolved in 10–15 ml of acetonitrile and to the stirred solution was added a severalfold excess of the nucleophile and approximately 1 ml of water. The mixture was stirred for an additional period of time depending on the nucleophile. TLC was carried out to monitor the reaction and when two spots (thianthrene and an unknown one) appeared only or predominantly, the solvent was evaporated under vacuum at room temperature. The times of stirring are given in parentheses, and

they may or may not be significant. After evaporation of the solvent the residue was chromatographed on a column of silica gel (Merck 7733). Elution with benzene gave thianthrene and elution with ether gave the α-substituted methyl 2-naphthyl ketone (**13**). The results of reactions which led to known compounds are listed in abbreviated form [reagent (time), % yield of thianthrene, X in XCH_2CO-2-naphthyl, % yield, mp (lit. mp)]: KCN (24 hr), 98, -CN, 98, 126–127° (126.6–128.2°);[29] NaSCN (2 hr), 95, -SCN, 94, 105–106° (109–110°);[29] NaN_3 (1.5 hr), 99, $-N_3$, 100, 63–64° (66–67°);[30] Me_4NCl (30 min), 92, -Cl, 97, 64–65° (65–66°);[31] Bu_4NI (2 min), 101, -I, 97, 90–91° (91–91.5°);[32] $AgNO_2$ (10 min), 94, -OH, 96, 114° (114°);[33] $NaNO_2$ (20 min), 90, -OH, 54, 114°; $AgNO_3$ (16 hr), 93, -OH, 63, 114°; $NaNO_3$ (11 hr), 47, -OH, 73, 105–112°; Me_2SO (2 hr), 99, -OH, 98, 109–110°; concentrated HCl (16 hr), 111, -Cl, 81, 61–62°; concentrated HBr (30 min), 97, -Br, 96, 78–80° (80–82°);[33] 50% HI (5 hr), 103, -I, 87, 90–91°.

Reaction of 2d with Sodium *p*-Toluenesulfinate Dihydrate. Formation of 13a. Reaction carried out as above (15 hr) gave 99% of thianthrene and 78% of α-(*p*-toluenesulfinyl)methyl 2-naphthyl ketone (**13a**): mp 149–150° (methanol); λ_{max} (MeCN) (10^{-4} ε) 228 nm (2.15), 253 (4.04), 285 (1.00), and 294 (1.05); ^1H NMR ($CDCl_3$) δ 7.67 (m, 11 H, aromatic), 4.86 (s, 2 H, $-CH_2-$), 2.39 (s, 3 H, Me).

Anal. Calcd for $C_{19}H_{16}O_3S$: C, 70.3; H, 4.97; S, 9.88. Found: C, 70.2; H, 5.19; S, 10.1.

Reaction of 2d with Potassium Ethyl Xanthate. Formation of 13b. Reaction gave 85% of thianthrene and 86% of the ethyl ester of *S*-(2-naphthoyl)methylxanthic acid (**13b**) (X = $EtOCS_2^-$): mp 92–93° (aqueous methanol); λ_{max} (MeCN) (10^{-4} ε) 243 nm (4.63), 248 (5.20), and 282 (2.05); ^1H NMR ($CDCl_3$) δ 7.7 (m, 7 H, aromatic), 4.81 (s, 2 H, $-CH_2-$), 4.65 (q, 2 H, $-CH_2-$), 1.37 (t, 3 H, Me).

Anal. Calcd for $C_{15}H_{14}O_2S_2$: C, 62.0; H, 4.85; S, 22.1. Found: C, 62.2; H, 4.93; S, 22.2.

Reactions of 2c with Nucleophiles. Formation of α-Substituted Acetophenones (14). The same procedure was used as with **2d** except that cyclohexane instead of benzene was used to elute thianthrene from the column. Known phenacyl compounds, $XCH_2COC_6H_5$ (**14**), were formed: Me_4NCl (1 min), 104, -Cl, 99, 54–55° (55–56°);[34] Me_4NBr (2 min), 95, -Br, 100, 48–49° (50°);[34] Bu_4NI (17 min), 99, -I, 81, oil (34.4°);[34] NaSCN (10 min), 100, -SCN, 103, 71–72° (74.1–74.6°);[29] NaN_3 (75 min), 101, $-N_3$, 101, oil (17°).[35]

Reaction of 2c with Sodium *p*-Toluenesulfinate Dihydrate. Formation of 14a. Reaction gave 99% of thianthrene and 99% of α-(*p*-toluenesulfinyl)acetophenone (**14a**): mp 106.5–107.5° (aqueous methanol); λ_{max} (MeCN) (10^{-4} ε) 228 nm (1.25), 251 (1.42); ^1H NMR ($CDCl_3$) δ 7.57 (m, 9 H, aromatic), 4.70 (s, 2 H, $-CH_2-$), 2.40 (s, 3 H, Me).

Anal. Calcd for $C_{15}H_{14}O_3S$: C, 65.7; H, 5.14; S, 11.7. Found: C, 65.8; H, 5.25; S, 12.3.

Reaction of 2c with Potassium Ethyl Xanthate. Formation of 14b. Reaction gave 100% of thianthrene and 97% of the ethyl ester of phenacylxanthic acid (**14b**): mp 32–32.5° (aqueous ethanol); λ_{max} (MeCN) (10^{-4} ε) 241 nm (0.29), 277 (0.26); ^1H NMR ($CDCl_3$) δ 8.12 (m, 3 H, aromatic), 7.63 (m, 2 H, aromatic), 4.71 (s, 2 H, $-COCH_2-$), 4.64 (q, 2 H, $-CH_2-$), 1.40 (t, 3 H, Me).

Anal. Calcd for $C_{11}H_{12}O_2S_2$: C, 55.0; H, 5.03; S, 26.7. Found: C, 54.9; H, 5.29; S, 27.0.

Reaction of 1 with Diisopropyl Ketone. Formation of 2,4-Dimethyl-2-(*p*-toluenesulfinyl)pentan-3-one (17). Reaction of **1** with 2,4-dimethylpentanone followed by column chromatography gave 86% of thianthrene and a yellow oil from which trituration with ethyl acetate gave 164 mg (37%) of a white solid which we believe to be the anticipated β-ketoalkylsulfonium perchlorate (**16**), mp 93° dec, infrared ClO_4^- band. Attempts to recrystallize this solid from common solvents (ethyl acetate, methanol, ethanol, Me_2SO) caused its decomposition. Therefore, the solid was treated in acetoritrile with sodium *p*-toluenesulfinate dihydrate and gave on column chromatography with cyclohexane 103% of anticipated thianthrene and 33% of the anticipated **17**: mp 76–77°; λ_{max} (MeCN) (10^{-4} ε) 227 nm (1.83); ^1H NMR ($CDCl_3$) δ 7.37 (2 d, 4 H, aromatic), 3.45 (heptet, 1 H, -CH-), 2.44 (s, 3 H, Me), 1.54 (s, 6 H, Me), 1.15 (d, 6 H, Me).

Anal. Calcd for $C_{14}H_{20}O_3S$: C, 62.7; H, 7.51; S, 11.9. Found: C, 62.8; H, 7.45; S, 12.1.

Reaction of 1 with Ethyl Acetoacetate. A. Formation of 5-(Ethoxycarbonylmethyl)thianthreniumyl Perchlorate (20). Reaction of **1** with ethyl acetoacetate was carried out and the yellow oil (**18**) was obtained as in B below. A solution of 814 mg of this in 10 ml of acetonitrile was stirred for 1 min with 323 mg of sodium *p*-toluenesulfinate dihydrate. Work-up and column chromatography gave no thianthrene (cyclohexane elution). Acetone elution gave a yellow oil from which trituration with methanol gave 132 mg (39%) of what we believe to be **20**: mp 169.5–170.5° (methanol); λ_{max} (MeCN) (10^{-4} ε) 227 nm (1.39), 255 (1.73), 291 (0.38); ^1H NMR (Me_2SO-d_6) δ 7.86 (m, 8 H, aromatic), 4.94 (s, 2 H, $-CH_2-$), 4.18 (q, 2 H, $-CH_2-$), 1.19 (t, 3 H, Me).

Anal. Calcd for $C_{16}H_{15}S_2ClO_6$: C, 47.7; H, 3.75; S, 15.9; Cl, 8.80. Found: C, 47.3; H, 3.68; S, 15.7; Cl, 8.56.

Attempts to make **20** by direct reaction of **1** with ethyl acetate failed. The only product was from the dimerization of **1**.[36] Attempts to prepare **20** by reaction of thianthrene with ethyl α-bromoacetate, both in the presence and absence of silver perchlorate, also failed. Thianthrene was recovered quantitatively.

Reactions of β-Ketoalkylsulfonium Perchlorates with Triethylamine. Formation of Ylides 21 and 22. 1. Reaction of 1 with Ethyl Acetoacetate (B). Use of 1.1 g (3.51 mmol) of **1** and an excess of ethyl acetoacetate followed by column chromatography, as described earlier, gave a brownish-yellow oil, assumed to be the anticipated β-ketoalkylsulfonium perchlorate. However, in that case the yield (1.42 g, 3.19 mmol) is far too high. The oil could not be rendered crystalline, and it was treated with 1.6 ml of triethylamine in 10 ml of acetonitrile. The solvent was removed after 20 hr and the residue was chromatographed on silica. Elution with benzene gave 327 mg of thianthrene, while elution with ether gave 542 mg (1.57 mmol) of what we deduce to be the ylide **21**: mp 179–180° (petroleum ether–CCl_4); λ_{max} (MeCN) (10^{-4} ε) 236 nm (2.77); ^1H NMR ($CDCl_3$) δ 7.47 (m, 8 H, aromatic), 4.14 (q, 2 H, $-CH_2$), 2.70 (s, 3 H, Me), and 1.03 (t, 3 H, Me).

Anal. Calcd for $C_{18}H_{16}O_3S_2$: C, 62.8; H, 4.68; S, 18.6. Found: C, 62.7; H, 4.73; S, 18.6.

Elution of the column with acetone gave 749 mg of a reddish-yellow gum which has not been identified.

2. To a solution of 214 mg (0.51 mmol) of **2b** in 10 ml of ethanol was added 1 ml (ca. 7.2 mmol) of triethylamine. After stirring for 14 hr TLC showed only very weak spots corresponding to thianthrene and **2b**, but a large spot of an unknown. The solvent was removed under vacuum and the white residue was chromatographed on a column of silica. Elution with benzene gave 3 mg of thianthrene and 77 mg (0.24 mmol, 47%) of the ylide **22b**: mp 189–190° (petroleum ether–CCl_4); λ_{max} (MeCN) (10^{-4} ε) 238 nm (0.52) 249 (0.47), 286 (0.21); ^1H NMR ($CDCl_3$) δ 7.44 (m, 8 H, aromatic), 4.06 (s, 1 H, =CH-), 1.35 (s, 9 H, *t*-Bu).

Anal. Calcd for $C_{18}H_{18}OS_2$: C, 68.7; H, 5.53; S, 20.39. Found: C, 68.9; H, 5.83; S, 20.43.

3. A similar reaction with **2d** gave the ylide **22d**: mp 81–86° (from petroleum ether–CCl_4); ^1H NMR ($CDCl_3$) δ 7.86 (m, 15 H, aromatic), 4.76 (s, 1 H, =CH-).

Registry No.—**1**, 21299-20-7; **2b**, 55116-86-4; **2c**, 55116-88-6; **2d**, 55116-90-0; **3**, 56817-58-4; **4a**, 56817-60-8; **4b**, 56817-62-0; **4c**, 56817-64-2; **4d**, 56817-66-4; **5**, 56817-68-6; **6**, 56817-70-0; **7**, 56817-72-2; **8**, 56817-74-4; **9**, 56817-76-6; **10**, 56817-77-7; **11**, 56817-79-9; **12**, 56817-81-3; **13a**, 56817-82-4; **13b**, 56817-83-5; **14a**, 31378-03-7; **14b**, 56817-84-6; **17**, 56817-85-7; **20**, 56817-87-9; **21**, 56817-88-0; **22b**, 55116-97-7; **22d**, 55116-98-8; indanone-1, 83-33-0; 4-*tert*-butylcyclohexanone, 98-53-3; acetone, 67-64-1; pinacolone, 75-97-8; acetophenone, 98-86-2; 2-acetonaphthone, 93-08-3; butanone, 78-93-3; pentan-3-one, 96-22-0; cyclohexanone, 108-94-1; cyclopentanone, 120-92-3; dibenzoylmethane, 120-46-7; 2,4-pentanedione, 123-54-6; sodium *p*-toluenesulfinate, 824-79-3; potassium ethyl xanthate, 140-89-6; diisopropyl ketone, 565-80-0; ethyl acetoacetate, 141-97-9.

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Different Reactivities of 5-Bromo-2′-deoxyuridine and 5-Bromouracil in the Bisulfite-Mediated Debromination

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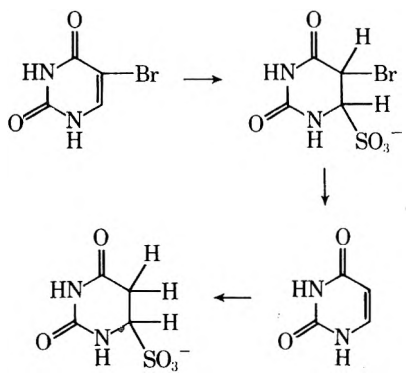
Sodium bisulfite mediated debromination of 5-bromo-2′-deoxyuridine, 1-methyl-5-bromouracil, and 5-bromouracil was studied. Spectroscopic determination of the velocity at pH 7.0 and 17° showed that 5-bromo-2′-deoxyuridine undergoes debromination two orders of magnitude more slowly than 5-bromouracil. The debromination of 1-methyl-5-bromouracil in this system was also slow, only several times faster than that of 5-bromo-2′-deoxyuridine. The optimum pH for the debromination of both 5-bromo-2′-deoxyuridine and 5-bromouracil was about 7. In the debromination of 5-bromo-2′-deoxyuridine, the existence of the intermediate 5,6-dihydro-5-bromo-2′-deoxyuridine 6-sulfonate was proved by NMR and by the reversal to 5-bromo-2′-deoxyuridine upon dilution of the reaction mixture. The formation of the intermediate from 5-bromo-2′-deoxyuridine was a rapid process, whereas the subsequent debromination was a slow process which was the rate-limiting step of the overall reaction. The facile debromination of 5,6-dihydro-5-bromouracil 6-sulfonate, in contrast to its N^1-substituted derivatives, was explained in terms of participation of an intermediate formed by elimination of HSO_3^- from the N^1–C^6 linkage of this dihydro compound.

Recent research in several laboratories has shown that sulfur nucleophiles, such as bisulfite and cysteine, bring about dehalogenation of 5-halogenouracil derivatives under mild conditions in aqueous solution.[1-4] Sander and coworkers[1a,b] reported that the bisulfite-mediated decomposition of 5-bromouracil proceeds as illustrated in Scheme I,

Scheme I



which involves addition of bisulfite across the 5,6 double bond of the pyrimidine ring followed by elimination of bromonium and sulfite ions to give uracil. The uracil in turn produces 5,6-dihydrouracil 6-sulfonate upon reaction with bisulfite.

The formation of the intermediate, 5,6-dihydro-5-bromouracil 6-sulfonate, was assumed by the analogy to the well-established 5,6-dihydrouracil 6-sulfonate formation from uracil and bisulfite.[5,6] This assumption was supported by the fact that in the case of the reaction between 5-fluorouracil and bisulfite, the formation of 5,6-dihydro-5-fluorouracil 6-sulfonate was demonstrated both by NMR studies and by reversal to 5-fluorouracil.[1a] However, since the bisulfite adduct of 5-bromouracil cannot be observed as a discrete species, it was not possible to determine whether the rate-determining step of the bisulfite-promoted debromination was the addition of bisulfite to 5-bromouracil or the subsequent dehalogenation.

Although Fourrey[2] reported that 5-bromouridine can also be converted to 5,6-dihydrouridine 6-sulfonate by treatment with sodium bisulfite, the study was not performed under kinetically controlled conditions. When we compared reactivities of 5-bromouracil, 1-methyl-5-bromouracil, and 5-bromo-2′-deoxyuridine toward bisulfite under defined conditions, a great difference was observed between these substrates; the N^1-substituted substrates react much more slowly than 5-bromouracil, and the intermediate 5,6-dihydro-5-bromo-2′-deoxyuridine 6-sulfonate can be detected as a discrete species. This paper reports the results of these studies, which show that in the bisulfite-promoted debromination of 5-bromo-2′-deoxyuridine the rate-determining step is the debromination reaction

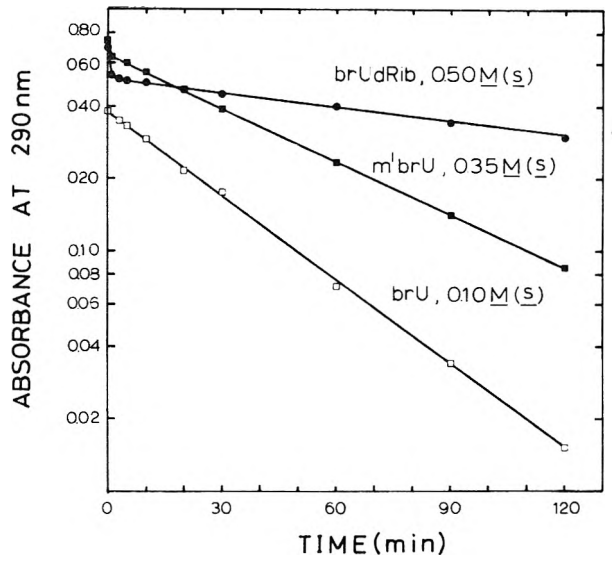


Figure 1. Comparison of absorbance changes of 5-bromouracil, 1-methyl-5-bromouracil, and 5-bromo-2′-deoxyuridine in the reaction with sodium bisulfite. Concentration of the bromouracil derivatives at time zero was 1.0×10^{-3} *M*. Incubations were at pH 7.0 and 17°. (*s*) represents total bisulfite buffer concentration.

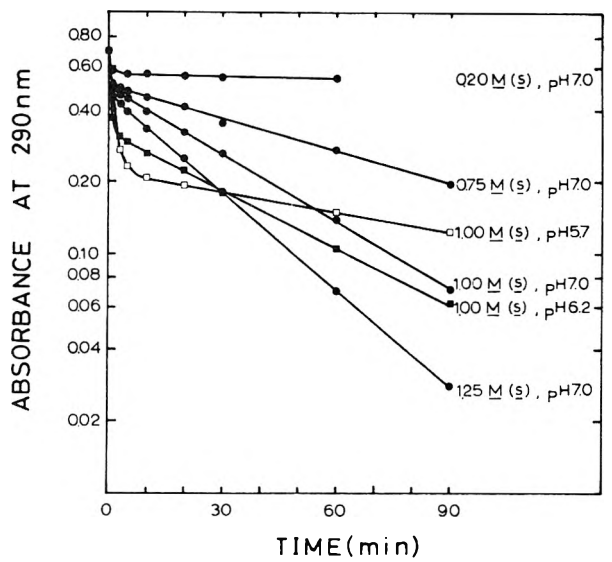


Figure 2. Reaction of 5-bromo-2′-deoxyuridine (1.0×10^{-3} *M*) with sodium bisulfite as functions of the bisulfite buffer concentration (*s*) and the pH. Reaction temperature was 17°.

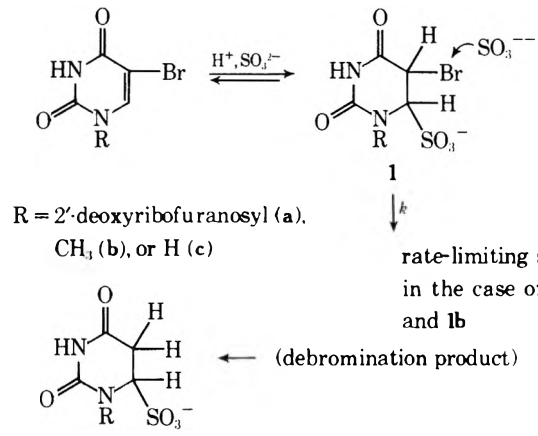
but not the initial addition of bisulfite to the pyrimidine ring.

Results

The reactions were carried out with 1.0×10^{-3} *M* brU (see ref 7), m¹brU or brUdRib, in sodium bisulfite buffer [5×10^{-2} to 1.25 *M* (see ref 8)] at 17°, and the progress of the reactions was followed spectrophotometrically. The change in ultraviolet spectra of brU that occurred on treatment with 0.10 *M* bisulfite at pH 7.0 was similar to that previously reported:[1a] a rapid decrease of the absorbance at the 280–290-nm region and transient appearance of a 260-nm peak, which indicated uracil formation, were observed, followed by a final establishment of an end absorption. On the other hand, in the reaction of brUdRib only a very slow spectroscopic change was detected under identical conditions. At higher bisulfite concentrations, spectral changes of brUdRib were more evident, but in such conditions intermediate formation of 2′-deoxyuridine was difficult to detect since any deoxyuridine formed would have been rapidly converted to 5,6-dihydro-2′-deoxyuridine 6-sulfonate (see below). Thus, the spectra of a solution of brUdRib in 1.0 *M* sodium bisulfite, pH 7.0, did not give any detectable 260-nm peak during the course of the reaction and became finally an end absorption. When the reaction mixture was treated with sodium hydroxide and then analyzed by paper chromatography (solvent, 1-butanol–acetic acid–water, 2:1:1 v/v), 2′-deoxyuridine wac recovered as a sole uv-absorbing product. The identification of 2′-deoxyuridine was made by comparing the R_f value and the uv spectra in neutral and alkaline media with those of an authentic specimen.

The progress of the reactions was determined by the decrease in absorbance of the derivatives at 290 nm where uracil, 1-methyluracil, or 2′-deoxyuridine, if they were formed, do not exhibit any absorbance. Typical examples are shown in Figures 1 and 2, in which A_{290} is plotted on a semilogarithmic scale against time of reaction. Both in the brUdRib– and the m¹brU–bisulfite reactions, a rapid, initial drop and a subsequent, slow and linear decrease of the absorbance were observed. In contrast, the brU reaction did not show such an initial drop and instead gave a straight line, consistent with the previous observation of other workers.[1a] This linear decrease should represent the decrease of the starting material, brU. As can be seen from the figures, the extent of the initial drop was a function of both the bisulfite concentration and the pH of the solution. Thus, the drop was larger at higher bisulfite concentrations and at more acidic conditions. The drop was obviously due to the equilibrium between brUdRib (or m¹brU) and 5,6-dihydro-5-bromo-2′-deoxyuridine 6-sulfonate (**1a**) (Scheme II). It is known that bisulfite adds reversibly to the 5,6 dou-

Scheme II



ble bond of uracil, thymine, and cytosine forming 5,6-dihydropyrimidine 6-sulfonates, and that the latter compounds are stable in acid.[5,6] The formation of the bisulfite adduct **1a** was demonstrated by the following experiments. A solution of 1.0×10^{-3} *M* brUdRib in 1 *M* sodium bisulfite, pH 5.7, was allowed to stand at 17° for 10 min. The A_{290} value of this solution measured in a cuvette of 1 mm light path was approximately 30% of the value for 1.0×10^{-3} *M* brUdRib in water. When the solution was diluted 100 times with 0.1 *M* sodium phosphate buffer of pM 5.8, and the A_{290} was measured in a 10-mm light-path cuvette, a gradual increase of the absorbance was observed. On standing for 90 min, the spectral curve of the solution became identical with that of 1.0×10^{-5} *M* brUdRib (both at pH 5.8 and pH 13), indicating quantitative regeneration of brUdRib from the adduct **1a**. Furthermore, the ^{1}H NMR spectrum of a 10-min incubated solution of brUdRib in 1 *M* sodium bisulfite (pD 5.7) in D_2O gave two singlets at δ 5.23

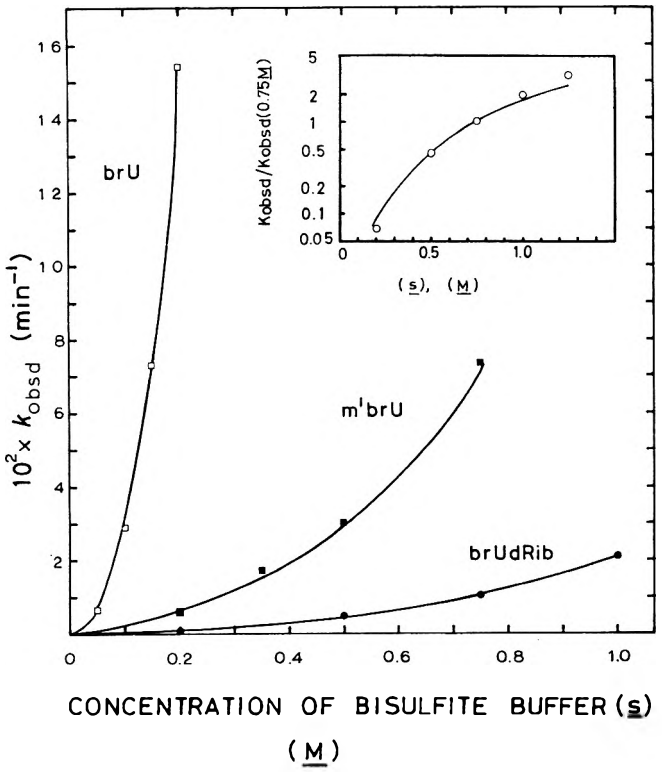


Figure 3. Pseudo-first-order rate constants of the reaction between 5-bromouracil derivatives and sodium bisulfite as a function of the bisulfite buffer concentration. In the inset, the relative rates for the brUdRib–bisulfite reaction are shown in semilogarithmic scale against concentration of bisulfite buffer. The curve in the inset was drawn by the calculation described in the text and the points represent the experimentally observed values.

and 5.35 ppm, assignable[5,6] to the protons at position 6 of two epimers of the adduct **1a**. When the sum of the areas of these two singlets was compared with that of the 6-H signal (8.23 ppm) of brUdRib in this solution, it was found that the ratio of the former to the latter was 7:3. This value is coincident with that (69:31) obtained by the uv measurement (Figure 2).

It can therefore be concluded that the initial rapid decrease of the A_{290} value in the brUdRib and m¹brU reactions represents the accumulation of the bisulfite adduct (1). Subsequent slow, linear decrease must be a reflection of further decomposition of the adduct (1) into debrominated product(s). Furthermore, it is clear that this debromination is the rate-determining step of the overall reaction for brUdRib.

By extrapolating the linear portions to time zero, the A_{290} values at the equilibrium were determined and the values of [**1a**]/[brUdRib][total bisulfite] were found to be 0.51 M^{-1} with 0.5 M bisulfite, 0.47 M^{-1} with 0.75 M bisulfite, 0.44 M^{-1} with 1.0 M bisulfite, and 0.45 M^{-1} with 1.25 M bisulfite. The equilibrium constant for buUdRib + sodium bisulfite $\rightleftarrows$ **1a** was thus estimated at 0.47 ± 0.02 M^{-1} (pH 7.0, 17°).

In the brU–bisulfite reaction, in which no initial drop of A_{290} was noted, there are two possibilities concerning the rate-determining step. First the addition of bisulfite to the 5,6 double bond of brU is the rate-determining step in the overall reaction sequence, and the subsequent debromination of the adduct **1c** is faster than the first step. In this case, the linear decrease in A_{290} should represent the velocity of addition of bisulfite across the 5,6 double bond of brU [assuming that the reverse reaction (elimination) is much slower than the forward reaction]. Second, the amount of the intermediate **1c** is undetectably small and the rate-determining step is the debromination rather than the formation of **1c**. These two alternatives cannot be distinguished by the present data.

Figure 3 summarizes the apparent pseudo-first-order rate constants obtained from the linear portions of the curves such as those in Figures 1 and 2, and shows them as a function of the bisulfite concentration. A strikingly great difference in the reactivity of brU and brUdRib is obvious from this figure. At one bisulfite concentration the rates for these three substrates were compared. Thus, the k_{obsd} values in 0.20 M sodium bisulfite, pH 7.0, were 0.154, 0.0059, and 0.00072 min^{-1} for brU, m¹brU, and brUdRib. It can therefore be estimated that the debromination of brU is two orders of magnitude faster than that of brUdRib. It should be noted that the rates for brU may represent merely the velocity of the adduct **1c** formation and, if so, the rate of the subsequent debromination step must be larger than the observed rate. m¹BrU was more reactive than brUdRib but the difference between brU and m¹brU was much larger than that between m¹brU and brUdRib.

We examined the possibility that the pH profile of the reaction might be greatly different among the substrates and the phenomenon we were observing was an extreme case. That this was not so was shown by the fact that both the brUdRib– and the brU–bisulfite reactions are optimal at pH about 7. Thus, the k_{obsd} (min^{-1}) values follow: with brUdRib (in 1.0 M bisulfite), 0.0061 at pH 5.7, 0.018 at pH 6.2, 0.021 at pH 7.0, and 0.003 at pH 7.9; with brU (in 0.10 M bisulfite), 0.0077 at pH 5.7, 0.029 at pH 7.0, and 0.0088 at pH 8.0.

The results in Figure 3 also indicate that the rate for either of the three substrates is a function of more than first order of the total bisulfite–buffer concentration. A similar relationship was previously observed for the brU–bisulfite system.[1b]

In the reaction of brUdRib (and m¹brU) with bisulfite, the expression

$$k_{obsd} = kK(s)^2/[1 + K(s)] \quad (1)$$

can be derived, where k represents the rate constant for the debromination, K the equilibrium constant for brUdRib + HSO_3^- (total buffer) $\rightleftarrows$ **1a**, and (s) total bisulfite buffer concentration. Expression 1 indicates that the experimentally determined k_{obsd} values at various bisulfite concentrations should be related by [k_{obsd} at buffer concn (s)]/[k_{obsd} at buffer concn (s')] = $(s)^2[1 + K(s')]/(s')^2[1 + K(s)]$. Employing the K value 0.47 M^{-1} experimentally determined as already described, theoretical relative rates were plotted against (s) and compared with those observed. As shown in the inset of Figure 3, the experimental values were reasonably coincident with the theoretical ones. It was therefore concluded that the reaction scheme illustrated in Scheme II is basically correct.

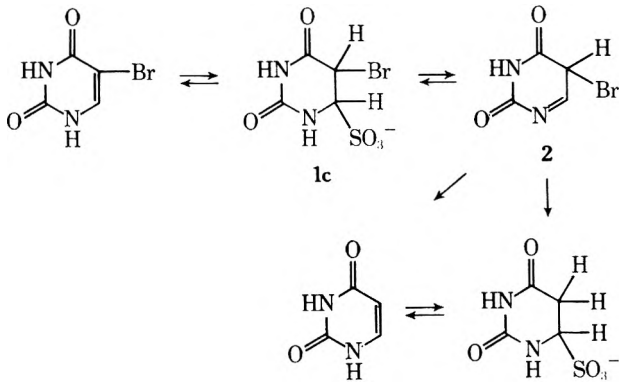
By use of expression 1 and the k_{obsd} values, the rate constant k can be calculated. From the k_{obsd} values found for the 0.5, 0.75, 1.0, and 1.25 M bisulfite reactions, the k value was estimated to be 0.061 ± 0.008 l. mol^{-1} min^{-1}.

We measured velocity of bisulfite addition to 2′-deoxyuridine under conditions identical with those employed in the brUdRib–bisulfite reaction and found that it is greater than the velocity of the decomposition of the adduct **1a**. The apparent pseudo-first-order rate constants found were 0.0533 min^{-1}/1.0 M sodium bisulfite, and 0.0147 min^{-1}/0.50 M sodium bisulfite at pH 7.0 and 17°, the initial deoxyuridine concentration being 0.010 M. This finding indicates that if ever deoxyuridine is produced from the adduct **1a** it will escape detection.

Discussion

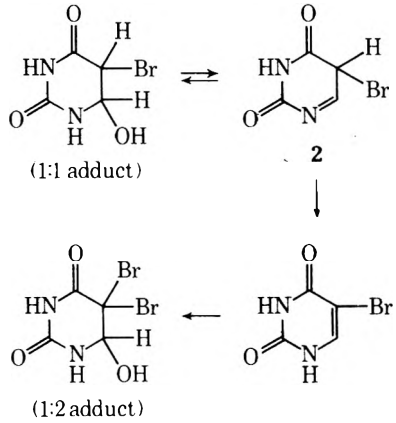
The results presented above showed that the breakdown of the adduct **1c** is very much faster compared with the N^1-substituted adducts **1a** and **1b**. Although the different reactivities of these substrates might be attributable to steric hindrance of the N^1 substituents, a more likely explanation for the very large reactivity difference is provided by postulating the intermediate **2** in the brU–bisulfite reaction (Scheme III). Sulfite will reductively subtract the bromine

Scheme III



atom[1b] of **2** to give uracil and 5,6-dihydrouracil 6-sulfonate. It is known that the 5,6-dihydrouracil 6-sulfonate is produced not necessarily via uracil.[4] Support for the possibility of the existence of intermediate **2** is found in the recent finding that titration of uracil with bromine results in the formation of an uracil–bromo (1:2) adduct, whereas titration of 1-methyluracil gives a 1:1 adduct.[10] In explanation, the intermediate **2** was postulated, whose formation is the

Scheme IV



crucial step for the generation of the 1:2 adduct (Scheme IV). In contrast to the sulfite-mediated debromination, in which a bromonium ion rather than a proton is subtracted at position 5 of **2**, bromine deprotonates **2** to give brU. The workers[10] postulated that this occurs via the formation of an *N*-bromo derivative of **2**.

In the brUdRib- and m^{1}brU–bisulfite reactions, the formation of intermediate **2** would be blocked or extremely difficult because it requires quaternization of the nitrogen at position 1. Direct reduction of the adduct **1** by sulfite anion will also be a slow reaction owing to electronic repulsion by the sulfonate group at position 6. Therefore, the debromination of brUdRib and m^{1}brU will proceed much more slowly than that of brU, by taking either the direct route or the indirect route to the final product.

Besides bisulfite, cysteine debrominates both brU and brUdRib under mild conditions. In the case of cysteine, however, no great difference is existent between the reactivities of brU[1c] and brUdRib.[3] An explanation for this is the following. In the cysteine-mediated debromination of brUdRib, the initial addition of the nucleophile across the 5,6 double bond of the pyrimidine was supposed to be the rate-determining step. In this regard, the bisulfite-mediated debromination of brUdRib is different from the cysteine reaction, because its rate-determining step is not the initial addition of the nucleophile but the subsequent debromination.

It is interesting that the reactivity at the position β to the glycosidic linkage is so much different between a nucleoside and the corresponding base. The present finding indicates that reactions at position 5 of pyrimidine nucleosides and bases should always be carefully compared.

Experimental Section

General. BrUdRib and brU were products of Sigma Chemical Co. and were used without further purification. m^{1}BrU was prepared according to the literature.[11] Proton magnetic resonance spectra (100 MHz) were measured on a Jeol NM-4H-100 spectrometer.

Kinetic Measurements. All reactions were performed in deionized, distilled water. Sodium bisulfite buffers were always freshly prepared before use. The pH was fixed by mixing appropriate amounts of $NaHSO_3$ and Na_2SO_3. The reactions were run under nitrogen atmosphere at room temperature which was maintained at 17 ± 0.5°. Progress of the reaction was monitored by determining A_{290} in a cuvette of 1-mm light path against a reference in which brU derivative was omitted from the reaction mixture, using a Beckman Acta CIII spectrophotometer. The pH of the reaction mixture was measured both at zero time and after the incubation was over. The value generally did not exhibit any change, except in the case where 0.050 *M* bisulfite buffer was used, and the pH was 7.0 at zero time and 6.85 after 180-min incubation. The zero time A_{290} values employed were those obtained with solutions omitting the bisulfite buffer from the reaction mixture (reference, H_2O).

Acknowledgments. We thank Dr. Y. Kawazoe of National Cancer Center Research Institute and Mr. M. Shiragami of this laboratory for valuable discussions.

Registry No.—5-Bromo-2′-deoxyuridine, 59-14-3; 1-methyl-5-bromouracil, 6327-97-5; 5-bromouracil, 51-20-7.

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(7) Abbreviations used are: brU, 5-bromouracil; m^{1}brU, 1-methyl-5-bromouracil; and brUdRib, 5-bromo-2′-deoxyuridine.
(8) The concentrations represent total buffer concentrations.
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Synthesis in the Pyrrolizidine Class of Alkaloids. *dl*-Supinidine[1]

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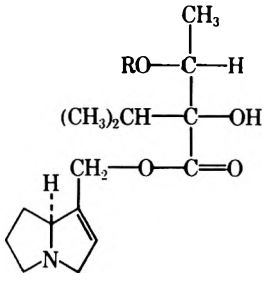
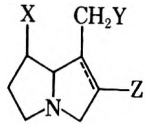
A nitrone based entry to the pyrrolizidine class of alkaloids is described. The synthesis of supinidine (3), the necine base obtained from supinine (**1a**) and heleurine (**1b**), illustrates the approach used.

Pyrrolizidine alkaloids, also referred to as the Senecio alkaloids, occur naturally in various plant species and have been the subject of several excellent reviews.[2-5] Many of the alkaloids of this class are toxic, causing liver tumors and lung damage in animals feeding on plants containing these compounds. The alkaloids usually consist of a pyrrolizidine ("necine") base and a carboxylic ("necic") acid coupled by an ester linkage (cf. **1**).



1a, R = H
b, R = CH_3



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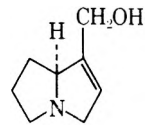
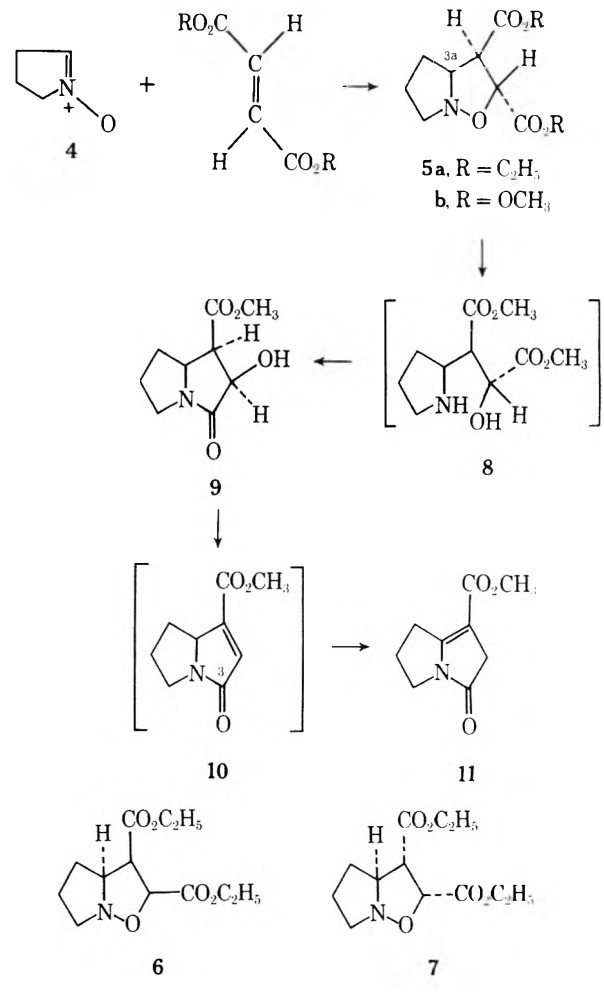


3

The necine bases embody a pyrrolizidine nucleus with a one-carbon side chain and usually one or more hydroxyl groups positioned as shown in structure **2**, where X, Y, and Z may be H or OH, and a double bond is frequently located (i.e., when Z = H) at the position indicated by a dotted line. It is the unsaturated pyrrolizidine alkaloids that are principally involved in the hepatotoxicity of these compounds.[5] Although considerable synthetic effort has been directed toward the pyrrolizidine bases, the synthesis of supinidine[6] (**3**), the necine base derived from supinine (**1a**) and heleurine (**1b**), was not achieved[7-10] at the outset of this work.[7]

Synthetic Approach. Initially, we sought a nitrone based approach to supinidine which would involve an addition to a symmetrical dipolarophile, thereby avoiding any potential problems involving the regioselectivity of the cycloaddition. Toward this end, we examined the reaction of 1-pyrroline 1-oxide (**4**) with both diethyl fumarate and diethyl maleate. Each reaction provided two isomeric adducts in a 2:1 ratio (e.g., **6** and **7** from diethyl maleate and **4**). The stereochemistry of the hydrogen at C_{3a} in adduct **5a** is unspecified in Chart I. In an effort to simplify the NMR spectra of the adducts, the cycloaddition of the nitrone **4** with dimethyl fumarate was investigated. Once more a mixture of two isomeric adducts was produced with properties similar to those observed for the diethyl fumarate adducts. No effort was made to separate these adducts since both isomers would, by the synthetic plan, lead to the same target. Hydrogenolysis of the nitrogen–oxygen bond in the dimethyl maleate adduct mixture led to the formation of hydroxylactam **9**, presumably as a mixture of two stereoisomeric adducts. This mixture was dehydrated via the corresponding tosylate according to the procedure of Nair and Adams.[9] A solid unsaturated ester (i.e., **11**) was obtained which did not exhibit olefinic protons in its NMR spectrum but which did have spectral properties identical with those of **11** previously reported by Goldschmidt.[10] Thus, the

Chart I

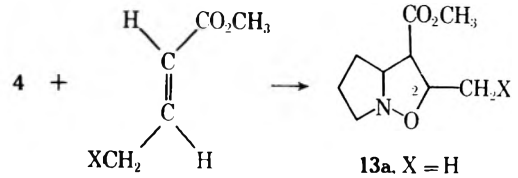


elimination apparently proceeded through the intermediacy of the desired cross conjugated keto ester **10** on the way to the undesirable vinylogous lactam **11**.

Several attempts were made to dehydrate **9** directly. Geissman's method[11] (employing barium hydroxide), phosphorus pentoxide in benzene, or *p*-toluenesulfonic acid in benzene did not lead to readily identifiable material.

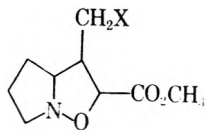
The facility of the isomerization of **10** → **11**, coupled with the failure of a similar dehydration to occur in Geissman's retronecine synthesis,[11] suggests that the cross conjugated nature of **10** may be responsible for its facile transformation into **11**. Thus, we sought to explore synthetic possibilities which precluded the existence of a carbonyl group at C_3 in **10**. This led us to explore the reaction of 1-pyrroline 1-oxide (**4**) with unsymmetrical dipolarophiles.

Unsymmetrical Dipolarophiles. The major difficulty envisioned with the use of unsymmetrical dipolarophiles, such as γ-substituted crotonates (e.g., **12**), was the possibility of a substantial stereochemical preference for the undesirable α-oxy ester isomer **14**.[12,13]



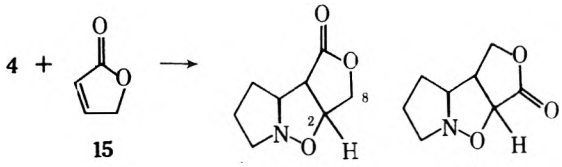
12a, X = H,
b, X = OH

13a, X = H
b, X = OH
c, X = OMs



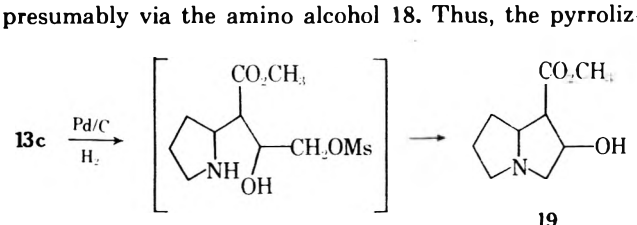
14a, X = H
b, X = OH

Our initial regiochemical probe was 1-butenolide[14] (15). Reaction of nitrone 4 with 15 resulted in the isolation of a single adduct, 16, the orientation of which encouraged further exploration of this approach. The orientation was assigned on the basis of a spin decoupling experiment. The NMR spectrum of 16 exhibits a seven-line pattern at 4.9 ppm, attributed to the proton at C_2. Double irradiation of this signal caused the signal due to the adjacent methylene protons at 4.4 ppm to collapse to a singlet. Similarly, double irradiation of the methylene signal caused the multiplet at 4.9 ppm to collapse to the expected doublet ($J_{2,3}$ = 7, $J_{2,8e}$ = 5 Hz). Clearly, one would expect H_2 for the alternate adduct 17 to be a doublet prior to irradiation, and the downfield methylene protons should not have been coupled to the proton at C_2. While efforts to convert 16 into supinidine met with difficulty, the regiochemistry of the cycloaddition involving 1-butenolide encouraged us to pursue similar chemistry using substituted crotonates of the type 12. We found that the addition of methyl crotonate (12a) to nitrone 4 afforded 13a, consistent with similar findings of Murray and Turner[15] in a related reaction. Hydrogenolytic cleavage of 13a gave a compound which exhibited a positive iodoform test. In addition, the NMR spectrum of 13a shows the H_2 proton signal to be a multiplet ($J_{2,3}$ = 8.6, $J_{2,8}$ = 6.1 Hz) rather than the doublet anticipated for 14a.

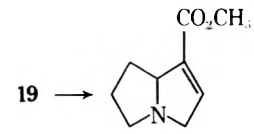


15 16 17

The cyclization was studied using methyl γ-hydroxycrotonate (12b). A light yellow liquid was obtained in 80% yield which, upon chromatography through Florisil, afforded the adduct 13b as colorless crystals. The NMR spectrum of this adduct contained a six-line pattern at 4.23 ppm integrating for one proton, strongly suggesting that the adduct had the orientation depicted by 13b, and not by 14b. Conversion to the methanesulfonate proceeded in 94% yield. Hydrogenolysis occurred over 10% palladium on carbon to give β-hydroxy ester 19 as a white solid in 95% yield, presumably via the amino alcohol 18. Thus, the pyrrolizidine system has been assembled with functionality appropriate for the subsequent elaboration into supinidine. To effect this transformation, 19 was subjected to dehydration conditions with phosphorus oxychloride in pyridine at 20° or below. A pale yellow liquid was isolated which exhibited an olefinic stretching band at 6.08 μ in its ir spectrum and a band at λ_{max} (ethanol) 214 nm (ε 7375) in its uv spectrum. The NMR spectrum contained a one-proton multiplet at δ (Me_4Si, carbon tetrachloride) 6.7 ppm attributed to the vinyl proton in 20. The β-vinyl protons in methyl crotonate, methyl γ-hydroxycrotonate, methyl γ-chlorocrotonate, and methyl 1-cyclopentenecarboxylate fall in the range (Me_4Si) 6.7–7.0 ppm in carbon tetrachloride solution.

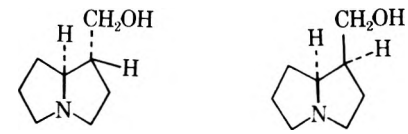


18 19



20

Finally, the unsaturated ester 20 was converted into *dl*-supinidine (3) using a mixed hydride reagent prepared from lithium aluminum hydride and aluminum chloride.[17] Reduction with lithium aluminum hydride also led to extensive reduction of the double bond.[18] The mixed hydride method led to a 3:2:6 mixture, the major constituent of which was *dl*-supinidine, purified by preparative gas–liquid phase chromatography, as determined by spectral comparisons with authentic material. The *dl*-supinidine (3) so obtained possessed NMR, ir, and mass spectra virtually identical with those of supinidine obtained by hydrolysis of supinine (1a). The other constituents of the reduction mixture were presumably trachelanthamidine (21) and isoretronecanol (22). The infrared spectra of both compounds were very similar to the published spectrum[8] of 1-hydroxymethylpyrrolizidine. A mass spectrum of the major saturated isomer was virtually identical with the corresponding spectrum of trachelanthamidine (21).



21 22

Experimental Section

All melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on the Beckman IR-5a spectrophotometer and calibrated using the 6.24-μ band of polystyrene. Proton magnetic resonance spectra were obtained using a Varian A-60 spectrometer using tetramethylsilane as the internal standard. Notations s, d, t, q, m, and br designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. Mass spectra were recorded on a CEC-120 spectrometer at an ionization potential of 77.5 V. Ultraviolet spectra were obtained on a Perkin-Elmer Model 202 spectrophotometer.

1-Pyrroline 1-Oxide (4). 1-Pyrroline 1-oxide was prepared according to the method of Thesing and Sirrenberg[20] in an overall yield of 40%: bp 74–76° (0.1 mm) [lit.[20] bp 65° (0.07 mm)]; ir (film) 6.32 (s), 7.98 μ (s).

Addition of 1-Pyrroline 1-Oxide to Diethyl Maleate. A 1.3-g (15 mmol) sample of 1-pyrroline 1-oxide was dissolved in 150 ml of chloroform and to this was added 2.53 g (15.3 mmol) of diethyl maleate. The solution was stirred at 25° for 1 hr. A 10% excess of diethyl maleate was then added and the solution was refluxed for 1 hr. Evaporation of the chloroform under reduced pressure afforded a light yellow liquid. Distillation gave 1.17 g (24% yield) of a clear liquid, bp 95–97° (4 mm). Chromatography ofthe liquid through Florisil afforded two fractions, both liquids, which appeared to be isomers. Isomer A obtained from elution with 1:1 ether–acetone gave an analytical sample with ir (film) 5.75–5.80 (s), 8.3–8.55 μ (s);

λ_{max} (EtOH) 206 nm (ϵ 383); NMR (CCl_4) δ 4.7 (d, 1), 4.15 (cp, 5), 2.95–3.25 (j, 3), 1.6–2.2 (m, 4), and 1.15–1.45 ppm (two overlapping triplets, 6).

Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found (isomer A): C, 56.24; H, 7.66; N, 5.78. Found (isomer B): C, 55.90; H, 7.41; N, 5.75.

Addition of 1-Pyrroline 1-Oxide to Diethyl Fumarate. To a well-stirred solution of 6.65 g (78 mmol) of 1-pyrroline 1-oxide and 75 ml of chloroform was added 13.4 g (78 mmol) of diethyl fumarate and the resulting solution was refluxed for 1 day. Evaporation of the chloroform under reduced pressure followed by distillation of the liquid residue gave a light yellow liquid: 18 g, 90% yield; bp 116–117° (0.4 mm); ir (film) 5.71–5.75 (s), 8.3–8.35 μ (s); NMR (CCl_4) δ 4.75 (d, J = 5 Hz) and 4.55 ppm (d, J = 8 Hz) in a 1:2 area ratio, respectively, corresponding to H_2 of two different stereoisomers. No attempt was made to separate the isomers.

Dimethyl Hexahydropyrrolo[1,2-*b*]isoxazole-2,3-carboxylate (5b). Dimethyl fumarate (2.1 g, 15 mmol) was added to a stirred solution of 25 ml of chloroform and 1.3 g (15 mmol) of 1-pyrroline 1-oxide. A 24-hr reflux period afforded a light yellow solution. The chloroform was evaporated under reduced pressure and the remaining liquid distilled under vacuum. A yellow liquid was obtained: 2.17 g, 62% yield; ir (film) 5.69–5.76 μ (s); NMR ($CDCl_3$) δ 1.6–2.25 (cp, 4), 2.83–3.55 (cp, 3), 3.75–4.18 (cp, 7), and 4.58–4.98 (cp, 1).

Methyl 2-Hydroxy-3-oxopyrrolizidine-1-carboxylate (9). A solution of 2 g (8.7 mmol) of dimethyl hexahydropyrrolo[1,2-*b*]isoxazole-2,3-carboxylate (**5b**) in 60 ml of methanol was hydrogenated for 4 hr using 100 mg of 10% palladium on carbon. Filtration through Celite followed by removal of the methanol under reduced pressure afforded a greenish-white solid. Recrystallization from acetone–hexane gave a brownish solid: mp 118–128°; ir 2.96 (m), 5.75 (s), and 5.92 μ (2).

Dehydration of Methyl 2-Hydroxy-3-oxopyrrolizine-1-carboxylate. Following the procedure of Nair and Adams,[9] 500 mg (2.5 mmol) of methyl 2-hydroxy-3-oxopyrrolizidine-1-carboxylate (**9**) in 5 ml of pyridine was cooled to −10°. To this was added 477 mg (2.5 mmol) of toluenesulfonyl chloride in one portion and the resulting solution was stored at 0° for a short time. Small pieces of ice were slowly added until ca. 25 ml of water had been introduced. The solution was then acidified with 20% HCl and extracted with chloroform. The chloroform solution was dried over anhydrous magnesium sulfate. Evaporation of the chloroform under reduced pressure afforded a brown liquid which was chromatographed through alumina (Woelm). Elution with 50:50 ether–chloroform gave a pale yellow solid: uv λ_{max} (ethanol) 218 nm (ϵ 4600) and 289 (12700) [lit.[10] λ_{max} (ethanol) 218 nm (ϵ 4600) and 288 (12000)]; ir ($CHCl_3$) 5.84 (s), 5.98 (s), and 6.02 μ (m), very similar to that reported by Goldschmidt.[10]

Methyl γ-Bromocrotonate. A well-stirred mixture of 20.5 g (0.205 mol) of methyl crotonate, 110 ml of carbon tetrachloride, 29.1 g (0.164 mol) of *N*-bromosuccinimide, and a small amount (ca. 10 mg) of benzoyl peroxide was refluxed for 48 hr. Filtration and evaporation of the carbon tetrachloride under reduced pressure afforded a yellow liquid. Distillation of the liquid gave a clear liquid: 23 g, 80% yield; bp 92–95° (10 mm) [lit.[19] bp 83–85° (13 mm)]; ir (film) 5.77 (s), 5.97 (w), 10.22 μ (m); NMR (CCl_4) δ 3.72 (s, 3), 409 (q, 2), 606 (m, 1), 7.0 (m, 1).

1-Butenolide (15). The unsatured lactone 1-butenolide was prepared in a two-step synthesis according to the method of Judge and Price[14] in an overall yield of 16%: ir (film) 5.63 (s), 5.73 (s), 6.20 μ (w); NMR (CCl_4) δ 4.95 (q, 2), 6.15 (m, 1), 7.8 (m, 1); bp 88–89° (2 mm) [lit.[14] bp 94–98° (2 mm)].

Hexahydro-2-(hydroxymethyl)pyrrolo[1,2-*b*]isoxazole-3-carboxylate Lactone (16). A stirred solution of 2.7 g (3.3 mmol) of 1-pyrroline 1-oxide, 2.7 g (3.3 mmol) of 1-butenolide, and 70 ml of chloroform was refluxed for 8 hr and stirred at 25° for 24 hr. Evaporation of the chloroform under reduced pressure left a brown solid. Recrystallization using hexane afforded white needles: 2.3 g, 43% yield; mp 87–89°; ir (film) 5.59–5.66 (s), 8.46 μ (s); uv λ_{max} (MeOH) 206 nm (ϵ 422); NMR ($CDCl_3$) δ 1.5–2.4 (cp, 4), 3.0–3.58 (cp, 3), 3.68–4.02 (broad triplet, 1), 4.35–4.5 (t, 2), 4.8–5.08 (m, 1).

Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 57.08; H, 6.58; N, 8.26.

Methyl Hexahydro-2-methylpyrrolo[1,2-*b*]isoxazole-3-carboxylate (13a). A solution of 2.7 g (31 mmol) of 1-pyrroline 1-oxide and 10 g of methyl crotonate was stirred at 25° for 24 hr. The excess methyl crotonate was removed under reduced pressure and the remaining liquid was distilled under vacuum. A clear liquid, 5.0 g (87% yield), was obtained: bp 77–79° (0.2 mm); ir (film) 5.74 (s), 8.31 μ (s); NMR (CCl_4) δ 4.25 (m, 1), 3.6–4.0 (m, 1), 3.7 (s, 3), 3.05 (m, 3), 1.5–2.0 (cp, 4), and 1.25 ppm (d, 3, J = 7 Hz).

Methyl 2-(Pyrrolidin-2-yl)-3-hydroxybutyrate. Catalytic hydrogenation using 160 mg of 10% Pd/C was carried out on a solution of 4.4 g (24 mmol) of methyl hexahydro-2-methylpyrrolo[1,2-*b*]isoxazole-3-carboxylate in 150 ml of methanol for 6 hr. The methanol was removed under vacuum and the residue taken up in ether and dried over calcium chloride. Evaporation of the ether under reduced pressure afforded a yellow liquid: 4.3 g, 96% yield; ir (film) 2.97 (m), 5.77 (s), 9.04 μ (s); NMR (CCl_4) δ 1.05 (d, 30), 1.4–1.97 (cp, 4), 2.32–2.96 (cp, 3), 3.18–3.38 (cp, 2), 3.56 (s, 3), 3.77–4.32 (cp, 2). The OH proton signal at 3.77–4.32 ppm disappeared on shaking with D_2O. The product also gave a positive iodoform test.

Methyl γ-Hydroxycrotonate (12b). An adaptation of the method of Rambaud[16] was employed. To a well-stirred mixture of 105 ml of water and 11.6 g (0.05 mol) of silver oxide was added 17.9 g (0.1 mol) of methyl γ-bromocrotonate. The mixture was stirred for 24 hr at 25° and then heated for 6 hr at 60°. Filtration and evaporation of the water under reduced pressure gave a liquid residue which was distilled under vacuum. A clear liquid was obtained: 6.0 g, 51%; bp 77–80° (0.3 mm) [lit.[16] bp 118° (15 mm)]; ir (film) 2.9 (s), 5.77 (s), and 5.98 μ (m); NMR (CCl_4) δ 3.65 (s, 3), 4.8 (s, 3), 6.0 (m, 1), 7.0 (m, 1).

Methyl Hexahydro-2-hydroxymethylpyrrolo[1,2-*b*]isoxazole-3-carboxylate (13b). To a stirred solution of 19 g (0.164 mol) of methyl γ-hydroxycrotonate in 65 ml of chloroform was added 14 g (0.164 mol) of 1-pyrroline 1-oxide under a nitrogen atmosphere. The mixture became warm on addition and was stirred for 4 hr at 25°, then refluxed for 12 hr. The chloroform was evaporated under vacuum and the residue chromatographed through 340 g of silica gel. Elution with chloroform, ethyl acetate, and acetone, respectively, afforded a yellow liquid: 26.4 g, 80%; ir (film) 2.96 (s), 5.73 (s), 6.91 μ (s); NMR (CCl_4) δ 1.5–2.25 (cp, 4), 3.0–3.4 (cp, 2), 3.45–4.1 (cp, 7), 4.2–4.5 (sextet, 1), 4.75 (s, 1, a hydroxyl proton). Careful chromatography of a small amount of this liquid through Florisil afforded a white, crystalline material on elution with benzene–ether. Recrystallization of the solid using ether afforded white prisms: mp 61–63°; ir (KBr) 3.12 (m), 5.75 (s), 6.94 μ (m); the NMR spectrum of the solid was the same as that of the liquid; NMR ($CDCl_3$) δ 4.35 (m, 1), 4.15 (s, 1, OH), 3.70 (s, 3) 3.50–4.00 (cp, 4), 3.18 (cp, 2), and 1.5–2.3 (cp, 4).

Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.14; N, 6.96. Found: C, 53.42; H, 7.17; N, 7.20.

The Methanesulfonate of Methyl Hexahydro-2-hydroxymethylpyrrolo[1,2-*b*]isoxazole-3-carboxylate (13c). Methyl hexahydro-2-hydroxymethylpyrrolo[1,2-*b*]isoxazole-3-carboxylate (**13b**, 5 g; 24.8 mmol) was dissolved in 50 ml of anhydrous pyridine and the solution was cooled to −15°. To this solution was added 3.1 g (27.5 mmol) of methanesulfonyl chloride and the solution was kept at 0° for 3 hr. Small pieces of ice were then introduced until ca. 10 ml of water had been added. Ice–water (50 ml) was then added and the resulting aqueous solution was extracted with four 125-ml portions of chloroform. The combined chloroform extracts were shaken with 200 ml of a sodium bicarbonate solution. The chloroform layer was dried over anhydrous magnesium sulfate. Evaporation of the chloroform and pyridine under vacuum afforded a light yellow liquid: 6.5 g, 94% yield; ir (film) 5.75 (s), 6.92 (m), 7.38 (s), 8.50 μ (s); NMR ($CDCl_3$) δ 1.45–2.3 (cp, 4), 2.9–4.15 (cp, includes two singlets, 10), 4.2–4.4 (d, 2), 4.42–4.8 (cp, 1).

Methyl 2-Hydroxypyrrolizidine-1-carboxylate (19). Compound **13c**, the methanesulfonate of methyl hexahydro-2-hydroxymethylpyrrolo[1,2-*b*]isoxazole-3-carboxylate (6.58 g, 24 mmol), was dissolved in 50 ml of methanol and to this was added 300 mg of 10% Pd/C. The mixture was hydrogenated for 24 hr and filtered and the methanol was removed under vacuum. A light yellow oil remained which was dissolved in chloroform (150 ml) and shaken with 35 ml of a 1 *N* sodium hydroxide solution. The chloroform layer was dried over anhydrous magnesium sulfate. Evaporation of the chloroform left 4.2 g (95% crude yield) of a white solid. Recrystallization from hexane gave white crystals, mp 97–101°. Sublimation, followed by two successive recrystallizations, afforded white, powdery needles: mp 100–101°; ir (KBr) 2.90 (m), 5.77 (s), 8.61 μ (s); NMR ($CDCl_3$) δ 1.6–2.2 (cp, 4), 2.7–3.5 (cp, 5), 3.65–4.0 (cp, includes a singlet, 4), 4.35–4.65 (cp, 1), and 5.85 (s, 1, OH proton); mass spectrum *m/e* 185, 154, 136, 126, 108, 98, 83 (100), 70, and 55.

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.03; H, 8.31; N, 7.04.

Methyl Pyrrolizid-1-ene-1-carboxylate (20). To an ice-cooled, stirred solution of 11 g (50 mmol) of methyl 2-hydroxypyrrolizidine-1-carboxylate (19) in 100 ml of anhydrous pyridine was slowly added 11.3 g (73 mmol) of phosphorus oxychloride over a 15-min period. The dark brown solution was stirred for 12 min at 0° and the pyridine was then removed under reduced pressure, leaving a dark brown oil. This material was dissolved in 15 ml of ice-cold water and the solution made basic with potassium carbonate. The basic solution was then extracted with six 150-ml portions of ether and the combined ether extracts were dried over magnesium sulfate. Evaporation of the ether under vacuum afforded a dark brown liquid which distilled at reduced pressure. A light yellow liquid was obtained, bp 61–62° (0.05 mm), which was 90% pure as determined by GLC analysis using a 4 ft × 0.25 in. 15% QF-1 column at 140°: yield 3.7 g (35%); ir (film) 5.79 (s), 6.08 (m), 6.92 (m), 7.91 (s), 12.90 (m), 13.42 μ (m); uv λ_{max} (EtOH) 214 nm (ϵ 7375); NMR ($CDCl_3$) δ 6.70 (m, 1), 4.3 (m, 1), 3.75 (s, 3), 1.0–4.0 ppm (m, 8); picrate, mp 160–161° (methanol).

Anal. Calcd for picrate $C_{15}H_{16}N_4O_9$: C, 45.46; H, 4.07; N, 14.14. Found: C, 45.64; H, 4.26; N, 14.45.

***dl*-Supinidine (3).** A mixture of 700 mg of lithium aluminum hydride, 600 mg of aluminum chloride, and 50 ml of anhydrous ether was prepared according to the method of Jorgenson.[17]

To this cooled, stirred solution was slowly added 2.1 g (12.5 mmol) of methyl pyrrolizid-1-ene-1-carboxylate in 10 ml of ether. The mixture was then stirred for 15 min at room temperature and the excess hydride destroyed by adding successive portions of 1 ml of water, 2 ml of 10% sodium hydroxide solution, and 2 ml of water. The ether solution was then filtered and dried over magnesium sulfate. Evaporation of the ether afforded a light yellow liquid which was distilled through a short-path distillation apparatus to give 900 mg of a clear liquid which turned yellow on exposure to air. Gas–liquid chromatographic analysis using a 6 ft × 0.25 in. 20% FFAP-4% KOH column at 160° showed the material to be 50% *dl*-supinidine. The *dl*-supinidine was separated and collected using this column. The infrared spectrum was identical with that of natural supinidine. The NMR spectrum and the mass spectrum were also identical with those of the natural material: ir (neat) 3.2, 3.5, 6.8, 7.5, 8.4, 8.6, 9.0, 9.2, 9.5, 9.8, 11.2, 11.6, 12.4, and 12.7 μ; NMR ($CDCl_3$) 5.8 (br s, 1, OH), 5.50 (m, 1), 2.3–4.5 (cp, 7), 1.3–2.2 ppm (cp, 4); MS *m/e* 139, 138, 122, 111, 108, 94, and 80 (100); picrate mp 124–126° (methanol).

Anal. Calcd for picrate $C_{14}H_{16}N_4O_8$: C, 45.60; H, 4.38; N, 15.21. Found: C, 45.60; H, 4.42; N, 15.22.

Also separated on the above column, under the same conditions, were two compounds in a 3:2 ratio, which afforded ir spectra virtually identical with the published[8] spectrum of 1-hydroxymethylpyrrolizidine. A mass spectrum of the major constituent was virtually identical with the mass spectrum of trachelanthamidine (**21**).[21]

Acknowledgment. We thank Dr. C. C. J. Culvenor for the NMR and ir spectra of natural (−)-supinidine and for the supply of supinine.

Registry No.—**3**, 23185-51-5; **3** picrate, 56783-26-7; **4**, 24423-88-9; **5a** isomer A, 56783-27-8; **5a** isomer B, 56816-53-6; **5b** isomer A, 56783-28-9; **5b** isomer B, 56816-54-7; **6**, 56816-55-8; **7**, 56816-56-9; **9** isomer A, 56783-29-0; **9** isomer B, 56783-30-3; **11**, 56783-09-6; **12a**, 18707-60-3; **12b**, 4508-99-0; **13a**, 56783-10-9; **13b**, 32790-65-1; **13c**, 56783-11-0; **15**, 497-23-4; **16**, 56783-12-1; **19**, 56783-13-2; **20**, 56783-14-3; **20** picrate, 56783-15-4; diethyl maleate, 141-05-9; diethyl fumarate, 623-91-6; dimethyl fumarate, 624-49-7; methyl γ-bromocrotonate, 1117-71-1; *N*-bromosuccinimide, 128-08-5; methyl 2-(pyrrolidin-2-yl)-3-hydroxybutyrate, 56783-16-5; methanesulfonyl chloride, 124-63-0.

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Improved Sulfonate Leaving Groups for the Displacement and Elimination of 3β-Hydroxy and 11α-Hydroxy Steroids

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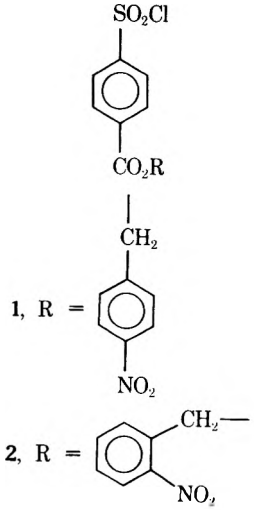
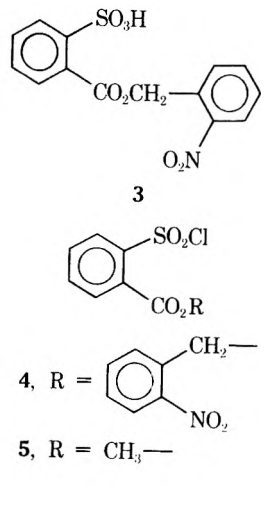
Steroidal 3β- or 11α-3-pyridinesulfonates and various *o*- and *p*-(alkyloxycarbonyl)benzenesulfonates undergo facile displacement. Elimination of these sulfonates, and particularly of o-nitrobenzenesulfonate, is very rapid and results in the corresponding olefins with very good yield under mild conditions.

In the course of chemical synthesis and structural modification one is occasionally faced with cases of extremely difficult displacements of sulfonates, typically, methanesulfonates or the better leaving *p*-toluenesulfonates.[1] The displacement of methanesulfonate esters of 11α-hydroxy steroids is particularly difficult and, in the past, the conversion of 11α-hydroxy functions into 11β-fluoro and with lesser efficacy into other substituents was carried out employing *N*-(2-chloro-1,1,2-trifluoroethyl)diethylamine with the corresponding lithium salt in great excess.[2] In the above case one starts from the alcohol and proceeds to the final product without isolating an intermediate. Other similar approaches are known (examples can be found in ref 3). It is not apparent, however, how applicable they might be to certain polyfunctional molecules of interest to us. An alternative approach, presented here, would be the utilization of sulfonates with better leaving group properties.[4] These might be advantageous also in providing us with facile eliminations. Our study included 11α-sulfonates and also the less hindered 3β-sulfonates.

Results and Discussion

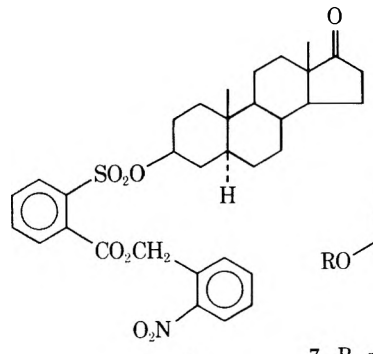
Compounds **1** and **2** were prepared by treating the corresponding nitrobenzyl alcohol with *p*-(chlorosulfonyl)benzoyl chloride.[5] Compounds **4** and **5** were prepared through

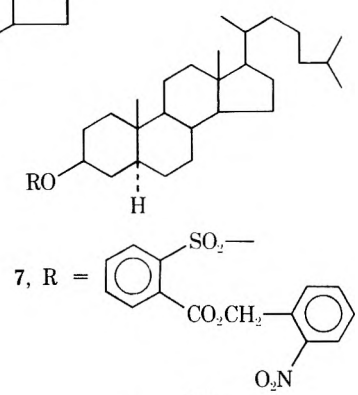


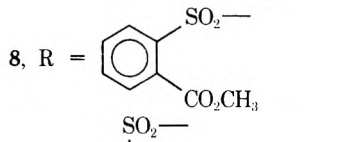


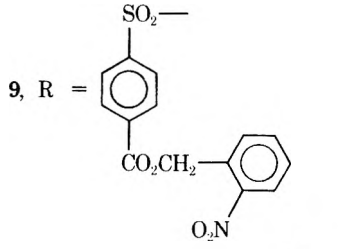
alcoholysis of sulfobenzoic anhydride with o-nitrobenzyl alcohol or with methanol[6] followed by treatment with phosphoric pentachloride. All the sulfonates described (compounds **6**, **7**, **8**, **9**, **13**, **14**, and **15**) were prepared by allowing the parent alcohol and the corresponding sulfonyl chloride to react in pyridine at room temperature.

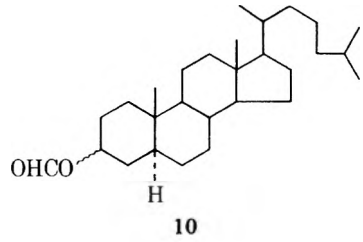
p-Toluenesulfonates, and in particular steroidal 3β-*p*-toluenesulfonyloxy compounds, are known[7] to undergo both displacement and elimination in dimethylformamide. When sulfonates **7**, **8**, **9**, and the corresponding *p*-toluenesulfonate were heated in dimethylformamide, they gave

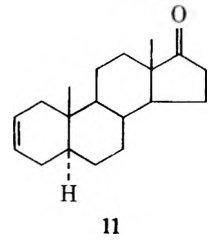






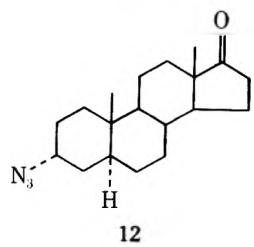






2,5α-cholestene and the 3-formate **10** in approximately 1:1 ratio. While a complete reaction for compound **7** required heating at 95° for 1 hr, the *p*-toluenesulfonate reaction proceeded under identical conditions to the extent of only 5%. The order of reactivity is **7** > **8**, **9** ≫ 3-*p*-toluenesulfonate. Elimination in hexamethylphosphoramide proceeded in a similar fashion. The reaction in dimethylformamide was further studied with compound **8**. The major products, 2,5α-cholestene and the formate **10** (apparently a result of inversion accompanied to a small extent by retention), were characterized.

Azide displacement of sulfonates in hexamethylphosphoramide occurs readily at the 3 position,[8] thus compound **6** was easily transformed to compound **12**. At the sterically hindered 11 position it is still a smooth reaction when the appropriate leaving groups are selected. Compounds **13** and



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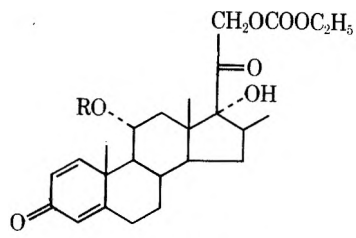
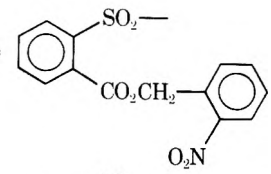
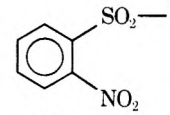
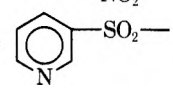
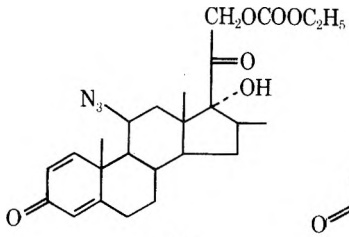


13, R = 

14, R = 

15, R = 

16, R = CH_3SO_2—



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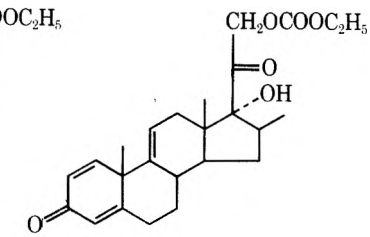

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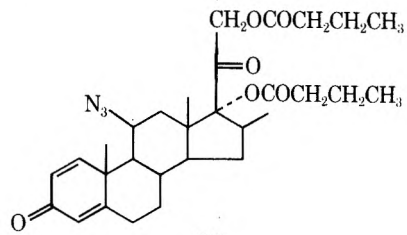

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15 were converted to compounds **17** (displacement and inversion) and **18** (elimination) in 30 min at 90°. Traces of the parent alcohol accompany these two major products. The configuration of compound **17** at C-11 was ascertained by NMR, employing a shift reagent. H-11 appears as a narrow multiplet, indicating that H-11 is equatorial. The reaction of the methanesulfonate **16** appears to be about 20 times slower. *o*-Nitrobenzenesulfonyloxy (compound **14**) can be considered to be an excellent leaving group. It leads, however, to a complication of aromatic ring substitution: formation of the partially characterized compound **19** containing nitro, azide, sulfur, and aromatic ring protons.

With respect to elimination (in hexamethylphosphoramide) the order is *o*-nitrobenzenesulfonyl > 3-pyridinesulfonyl > *o*-nitrobenzyl *o'*-(sulfonyl)benzoate ≫ *p*-toluenesulfonyl. The elimination of these improved leaving groups is not only fast; after 40 min at 85° compound **14** eliminates quantitatively. As the result, compound **11** was isolated in 93% yield and compound **18** in 87% yield.

It is pertinent to note that while in the sterically crowded 11α position elimination led always to compound **18**, azide displacement could be complicated by undesired reactions. Thus, in analogy with the results of Wu, Anderson, Slife, and Jensen,[9] which appeared while this work was in progress, the *o*-nitrobenzenesulfonate (**14**) gave elimination, aromatic ring substitution,[10] and cleavage to the 11α-alcohol. We overcame this difficulty by selecting the somewhat less reactive 3-pyridine sulfonate (**15**) and the *o*-nitrobenzyl *o'*-(sulfonyl)benzoate derivative (**13**) that were considered less likely to undergo aromatic ring substitution. As expected, these lead smoothly to the required 11β-azido derivative (**17**).

The reactions discussed may be carried out on various intermediates of steroidal hormones and could lead to a host of biologically interesting products. The reaction conditions used are mild and compatible with the usually very sensitive side chain of corticosteroids, protected as a 21-ester, and with the dienone system. These rapid reactions lead to displacements at reasonable yields and eliminations in very good yields.

Experimental Section

Melting points were determined on a Reichart instrument and are not corrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer in methylene chloride solutions. NMR spectra were obtained at 60 or 100 MHz on a Varian Model A-60A or on a XL-100-15 spectrophotometer, respectively. Mass spectra were recorded on a Varian MAT CH-5 spectrometer.

TLC was run on silica gel GF (Analtech, 250 μm) and materials were detected by uv, sulfuric acid, or phosphomolybdate sprays. Column chromatography was performed on silica gel (J. T. Baker, 60–200 mesh) presaturated with the indicated solvent.

***p*-(Chlorosulfonyl)benzoyl Chloride.** This compound was prepared according to ref 5, starting from *p*-(chlorosulfonyl)benzoic acid or starting from *p*-sulfobenzoic acid monopotassium salt and using a mixture of phosphoric oxychloride and phosphoric pentachloride. The product was crystallized from hexane, mp 58° (lit. 58°).

***p*-Nitrobenzyl *p'*-(Chlorosulfonyl)benzoate (1).** *p*-(Chlorosulfonyl)benzoyl chloride (2.2 g) and *p*-nitrobenzyl alcohol (1.28 g) were dissolved at room temperature in benzene (60 ml). Triethylamine (1.28 ml) was then added while the solution was stirred under a calcium sulfate seal. Immediate formation of a precipitate was observed. After a few minutes, the reaction mixture was diluted with benzene, washed with dilute hydrochloric acid and water, dried over magnesium sulfate, and concentrated. The product (2.04 g) crystallized as prisms following the addition of some hexane, mp 123–130°. For analysis it was recrystallized from benzene, mp 134°.

Anal. Calcd for $C_{14}H_{10}ClNO_6S \cdot \frac{1}{6}C_6H_6$ ($C_{15}H_{11}ClNO_6S$): C, 48.85; H, 3.00; Cl, 9.61; N, 3.80; S, 8.70. Found: C, 48.31; H, 2.84; Cl, 9.32; N, 3.90; S, 8.41.

***o*-Nitrobenzyl *p'*-(Chlorosulfonyl)benzoate (2).** This compound was prepared in the same manner as compound **1** but using *o*-nitrobenzyl alcohol. After recrystallization from benzene 2.0 g of prisms, mp 122°, was obtained.

Anal. Calcd for $C_{14}H_{10}ClNO_6S \cdot \frac{1}{6}C_6H_6$ ($C_{15}H_{11}ClNO_6S$): C, 48.85; H, 3.00; Cl, 9.61; N, 3.80. Found: C, 48.31; H, 3.42; Cl, 9.54; N, 3.82.

***o*-Nitrobenzyl *o'*-(Sulfonyl)benzoate (3).** Sulfobenzoic anhydride (18.4 g) and *o*-nitrobenzyl alcohol (15.3 g) in benzene (1000 ml) were refluxed for 4 hr and then allowed to crystallize at room temperature, yield 25.6 g of hygroscopic material, mp 102°, after recrystallization from benzene, mp 105–106°.

Anal. Calcd for $C_{14}H_{11}NO_7S \cdot \frac{1}{2}H_2O$: C, 48.55; H, 3.49; N, 4.04; S, 9.26; H_2O, 2.59. Found: C, 48.42; H, 3.73; N, 3.95; S, 9.27; H_2O (Karl Fischer), 2.2.

***o*-Nitrobenzyl *o'*-(Chlorosulfonyl)benzoate (4).** Compound **3** (18 g) was mixed with phosphoric pentachloride (42 g), fitted with a condenser and a calcium chloride seal (Teflon sleeves), and was immersed into a 170° bath for 10 min. The reaction mixture was then poured into ice–water (600 ml), extracted with chloroform (600 ml), and washed with water. The chloroform solution was dried over magnesium sulfate and evaporated, yielding 20.4 g of an oil that was crystallized from a mixture of benzene and hexane, mp 104–105° (12.8 g).

Anal. Calcd for $C_{14}H_{10}ClNO_6S$: C, 47.26; H, 2.83; Cl, 9.97; N, 3.94; S, 9.01. Found: C, 47.79; H, 2.93; Cl, 10.37; N, 3.85; S, 8.79.

Methyl *o*-(sulfonyl)benzoate was prepared according to ref 6.

Methyl *o*-(Chlorosulfonyl)benzoate (5). Methyl *o*-(sulfonyl)benzoate (10 g) and phosphoric pentachloride (25 g) were treated as described for the preparation of compound **4**, yield 14.4 g of oil that failed to crystallize and contained a slow-moving impurity (TLC, benzene or chloroform).

3-Pyridinesulfonyl chloride was prepared according to ref 11.

3α-Sulfonate Derivatives of 5α-Androstan-3β-ol-17-one (Epiandrosterone) and of 5α-Cholestan-3β-ol (β-Cholestanol). The steroid (2.0 mmol) and the respective sulfonyl chloride (2.25 mmol) were dissolved in pyridine (6.0 ml) at room temperature; the reaction mixture was then left at room temperature overnight. A few crystals of ice were added and after 1 hr the reaction mixture was extracted with chloroform (350 ml) and washed with dilute hydrochloric acid, water, dilute sodium hydroxide, and water. The chloroform solution was dried over magnesium sulfate and evaporated.

A. 5α-Androstan-3β-ol-17-one 3-[(Benzoic acid o-nitrobenzyl ester)-2-sulfonate] (6). This material was further purified on a column of silica gel (45 g, 1.5 cm in diameter) and eluted with chloroform–ethyl acetate (1:20), yield 0.95 g (77%), recrystallized from ethyl acetate, mp 146° (microcrystalline, light yellow), $[\alpha]^{26}D$ +37.0° (c 0.4, chloroform), λ_{max} ($CHCl_3$) 246 nm (ϵ 7.29 × 10^3).

Anal. Calcd for $C_{33}H_{39}NO_8S$: C, 65.01; H, 6.45; N, 2.30. Found: C, 65.06; H, 6.51; N, 2.09.

B. 5α-Cholestan-3β-ol 3-[(Benzoic acid o-nitrobenzyl ester)-2-sulfonate] (7). The residue crystallized as elongated yellow needles, mp 129–131°. It was recrystallized from ethyl acetate, mp 133–134°, $[\alpha]^{26}D$ +8.6° (c 0.32, chloroform), yield 580 mg (42%), λ_{max} ($CHCl_3$) 265 nm (ϵ 6.96 × 10^3).

Anal. Calcd for $C_{41}H_{57}NO_7S$: C, 69.55; H, 8.11; N, 1.98. Found: C, 69.54; H, 8.50; N, 2.25.

C. 5α-Cholestan-3β-ol 3-[(Benzoic acid methyl ester)-2-sulfonate] (8). The oily residue was purified on a silica gel column (20 g, 1.5 cm in diameter) using chloroform as the eluent. The product emerged as a broad peak starting after the initial 15 ml, yield 0.257 g (23%) of yellowish oil, homogeneous by TLC.

D. 5α-Cholestan-3β-ol 3-[(Benzoic acid o-nitrobenzyl ester)-4-sulfonate] (9). The solid residue was recrystallized from ethyl acetate–hexane, yielding 0.70 g (57%) of yellowish product, mp 126–127°, $[\alpha]^{26}D$ +8.9° (c 0.34, chloroform).

Anal. Calcd for $C_{41}H_{57}NO_7S$: C, 69.55; H, 8.11; N, 1.98. Found: C, 69.61; H, 8.37; N, 2.07.

Comparative Dimethylformamide Reaction, Compounds 7, 8, 9, and 5α-Cholestan-3β-ol 3-*p*-Toluenesulfonate. Each compound (0.014 mmol/ml in dimethylformamide) was kept in a closed vial at 95°. Equal volumes (marked capillaries of ca. 3 μl) were drawn and (a) applied directly to TLC (chloroform–ethyl acetate, 20:1) and the residual starting material and the products (sometimes not well separated) could be observed; (b) an equal volume of 0.2 *N* NaOMe was added to each capillary and the content was spotted after 10 min. Following this treatment, the faster moving 2,5α-cholestene remained unchanged, and compound **10** disappeared to yield mostly 5α-cholestan-3α-ol. For compounds **7** and **9** it was also apparent (unexplained) that the amount of 2-nitrobenzyl alcohol released increased when the dimethylformamide reaction proceeded.

The proportion of products was similar for the different sulfonates. A complete reaction for compound **7** required approximately 1 hr. The order of reactivity was **7** > **8**, **9** ≫ *p*-toluenesulfonate (approximately 5% reaction in 1 hr).

Comparative Elimination, Compounds 7, 9, and 5α-Cholestan-3β-ol 3-(*p*-Toluenesulfonate). Solutions were made in hexamethylphosphoramide and handled as described for the dimethylformamide reaction, section a. 2,5α-Cholestene was formed in the three cases. Ninety minutes were required for complete reaction of compound **7**, compound **9** eliminated somewhat slower, and the *p*-toluenesulfonate reacted to the extent of not more than 5% during the same time.

Reaction of Compound 8 in Dimethylformamide. Compound **8** (100 mg) was dissolved in dimethylformamide (0.2 ml) and was kept in a closed vial under argon at 85° for 3 hr. The reaction mixture was evaporated in vacuo and applied to a silica gel column (6.0 g, 1.0 cm in diameter), eluted with chloroform, 1.0 ml per fraction, and monitored by TLC (chloroform-ethyl acetate, 20:1).

A. Fractions 1–7 contained 32 mg (48%) of **2,5α-cholestene,** mp 72°, giving no depression in mixture melting point with an authentic sample (mp 68–69°). The ir and mass spectrum (M 370) were also as required for this compound.

B. Fractions 8–14 contained a solid, mp 64–70°, identified as the **5α-cholestan-3α- (or 3β-) ol 3-formate (10)** in 14-mg (20%) yield. The material had ir absorbances at 1190 (O–R) and 1720 cm^{-1} (C=O). The mass spectrum indicated a molecular peak at *m/e* 416 ($C_{28}H_{48}O_2$) and fragmentation that supports the proposed structure. When treated with 0.2 *N* NaOMe, product **10** was converted to **5α-cholestan-3α-ol** and to **5α-cholestan-3β-ol** in a ratio of 9:1 (TLC). The reaction mixture was extracted with ethyl acetate and washed with water and the ethyl acetate solution was dried with magnesium sulfate and evaporated. The residue was crystallized from ethyl acetate to yield almost pure (TLC) 5α-cholestan-3α-ol, mp 179°, giving no depression in mixture melting point with an authentic sample (mp 183–184°). Ir and the mass spectrum were as required.

C. Fractions 22–30 contained ca. 10% of 5α-cholestan-3α-ol and 5α-cholestan-3β-ol.

2,5α-Androsten-17-one (11). Compound **6** (107 mg) was dissolved in hexamethylphosphoramide (0.5 ml) and kept in a closed vial under argon for 120 min at 85°. From TLC (chloroform–ethyl acetate, 20:1) it was apparent that the starting material was converted to product **11** at least to the extent of 95%. The reaction mixture was extracted with chloroform, washed with water, dried over magnesium sulfate, evaporated, and applied to a column of silica gel (10 g, 1.0 cm in diameter). Fractions of 1.6 ml were checked by TLC (as above) and fractions 8–14 contained the pure product, yield 44.7 mg (93%), mp 103–104°, $[\alpha]^{26}D$ +143.2° *c* 0.38, ethanol). The product gave no depression of mixture melting point with an authentic sample (mp 103–106°, $[\alpha]D$ +137° in ethanol). Ir spectra of the two were superimposable and the product gave the required mass spectrum with a molecular peak at *m/e* 272.

3α-Azido-5α-androstan-17-one (12). Compound **6** (105 mg) and sodium azide (700 mg) in hexamethylphosphoramide (5.0 ml) were stirred in a closed vial, under argon, at 80° and for 90 min. TLC (chloroform–ethyl acetate) indicated the formation of two major products: compound **11** and the 3α-azide **12** in a ratio of 1:1. The reaction mixture was extracted with ether and washed with water. The ether solution was dried and evaporated to yield 42.6 mg of crude mixture. Product **12** was crystallized from methanol as plates, yielding 23 mg (43%), mp 118–120°, $[\alpha]^{26}D$ +70.7° (c 0.2, chloroform) (lit.[8a] mp 116–117°, $[\alpha]D$ +79.8°). The product had a strong absorbance at 2100 cm^{-1} (N_3). In the NMR (100 MHz, $CDCl_3$) H-3 appears as a narrow (10 Hz) multiplet at τ 6.14.

11α,17α,21-Trihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 11-[(Benzoic acid o-nitrobenzyl ester)-2-sulfonate] 21-Cathylate (13). 11α,17α,21-Trihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 21-cathylate[12] (893 mg) and the sulfonyl chloride **4** (1.6 g) were dissolved in pyridine (6 ml) and left at room temperature for 72 hr. A crystal of ice was added to the reaction mixture and after 1 hr the pyridine was evaporated in vacuo. The residue was extracted into ethyl acetate and washed with saturated sodium hydrogen carbonate solution and with water. The solution was dried over magnesium sulfate, evaporated in vacuo, and applied to a column of silica gel (35 g, 1.6 cm in diameter). The column was eluted with chloroform–ethyl acetate (1:2) and 1.2-ml fractions were collected. Fractions 33–53 contained the product (0.4 g) that was obtained as an amorphous solid from a mixture of chloroform and hexane, mp 101–104°, $[\alpha]^{26}D$ +32.6° (c 0.17, chloroform).

Anal. Calcd for $C_{39}H_{43}NO_{13}S$: N, 1.83. Found: N, 1.87.

11α,17α,21-Trihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 21-Cathylate 11-(*o*-Nitrobenzenesulfonate) (14). This compound was prepared with o-nitrobenzenesulfonyl chloride (0.5 g) by the procedure used for compound **13.** Similar fractionation was carried out by the use of 38 g of silica gel and collecting 1.5-ml fractions. Fractions 60–81 were pooled and evaporated to yield the pure product as needles (0.4 g), mp 101–104° dec. Recrystallization from ethyl acetate–hexane yielded the analytical sample, mp 104–106° dec, $[\alpha]^{26}D$ +80.4° (c 0.25, chloroform).

Anal. Calcd for $C_{31}H_{37}NO_{11}S$: C, 58.94; H, 5.90; N, 2.22; S, 5.08. Found: C, 59.38; H, 6.07; N, 2.16; S, 4.75.

11α,17α,21-Trihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 11-(3-Pyridinesulfonate) 21-Cathylate (15). This compound was prepared like compound **13** but using 470 mg of 3-pyridinesulfonyl chloride. The product was slower on TLC (chloroform–ethyl acetate, 1:2) than the starting material. It was eluted from the silica gel column as a wide peak at least partially contaminated with the starting material, yield 0.75 g. For analysis, compound **15** was obtained from a center cut and recrystallized from chloroform–hexane, mp 103°, $[\alpha]^{26}D$ +110.3° (c 0.49, chloroform).

Anal. Calcd for $C_{30}H_{37}O_9NS$: N, 2.38. Found: N, 2.04.

Comparative Azide Substitution. Compounds 13, 14, and 15. **A.** The reactivities of compound **13** and of the corresponding 11α-methanesulfonate **16** were compared. Each sample (0.013 mmol/ml in hexamethylphosphoramide) and sodium azide (100 mg/ml) were stirred in a closed vial at 90° and samples (5 μl) were drawn for TLC (chloroform–ethyl acetate, 1:2). After 30 min the conversion of compound **13** to the 11β-azido derivative **17** and to the triene **18** (ratio 6:4) was complete with only minute traces of slower moving

material. At the same time the conversion of the 11α-methanesulfonate **16** to the same products proceeded in ca. 5% yield. Even after 240 min approximately 30% of the latter compound remained unchanged and the reaction was accompanied by degradation.

B. In an analogous experiment, compound **14** was shown to convert completely to compound **19** and to compound **18** (ratio 6:4) in 30 min.

C. Compound **15**, under similar conditions, reacted very similarly (rate and products) to compound **13**. Since compound **15** is slower on chromatography than any of the other sulfonates described here, it provided improved separation of the starting material from compound **17** and the still faster compound **18**.

Comparative Elimination. Compounds 14, 15, and 13. A. Compounds **14** and **15** (0.015 mmol/ml in hexylmethylphosphoramide) were kept in closed vials at 85°. Samples (5 μl) were applied to TLC (chloroform–ethyl acetate, 2:1). After 40 min, compound **14** was almost completely converted into compound **18** while compound **15** was converted into compound **18** to the extent of approximately 70%.

B. Under similar conditions, compound **13** eliminated to compound **18** to the extent of approximately 20%.

17α,21-Dihydroxy-16β-methyl-1,4,9-pregnatriene-3,20-dione 21-Cathylate (18). Compound **14** (211 mg) was dissolved in hexamethylphosphoramide (1 ml) in a closed vial and heated in a 80° bath for 80 min. The total reaction mixture was applied to a silica gel column (35 g, 1.6 cm in diameter) and was eluted with chloroform–ethyl acetate (2:1). The product (needles), homogeneous according to TLC, mp 217–221° dec, emerged after 25 ml and was eluted with an additional 40 ml of solvent mixture, yield 125 mg (87%). The product was shown to be identical with an authentic sample (TLC, ir, mass spectrum).

11β-Azido-17α,21-dihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 21-Cathylate (17). A. Compound **13** (164 mg) and sodium azide (200 mg) in hexamethylphosphoramide (1 ml) were stirred in a closed vial at 85° (bath temperature) for 3 hr. TLC (chloroform–ethyl acetate, 1:2) indicated that compounds **17** and **18** were formed in a ratio of 7:3 and a minute amount of the 11α-hydroxy compound was also formed. The reaction mixture was extracted with ether, washed with water, and dried over magnesium sulfate. Product **17** was then isolated after chromatography on two thick (2 mm, 20 × 20 mm) plates and using the same solvent system. The yield was 42 mg (41%) of needles, mp 203–205°, after recrystallization from methylene chloride–hexane: mp 209°; ir shows absorbances at 1745 and 1760 (C=O), 2120 cm^{-1} (N_3); mass spectrum *m/e* 471 (M), 443 (M − N_2), 428 (M − HN_3) followed by fragmentation similar to compound **18**; NMR (100 MHz, $CDCl_3$) τ 2.84 (1 H, d, $J_{1,2}$ = 10 Hz, H-1), 3.67 (1 H, q, $J_{2,4}$ = 2 Hz, H-2), 3.96 (1 H, d, H-4), 5.02 (2 H, d, J = 1 Hz, H-21), 5.73 (3 H, apparent q, J = 7 Hz, OCH_2CH_3 and H-11). Eu(fod)$_3$ was added to the sample and the following resonances were recorded: τ 1.45 (1 H, apparent d, broad lines, J = 10 Hz, H-2), 1.83 (1 H, apparent s, H-4), 2.28 (1 H, d, $J_{1,2}$ = 10 Hz, H-1), 4.92 (2 H, apparent s, H-21), 5.34 (1 H, 15 Hz wide m, H-11α), 5.69 (2 H, q, J = 7 Hz, OCH_2CH_3).

B. Compound **15** (78 mg) was treated as described in section A, yield 6.0 mg of the azido derivative (**17**), mp 208°. It gave no depression of mixture melting point with compound **17** (section A) and these materials had identical ir spectra.

11β-Azido-17α,21-dihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 17α,21-Dibutyrate (20). A. Compound **17** (40 mg) was dissolved in a mixture of methanol (2.5 ml) and chloroform (0.5 ml). Aqueous sodium hydroxide (1 *N*, 0.09 ml) was added and the reaction mixture was kept in an ice bath for 65 min. It was then acidified with dilute acetic acid, extracted with ethyl acetate, washed with saturated sodium hydrogen carbonate and water, dried over magnesium sulfate, and evaporated in vacuo. TLC (chloroform–ethyl acetate, 1:2) showed a major slow-moving product that was purified on a thick plate (same solvent system): ir 1660, 1720 (C=O), 2100 cm^{-1} (N_3). The 1760-cm^{-1} absorbance in the starting material had disappeared.

B. The dihydroxy derivative of stage A was esterified according to Shapiro et al.[13] *p*-Toluenesulfonic acid (10 mg) was added to the sample followed by butyric acid and trifluoroacetic anhydride (1.0 ml, 10:4). The reaction mixture was allowed to stand overnight at room temperature. It was then poured into water, extracted with methylene chloride, washed with water, saturated sodium hydrogen carbonate, and water, and dried over magnesium sulfate. The product, almost pure by TLC, chloroform–ethyl acetate (1:2), was purified by using the same system, yield 7.2 mg of oil. The ir spectrum contained absorbances at 2100 (N_3), 1750 cm^{-1} (C=O, broad). Mass spectrum includes *m/e* 567 (M), 539 (M − N_2), 511, 494, 487, but also *m/e* 609 (M + N_3), 581 (M + N) that might result from an ion–molecule reaction.

Reaction of Compound 14 with Sodium Azide. Compound **14** (0.39 g) and sodium azide (400 mg) in hexamethylphosphoramide (3 ml) were stirred in a closed vial at 85° (bath temperature) for 30 min. TLC (chloroform–ethyl acetate, 1:2) indicated the formation of the substitution product **19** and the faster moving elimination product **18** alongside some 11α-hydroxy compound (6:3:2). The reaction mixture was extracted with ether, washed with water, dried over magnesium sulfate, evaporated, applied to a column of silica gel (35 g, 1.6 cm in diameter), and eluted with chloroform–ethyl acetate, 1:1. Fractions of 2.5 ml were collected. Fractions 36–41 contained product **19** homogeneous according to TLC (oil, 57 mg, more in mixed fractions). It was crystallized from chloroform–hexane), amorphous, mp 97–101°. Ir includes 2100 cm^{-1} (N_3) but different from compound **17**. The mass spectrum includes *m/e* 519, 501, 471, 428; NMR (100 MHz, $CDCl_3$) includes τ 1.8–2.7 (4 H, m, aromatic).

Anal. Calcd for $C_{31}H_{36}N_4O_{11}S$: N, 8.33; S, 4.76. Found: N, 7.50; S, 3.30

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Registry No.—**1**, 56650-26-1; **2**, 56650-27-2; **3**, 56650-28-3; **4**, 56650-29-4; **5**, 26638-43-7; **6**, 56650-30-7; **7**, 56650-31-8; **8**, 56650-32-9; **9**, 56650-33-0; **11**, 963-75-7; **12**, 7795-05-3; **13**, 56650-34-1; **14**, 56650-35-2; **15**, 56650-36-3; **17**, 56650-37-4; **18**, 56666-79-3; *p*-(chlorosulfonyl)benzoyl chloride, 7516-60-1; *p*-nitrobenzyl alcohol, 619-73-8; o-nitrobenzyl alcohol, 612-25-9; sulfobenzoic anhydride, 81-08-3; phosphonic pentachloride, 10026-13-8; 5α-androstan-3β-ol-17-one, 481-29-8; 5α-cholestan-3β-ol, 80-97-7; 5α-cholestan-3β-ol 3-*p*-toluenesulfonate, 3381-52-0; 11α,17α,21-trihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 21-cathylate, 56650-38-5; *o*-nitrobenzenesulfonyl chloride, 1694-92-4; 3-pyridinesulfonyl chloride, 16133-25-8.

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Reaction of Aminoquinones and Related Vinylogous Amides with Nitrous Acid. Synthesis and Chemistry of Cyclic Diazo Ketones

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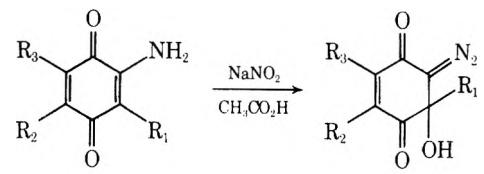
2-Amino-3-alkyl- (or aryl-) 1,4-quinones are shown to react with nitrous acid (sodium nitrite in glacial acetic acid) to give 5-diazo-6-alkyl- (or aryl-) 6-hydroxycyclohex-2-ene-1,4-diones **2**. Analogous reactions are observed for the related vinylogous amides, 4-amino-2,5-di-*tert*-butyl-2-cyano-4-cyclopentene-1,3-dione (**7**) and 2,5*H*-3-amino-4-methyl-6,7-benzoazepine-2,5-dione (**9**). The chemistry of the cyclic diazo compounds is discussed, and of particular interest are the thermal rearrangements of **2a, 2b,** and **4** to the corresponding ring-contracted 4-cyclopentene-1,3-diones, **24, 25,** and **27,** respectively. Also discussed is the thermal rearrangement of 4-acetyl-3-diazo-4-hydroxycarbostyril (**12**) to 3-acetyl-4-hydroxycarbostyril (**26**), the reductive cyclization of **12** to 3*H*,5*H*-1-methylpyrazolo[3,4-*c*]quinolin(4*H*)-one (**19**), and the acid-catalyzed conversion of **12** to 4*H*,6*H*(1*H*,5*H*)-dioxo-3,4-diazino[3,4-*c*]quinoline (**30**).

A vast methodology exists in the literature for the synthesis of aminoquinones. In fact, during the past 35 years alone well over 150 substituted primary amino-1,4-quinones have been reported. However, there is a paucity of information regarding the chemistry of these compounds. Our interest in the utility of quinones in organic synthesis[1] along with the plethora of such readily available starting materials[2] and the rich chemistry of the amino group[3] has stimulated an investigation of aminoquinones as potentially useful reagents. Reported here is a study of the reactions of selected 2-amino-1,4-quinones and certain related cyclic vinylogous amides with nitrous acid, a reaction resulting in the formation of cyclic α-diazo ketones. Also described is the pyrolytic ring contraction of such compounds. Of particular interest is the thermal rearrangement of the diazo ketones **2** to 2-acyl-4-cyclopentene-1,3-diones, a ring system found in a number of natural products.[4]

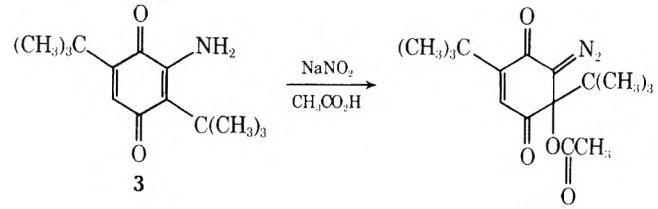
Synthetic Scope. Treatment of the aminoquinones **1a–d** with sodium nitrite in glacial acetic acid results in a rapid, exothermic reaction and gives fair to excellent yields of the corresponding diazo ketones **2a–d.** 2-Amino-3,6-di-*tert*-butyl-1,4-benzoquinone (**3**), having a bulky substituent adjacent to the amino group, behaves anomalously in that the acetoxy derivative **4** was obtained in 92% yield. The detailed scope of this reaction of aminoquinones has not been studied in detail. However, we have observed that 2-amino-1,4-quinones which are unsubstituted at the 3 position give complex reaction mixtures and that 2-amino-6-anilino-3-carbomethoxy-1,4-benzoquinone, a compound having a very nonnucleophilic amino group, fails to react. In addition, Mosby and Silva[5] found that 2-amino-3-chloro-1,4-naphthoquinone (**5a**) gave the diazo oxide **6** when treated with sodium nitrite in sulfuric acid. We have observed the same product when 2-amino-3-chloro- (**5a**), 2-amino-3-methoxy- (**5b**), 2-amino-3-azido- (**5c**), and 2-amino-3-thiophenyl-1,4-naphthoquinone (**5d**) are diazotized as described here.

To further probe the utility of these diazotization reactions, the scope was widened to include some nonquinoid cyclic 2-aminoenediones. Treatment of 4-amino-2,5-di-*tert*-butyl-2-cyano-4-cyclopentene-1,3-dione (**7**) with sodium nitrite in glacial acetic acid gave a 62% yield of the acetoxydiazo derivative **8.** A more interesting transformation was observed when 3-amino-2,5*H*-4-methyl-6,7-benzoazepine-2,5-dione (**9**) was subjected to the above reaction conditions. Here, rather than the seven-membered cyclic diazo compound **10,** the ring-contracted quinoline **12** was isolated. However, a dichloromethane extract of the reaction mixture showed (^{1}H NMR) two products in a ratio of 3:2 as evidenced by methyl absorptions at δ 1.52 and δ 2.20, respectively, and the minor product was the quinoline **12.** The major product is assumed to be the azepine **10** which rearranges to **12** via the ring-opened intermediate **11.** Such a transformation was easily induced when the above dichloromethane solution was treated with 3% methanolic potassium hydroxide. This resulted in the disappearance of the δ 1.52 absorption and the δ 2.20 peak increased in intensity. It was possible to interrupt the diazotization of **9** at the azepine stage when the reaction was carried out in 1:1 acetic acid–methanol. Here, the methoxy adduct **13** was isolated in 90% yield. (See Scheme I).

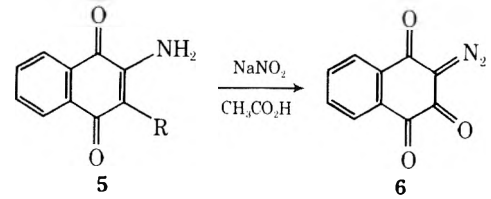


1 2

	R_1	R_2	R_3	Yield %
a	CH_3	$-CH{=}CHCH{=}CH-$		91
b	CH_3	H	CH_3	81
c	CH_3	N_3	CH_3	92
d	C_6H_5	H	C_6H_5	36



3 4

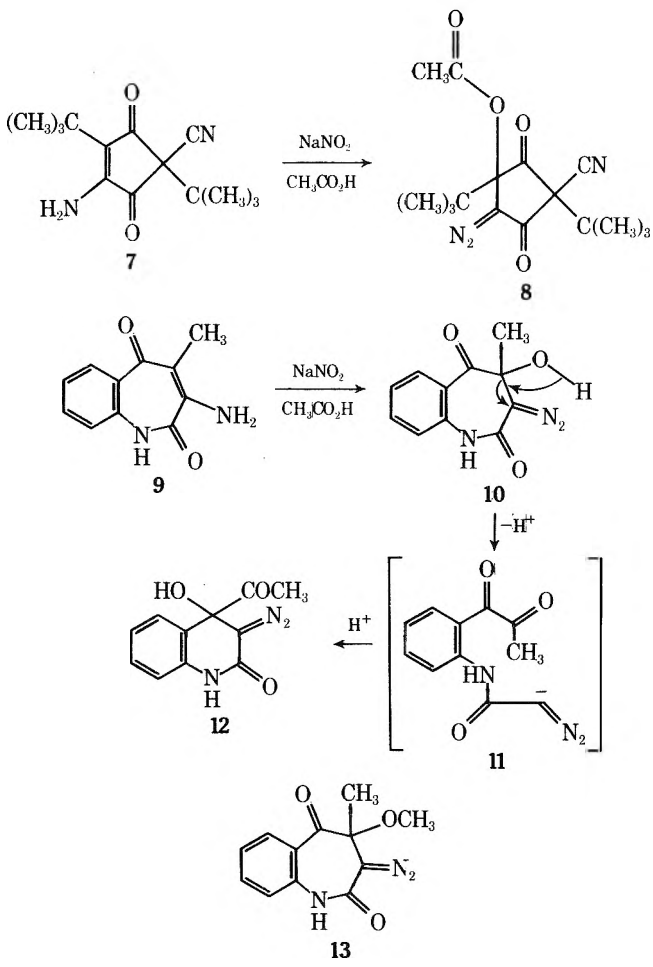


5 6

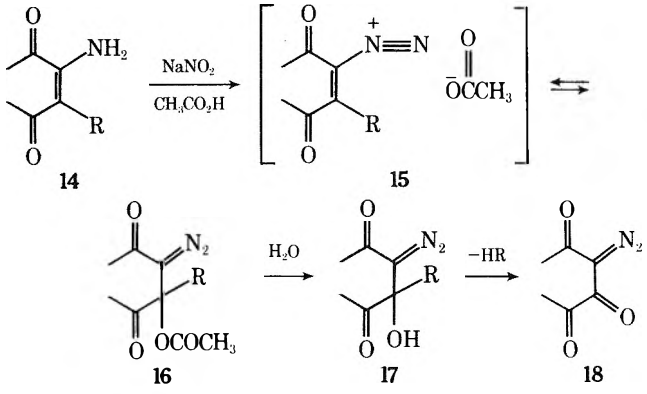
	R	Yield %
a	Cl	82
b	OCH_3	85
c	N_3	65
d	SC_6H_5	61

Mechanism. The products observed from the diazotization reactions described here are consistent with a mechanism (Scheme II) in which the vinylogous amide is initially converted to a diazonium salt **15** which then suffers nucleo-

Scheme I

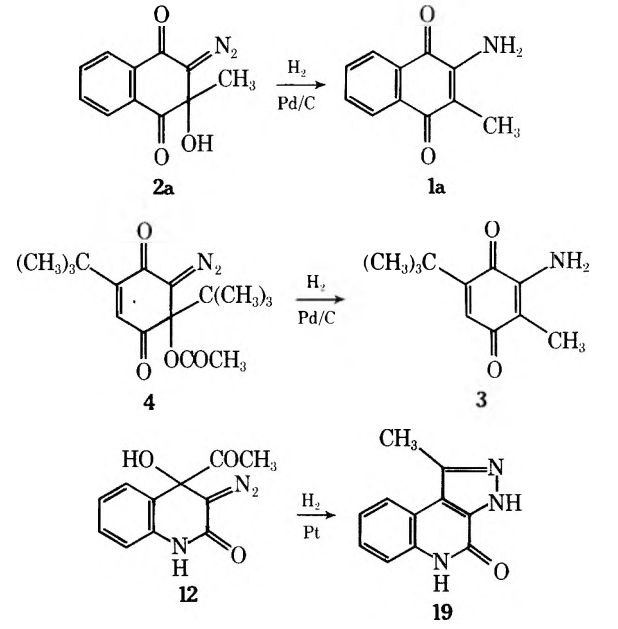


Scheme II

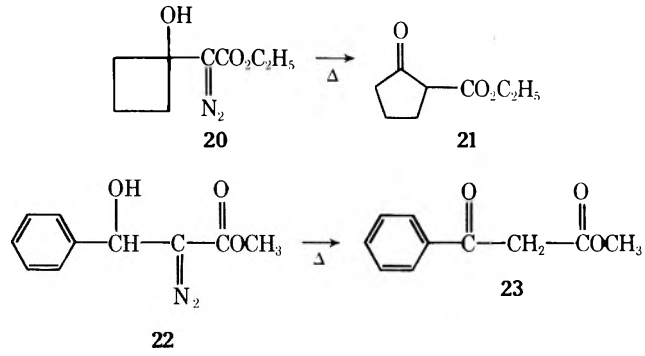


philic attack by solvent (CH_3CO_2H) to give the acetoxy derivative **16**. For those compounds having a relatively small substituent adjacent to the diazo linkage (**2a–d, 9**), hydrolysis of the acetoxy group during the aqueous work-up would result in the observed β-hydroxydiazo compounds. Steric retardation of such hydrolysis by the bulky *tert*-butyl groups in **4** and **8** would account for the interception of these esters. For those compounds having a potential leaving group (R = Cl, OCH_3, N_3, SC_6H_5) adjacent to the diazo linkage, hydrolysis and subsequent elimination would give the diazo oxide **18**.

Chemistry. Wenkert and McPherson[6] have shown that catalytic hydrogenation (Pd/C) of acyclic α-diazo-β-hydroxycarbonyl compounds gives the corresponding β-hydroxycarbonyl compounds. Therefore, an analogous transformation was anticipated for **2a** and **4**. However, these compounds were converted to 2-amino-3-methyl-1,4-naphthoquinone (**1a**) and 2-amino-3,6-di-*tert*-butyl-1,4-benzoquinone (**3**), respectively, when subjected to hydrogenation conditions. This reductive cleavage of the diazo nitrogen–nitrogen bond appears to be rare but not unprecedented; Birkofer[7] reported that α-diazoacetophenone gives α-aminoacetophenone when subjected to hydrogenation under slightly acidic condition in the presence of Pd/C. Hydrogenation of the diazoquinoline derivative **12** also resulted in the reduction of the diazo nitrogen linkage. In this case, **19** was obtained in >90% yield and is envisaged as arising from an intermediate hydrazine derivative which suffers intramolecular condensation.

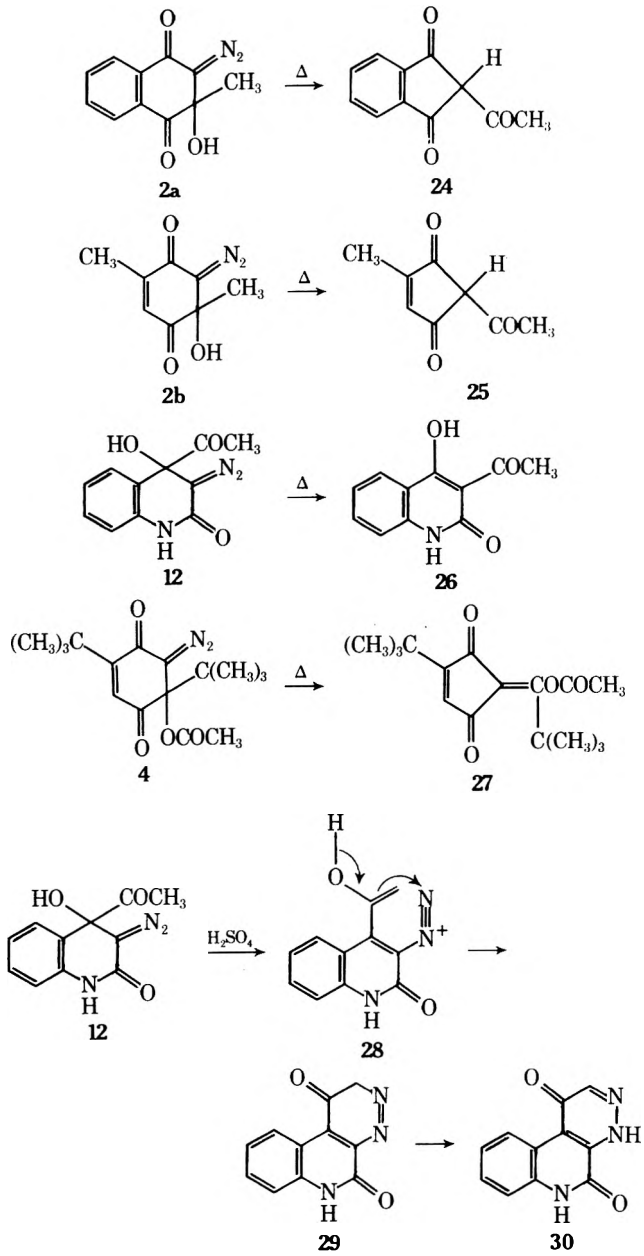


Wenkert and McPherson[6] have shown that acyclic α-diazo-β-hydroxy ketones and esters thermally rearrange with carbon or hydrogen migration as illustrated below. In



analogy to these rearrangements it was found that **2a** and **2b** thermally rearranged in refluxing chlorobenzene with acyl migration to give 2-acetyl-1,3-indandione[8] (**24**, 97%) and 2-acetyl-4-methyl-4-cyclopentene-1,3-dione (**25**, 86%), respectively. Also, **12** gave a 28% yield of 3-acetyl-4-hydroxycarbostyril (**26**)[9] and **4** gave a 90% yield of **27** when subjected to the thermolysis conditions.

The acid-catalyzed decomposition of two of the diazo compounds described here was also studied. Decomposition of **2a** in cold (5°) concentrated sulfuric acid gave the same product, i.e., **24**, that resulted from its thermolysis. An entirely different transformation was observed for the acid-catalyzed decomposition of **12**. Here, a fascinating ring closure to **30** took place in nearly quantitative yield. This product is viewed as arising from the diazonium salt **28** which electrophilically attacks the enol double bond. Such a ring closure to a diazine is well documented in that one of



the standard synthetic routes to the cinnoline nucleus involves the intramolecular cyclization of an aryldiazonium salt which contains a reactive unsaturated ortho substituent.[10,11]

Experimental Section

2-Diazo-3-hydroxy-3-methylbenzocyclohexane-1,4-dione (2a). To a solution of 1.0 g (5 mmol) of 2-amino-3-methyl-1,4-naphthoquinone (**1a**) in 50 ml of glacial acetic acid was added 0.5 g (12 mmol) of sodium nitrite. After stirring for approximately 5 min at ambient temperature the solution turned yellow and was then diluted with 200 ml of water and extracted three times with dichloromethane. The combined organic extract was washed twice with 5% sodium bicarbonate and dried ($MgSO_4$). The solvent was removed in vacuo (25°) to give 1.0 g (91%) of the yellow, crystalline diazo compound **2a**: mp 106–107° (from pentane–ether); ir (Nujol) 3300, 2110, 1705, 1660, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 s (3), 4.32 br (1), 7.65–8.25 m (4).

Anal. Calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.70; N, 12.96. Found: C, 60.99; H, 3.64; N, 12.89.

6-Diazo-5-hydroxy-2,5-dimethylcyclohex-2-ene-1,4-dione (2b). To a solution of 0.5 g (3.3 mmol) of 2-amino-3,6-dimethyl-1,4-benzoquinone (**1b**) in 20 ml of glacial acetic acid was added 0.3 g (4.3 mmol) of sodium nitrite. The initially purple solution turned yellow after approximately 5 min and was then diluted with 200 ml of an aqueous saturated sodium chloride solution and extracted four times with dichloromethane. The combined organic extract was washed twice with 5% sodium bicarbonate and dried ($MgSO_4$), and the solvent was removed in vacuo (25°) to give a yellow-orange oil. Trituration of this oil with cold pentane–ether gave 0.48 g (81%) of the yellow, crystalline diazo compound **2b**: mp 79–80° dec (pentane–ether); ir (Nujol) 3450, 2100, 1675, 1640, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) 1.62 s (3), 2.11 d (3) J = 2 Hz, 3.91 br (1), 6.60 q (1) J = 2 Hz.

Anal. Calcd for $C_8H_8N_2O_3$: C, 53.33; H, 4.44; N, 15.56. Found: C, 53.43; H, 4.41; N, 15.39.

3-Azido-6-diazo-5-hydroxy-2,5-dimethylcyclohex-2-ene-1,4-dione (2c). Treatment of 2-amino-5-azido-3,6-dimethyl-1,4-benzoquinone (**1c**, 0.5 g, 2.6 mmol) with sodium nitrite (0.24 g, 3 mmol) was carried out as described above for **1b** to give 0.54 g (92%) of the diazo compound **2c** as a golden, crystalline solid: mp 107–109° dec (pentane–ether); ir (Nujol) 3200, 2120, 1690, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) 1.68 s (3), 2.03 s (3), 3.52 br (1).

Anal. Calcd for $C_8H_7N_5O_3$: C, 43.44; H, 3.17; N, 31.67. Found: C, 43.55; H, 3.09; N, 31.57.

6-Diazo-5-hydroxy-2,5-diphenylcyclohex-2-ene-1,4-dione (2d). To a solution of 1.0 g (3.6 mmol) of 2-amino-3,6-diphenyl-1,4-benzoquinone (**1d**) in 50 ml of glacial acetic acid was added 0.48 g (7.2 mmol) of sodium nitrite. After stirring at ambient temperature for 15 min the initially purple solution turned yellow and the solution was diluted with 200 ml of water and extracted three times with diethyl ether. The combined organic extract was washed twice with 5% sodium bicarbonate and dried ($MgSO_4$) and the solvent was removed in vacuo (25°). The resulting orange oil was chromatographed on silica gel using 1:1 benzene–chloroform as the eluent to give 0.40 g (36%) of the diazo compound **2d**: mp 108–109° dec; ir (Nujol) 3400, 2100, 1700, 1625, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.65 br (1), 6.77 s (1), 7.25–7.70 m (10).

Anal. Calcd for $C_{18}H_{12}N_2O_3$: C, 71.05; H, 3.95; N, 9.21. Found: C, 71.07; H, 3.93; N, 9.25.

5-Acetoxy-6-diazo-2,5-di(1,1-dimethylethyl)cyclohex-2-ene-1,4-dione (4). A solution of 1.0 g (4.2 mmol) of 2-amino-3,6-di-*tert*-butyl-1,4-benzoquinone (**3**) in 75 ml of glacial acetic acid was treated with 0.44 g (6.3 mmol) of sodium nitrite at ambient temperature. After 15 min the reaction solution was diluted with 200 ml of water and extracted with three portions of dichloromethane. After drying ($MgSO_4$) the solvent was removed and the product recrystallized from methanol to give 1.3 g (92%) of the yellow diazo compound **4**: mp 83–84°; ir (Nujol) 2100, 1745, 1680, 1630, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 s (9), 1.32 s (9), 2.14 s (3), 6.59 s (1).

Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.72; H, 7.24, N, 9.15. Found: C, 62.55; H, 7.28; N, 8.93.

2-Diazobenzocyclohexane-1,3,4-trione (6). Treatment of acetic acid solutions of 2-amino-3-chloro- (**5a**),[5] 2-amino-3-methoxy- (**5b**),[5] 2-amino-3-azido- (**5c**),[5] and 2-amino-3-thiophenyl-1,4-naphthoquinone (**5d**) with a twofold molar excess of sodium nitrite gave the diazo oxide **6** in yields ranging from 61 to 85%. The product showed spectral and physical properties that were identical with those reported by Mosby and Silva.[5]

4-Diazo-5-acetoxy-2-cyano-2,5-di(1,1-dimethylethyl)cyclopentene-1,3-dione (8). A solution of 1.0 g (4.4 mmol) of 4-amino-2-cyano-2,5-di-*tert*-butyl-4-cyclopentene-1,3-dione (**7**) and 1.5 g of sodium nitrite in 70 ml of glacial acetic acid was stirred at ambient temperature for 12 hr. The solution was then diluted with 200 ml of water and extracted three times with dichloromethane. After drying, the solvent was removed in vacuo (25°) and the resulting yellow oil was crystallized from pentane–ether to give 0.87 g (62%) of the diazo compound **8**: mp 99–101°; ir (Nujol) 2220, 2120, 1760, 1725, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 s (9), 1.23 s (9), 2.15 s (3).

Anal. Calcd for $C_{16}H_{21}N_3O_4$: C, 60.19; H, 6.58; N, 13.17. Found: C, 60.25; H, 6.60, N, 13.36.

2,5-Di(1,1-dimethylethyl)-2-cyano-4-amino-4-cyclopentene-1,3-dione (7). A solution of 1 g (4.2 mmol) of 2,5-di-*tert*-butyl-3,6-diamino-1,4-benzoquinone and 3.72 g (8.4 mmol) of lead tetraacetate in 50 ml of chloroform was stirred at ambient temperatures for 5 min and then 5 ml of ethylene glycol was added. The reaction solution was then washed three times with water and dried ($MgSO_4$) and the solvent was removed in vacuo. The resulting residue was recrystallized from hexane to give 0.7 g (71%) of **7**: mp 82–84°; ir (Nujol) 3450, 3330, 2250, 1760, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 s (9), 1.40 s (9), 5.55 br (2).

Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.74; H, 8.06; N, 11.29. Found: C, 67.84; H, 8.12, N, 11.18.

2,5*H*-3-Azido-4-methyl-6,7-benzoazepine-2,5-dione. To a solution of 1.87 g (10 mmol) of 2,5*H*-4-methyl-6,7-benzoazepine-2,5-

dione[13] and 2.6 g (40 mmol) of sodium azide in 35 ml of dimethylformamide was added 5.08 g (20 mmol) of iodine and the resulting reaction mixture was stirred at ambient temperature. The course of the reaction was followed by ir spectroscopy and the mixture was worked up after all of the starting azepine had been consumed (~16 hr). Water was then added and the resulting white precipitate was collected and washed with methanol to give 1.67 g (73%) of 2,5*H*-3-azido-4-methyl-6,7-benzoazepine-2,5-dione, mp 161° dec. The analytical sample was obtained by recrystallization (30°) from dimethyl sulfoxide–methanol: ir (Nujol) 3125, 3005, 2130, 1650, 1585, 1315 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.05 s (3), 7.00–7.70 m (4), 11.32 br (1) exchanges with D_2O; mass spectrum (70 eV) *m/e* (rel abundance) 200 (40.9), 119 (100), 117 (27.8), 92 (53.6), 64 (39.0).

Anal. Calcd for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.51; N, 24.56. Found: C, 57.86; H, 3.53; N, 24.56.

2,5*H*-3-Amino-4-methyl-6,7-benzoazepine-2,5-dione (9). A suspension of 2.28 g (10 mmol) of 2,5*H*-3-azido-4-methyl-6,7-benzoazepine-2,5-dione and 50 mg of platinum oxide in 100 ml of 95% ethanol was treated with hydrogen at 50 psi for 9 hr. The catalyst and solvent were then removed to give 2.0 g (99%) of the amine **9**: mp 241–243° (95% ethanol); ir (Nujol) 3380, 3270, 3060, 1680, 1595 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.17 s (3), 6.67 br (2), 7.67–7.10 m (3), 8.23–7.98 m (1), 11.50 br (1).

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.95, N, 13.86. Found: C, 65.49; H, 4.97; N, 13.89.

4-Acetyl-3-diazo-4-hydroxycarbostyril (12). To a stirred solution of 1.04 g (15 mmol) of sodium nitrite in 20 ml of water was added a suspension of 2.02 g (10 mmol) of 2,5*H*-3-amino-4-methyl-6,7-benzoazepine-2,5-dione (**9**) in 60 ml of acetic acid. After 15 min the reaction solution was diluted with 200 ml of water and extracted with 200 ml of dichloromethane. The organic extract was washed with water and saturated sodium bicarbonate and then dried over anhydrous sodium sulfate. The dichloromethane extract was analyzed by ^1H NMR, which showed two methyl absorptions in a ratio of 3:2 coming at δ 1.52 and 2.20, respectively. The former absorption is assigned to the methyl group in the azepine **10** and the latter to the carbostyril **12**. The dichloromethane solution was then treated with 20 drops of 3% methanolic potassium hydroxide. The solvent was then removed by rotoevaporation at ambient temperature. The resulting residue (2.3 g) was analyzed by ^1H NMR (CH_2Cl_2) which showed only the δ 2.20 absorption in the methyl region of the spectrum. The crude product was recrystallized from benzene to give 1.02 g of pure **12**: mp 171° dec; ir (Nujol) 3380, 3100, 2105, 1720, 1675, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.22 s (3), 5.40 s (1), 7.78–6.90 m (4), 9.93 br (1).

Anal. Calcd for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.90; N, 18.18. Found: C, 57.16; H, 4.02; N, 18.07.

2,3,4,5*H*-3-Diazo-4-methoxy-4-methyl-6,7-benzoazepine-2,5-dione (13). A solution of 0.57 g (2.5 mmol) of 2,5*H*-3-amino-4-methyl-6,7-benzazepine-2,5-dione (**9**) in 40 ml of anhydrous methanol and 40 ml of glacial acetic acid (35°) was treated with 3.5 g of sodium nitrite in 0.5-g portions over a period of 4 hr. The reaction mixture was then diluted with 100 ml of water and extracted four times with 15-ml portions of dichloromethane. The combined organic extract was then washed twice with saturated aqueous sodium bicarbonate and dried (Na_2SO_4) and the solvent was removed in vacuo (40°). The resulting residue (0.70 g) was shown by ^1H NMR analysis to be composed of approximately 90% of **13**, 3% of the starting amine, and several unidentified minor products. It was then subjected to column chromatography on silica gel using ethyl acetate–petroleum ether (1:1) to give **13** as a yellow, crystalline solid: mp 133° dec; ir (Nujol) 3250, 3150, 2990, 2090, 1690, 1640, 1610, 1580 cm^{-1}; ^1H NMR ($CDCl_3$), 1.67 s (3), 3.17 s (3), 6.93–7.87 m 4), 9.40 br (1) exchanges with D_2O.

Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.78; H, 4.49; N, 17.14. Found: C, 58.84; H, 4.55; N, 16.70.

Catalytic Reduction of 2-Diazo-3-hydroxy-3-methylbenzocyclohexane-1,4-dione (2a). A suspension of 1.0 g (4.8 mmol) of **2a** and 0.5 g of 10% palladium on charcoal was subjected to 40 psi of hydrogen for 1.5 hr. After removal of the catalyst and solvent the residue was chromatographed on silica gel using chloroform as the eluent to give 0.4 g (47%) of 2-amino-3-methyl-1,4-naphthoquinone (**1a**) which was identical with an authentic sample.

Catalytic Reduction of 5-Acetoxy-6-diazo-2,5-di-*tert*-butylcyclohex-2-ene-1,4-dione (4). Catalytic reduction of **4** (0.5 g, 1.6 mmol) using 10% palladium on charcoal (0.2 g) in 30 ml of methanol for 1 hr gave a quantitative yield of 2-amino-3,6-di-*tert*-butyl-1,4-benzoquinone (**3**) which was identical with an authentic sample.

3*H*,5*H*-1-Methylpyrazolo[3,4-*c*]quinolin-(4*H*)-one (19). A suspension of 1.25 g (5.4 mmol) of 4-acetoxy-3-diazo-4-hydroxycarbostyril (**12**) and approximately 10 mg of platinum oxide in 25 ml of 95% ethanol was treated with hydrogen at 35 psi for 5 hr. Filtration and removal of the solvent in vacuo gave 1.0 g (93%) of **19**, mp 330–340°. This product was recrystallized from 95% ethanol to give the analytical sample: mp 356–358, sinter 345°; ir (Nujol) 3080, 1690, 1630 cm^{-1}; ^1H NMR (Me_2SO-d_6) 2.68 s (3), 7.58–7.15 m (3), 8.10–7.80 m (1), 11.73 br (1) exchanges with D_2O, 14.05 br (1) exchanges with D_2O; mass spectrum (70 eV) *m/e* (rel abundance) 200 (15.4), 199 (100), 170 (14.6), 130 (12.8), 115 (12.2), 103 (25.2), 76 (11.3).

Anal. Calcd for $C_{11}H_9N_3O$: C, 66.33; H, 4.52; N, 21.11. Found: C, 66.61; H, 4.72; N, 21.00.

2-Acetyl-1,3-indandione (24). A solution of 0.50 g (2.5 mmol) of 2-diazo-3-hydroxy-3-methylbenzocyclohexane-1,4-dione (**2a**) in 50 ml of dioxane was refluxed for 2 hr. Evaporation of the solvent in vacuo and recrystallization of the residue from methanol gave 0.42 g (97%) of **24**: mp 109–110 (lit.[8] mp 110–112°); ir (Nujol) 1720, 1700, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 s (3), 7.75 m (4), 10.92 br (1).

2-Acetyl-4-methyl-4-cyclopentene-1,3-dione (25). The title compound was prepared as described above for **24** except benzene was used as the solvent, i.e., 0.270 g (1.54 mmol) of **2b** give 0.20 g (86%) of **25**: mp 53–55° (methanol); ir (Nujol) 1710, 1670, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 d (3), J = 1.5 Hz, 2.35 s (3), 6.51 q (1), J = 1.5 Hz, 11.51 br (1).

Anal. Calcd for $C_8H_8O_3$: C, 63.16; H, 5.26. Found: C, 63.05; H, 5.32.

Acid-Catalyzed Rearrangement of 2-Diazo-3-hydroxy-3-methylbenzocyclohexane-1,4-dione (2a). To vigorously stirred, cold (5°) concentrated sulfuric acid was slowly added (20 min) 0.25 g (1.2 mmol) of **2a**. After gas evolution had ceased, the reaction mixture was diluted with ice water and the resulting precipitate was collected and dried to give 80 mg (38%) of 2-acetyl-1,3-indandione which was shown to be identical with an authentic sample.[8]

3-Acetyl-4-hydroxycarbostyril (26). A solution of 13.5 mg (0.05 mmol) of **12** in 5 ml of anhydrous benzene was refluxed for 72 hr. Upon cooling 3.5 mg of **26**, mp 254–257° (lit.[9] mp 258–259°), precipitated. This product was shown to be identical with an authentic sample of 3-acetyl-4-hydroxycarbostyril which was kindly supplied by Calvin M. Foltz.[9] This same compound was obtained in 74% yield when 50 mg of 2,3,4,5-tetrahydro-3-diazo-4-methyl-4-methoxy-6,7-benzoazepine-2,5-dione (**13**) was decomposed in 5 ml of refluxing chlorobenzene. After 10 min at the reflux temperature the solution was cooled to 80–100° and a few drops of water were added. The solvent was then removed and the residue was subjected to dry column chromatography over silica gel using methanol as the eluent to give 31 mg (74%) of **26**.

2-(1-Acetoxy-2,2-dimethylpropylidine)-4-(2,2-dimethylethyl)-4-cyclopentene-1,3-dione (27). A solution of 1 g (3.75 mmol) of 5-acetoxy-6-diazo-2,5-di(1,1-dimethylethyl)cyclohex-2-ene-1,4-dione (**4**) in 25 ml of chlorobenzene was refluxed for 2 hr and the solvent was removed in vacuo. The resulting yellow solid was recrystallized from heptane to give 0.83 g (90%) of **27**: mp 61–62°; ir (Nujol) 1815, 1750, 1710, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 s (18), 2.46 s (3), 5.16 s (1).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.16; H, 8.09.

4*H*,6*H*(1*H*,5*H*)-Dioxo-3,4-diazino[3,4-*c*]quinoline (30). Concentrated sulfuric acid (5 ml, 0.5°) was vigorously stirred while 0.231 g (1.0 mmol) of 1,2,3,4-tetrahydro-4-acetyl-3-diazo-4-hydroxy-2-oxoquinoline (**12**) was added over a period of 20 min. During the course of this addition, the temperature of the reaction solution raised to 30°. Thirty minutes after the addition was complete, the reaction solution was poured onto 20 ml of crushed ice. The resulting precipitate was collected to give 0.22 g of **29** as a light yellow solid, mp 430° dec, which was recrystallized from dimethylformamide to give the pure product as white microcrystals: mp 430° dec; ir (Nujol) 3160, 1675, 1580, 1570, 1545 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.57–7.17 m (3), 8.00 s (1), 9.60–9.37 m (1), 12.77 br (1), 14.20 br (1); mass spectrum *m/e* (rel abundance) 213 (100), 186 (14.6) 158 (12.5), 103 (15.6).

Anal. Calcd for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 61.91; H, 3.33; N, 19.63.

2-Amino-3-thiophenyl-1,4-naphthoquinone (5d). To a stirred solution of 1.0 g (5.0 mmol) of 2-azido-1,4-naphthoquinone[14] in 70 ml of absolute ethanol was added 0.83 g (7.5 mmol) of thiophenol in one portion; gas evolution was observed and the reaction solution gradually turned from yellow-orange to red. After 12 hr the re-

sulting precipitate was collected to give 1.15 g (82%) of the quinone **5d**: mp 164–166° (lit.[15] mp 172°); ir (Nujol) 3475, 3275, 1685, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) 6.05 br (2), 7.25 br (5), 7.62–8.33 m (4).

2-Amino-5-azido-3,6-dimethyl-1,4-benzoquinone (1c). A solution of 1.1 g (5.0 mmol) of 2,5-diazido-3,6-dimethyl-1,4-benzoquinone[14] in 200 ml of ether was treated with 100 ml of a saturated aqueous solution of sodium dithionite, and the mixture was vigorously stirred for 60 min under an atmosphere of nitrogen. The organic layer was washed several times with water and dried and the solvent was then removed in vacuo (25°). The resulting 2,5-diazido-3,6-dimethylhydroquinone was dissolved in 75 ml of acetone and small amount of sodium azide was added. This caused the rapid disproportionation[16] of the hydroquinone and gave the crude product, **1c**, after approximately 1 hr. Chromotography of this crude product on 100 g of silica gel using chloroform as the eluent gave 0.72 g (74%) of **1c**, which turns from purple to white at 132–134° with gas evolution and the white solid then melts at 150–151°: ir (Nujol) 3310, 3220, 2100, 1630, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) 1.84 s (3), 1.89 s (3), 5.00 br (2).

Anal. Calcd for $C_8H_8N_4O_2$: C, 50.00; H, 4.17; N, 29.17. Found: C, 49.83; H, 4.29; N, 28.93.

2-Amino-3-methyl-1,4-naphthoquinone (2a), 2-Amino-3,6-dimethyl- (2b), 2-Amino-3,6-diphenyl- (2d), 2-Amino-3,6-di(1,1-dimethylethyl)- (3) and 2,5-Diamino-3,6-di(1,1-dimethylethyl)-1,4-benzoquinone. The above aminoquinones were prepared in good yields (>75%) by catalytic reduction (PtO_2, 30–40 psi) of ethanolic solutions of the respective azidoquinones.[12,14,17]

2-Amino-3-methyl-1,4-naphthoquinone (**1a**), mp 164–165° (lit.[18] mp 162–163°).

2-Amino-3,6-dimethyl-1,4-benzoquinone (**1b**): mp 194–196°; ir (Nujol) 3420, 3300, 1640, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.82 s (3), 1.98 d (3), J = 2 Hz, 4.79 br (2), 6.42 q (1), J = 2 Hz.

Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 5.96; N, 9.27. Found: C, 63.71; H, 6.17; N, 9.12.

2-Amino-3,6-diphenyl-1,4-benzoquinone (**1d**): mp 244–246°; ir (Nujol) 3410, 3250, 1630, 1560 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.14 br (2), 6.65 s (1), 7.15–7.52 m (10).

Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.54; H, 4.72; N, 5.09. Found: C, 78.39; H, 4.71; N, 4.92.

2-Amino-3,6-di(1,1-dimethylethyl)-1,4-benzoquinone (**3**): mp 111–113°; ir (Nujol) 3450, 3320, 1675, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 s (9), 1.38 s (9), 5.49 br (2), 6.44 s (1).

Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.49; H, 8.94; N, 5.96. Found: C, 71.37; H, 9.10; N, 5.73.

2,5-Diamino-3,6-di(1,1-dimethylethyl)-1,4-benzoquinone: mp 192–193°; ir (Nujol) 3440, 3320, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 .

Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.20; H, 8.80; N, 11.20. Found: C, 67.15; H, 8.94; N, 11.12.

Acknowledgment. The authors gratefully acknowledge the financial support of the National Science Foundation (GP43712X) and the National Institutes of Health (CA 11890).

Registry No.—**1a**, 7427-09-0; **1b**, 31679-93-3; **1c**, 26351-46-2; **1d**, 56908-60-2; **2a**, 56908-61-3; **2b**, 56908-62-4; **2c**, 56908-63-5; **2d**, 56908-64-6; **3**, 35612-59-0; **4**, 56908-65-7; **5d**, 56908-66-8; **7**, 56908-67-9; 8, 56908-68-0; **9**, 56908-69-1; **12**, 56908-70-4; **13**, 56908-71-5; **19**, 56908-72-6; **24**, 1133-72-8; **25**, 4056-72-8; **26**, 26138-64-7; **27**, 56908-73-7; **30**, 56908-74-8; 2,5-di-*tert*-butyl-3,6-diamino-1,4-benzoquinone, 56908-75-9; 2,5*H*-3-azido-4-methyl-6,7-benzoazepine-2,5-dione, 56908-76-0; 2,5*H*-4-methyl-6,7-benzoazepine-2,5-dione, 10315-37-4; sodium azide, 26628-22-8; 2-azido-1,4-naphthoquinone, 15707-29-6; 2,5-diazido-3,6-dimethyl-1,4-benzoquinone, 27977-29-3.

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(4) For example, linderone, methyllinderone, lucidone, methyllucidone, calythrone, and a number of hop constituents are 2-acyl-4-cyclopentene-1,3-diones. In addition, variously 2-substituted indan-1,3-diones show marked pharmacological activity as anticoagulants, and pyrethrins, among the most important natural insecticides, are related structurally to the cyclopentene-1,3-dione ring system. Indeed, even the prostaglandins can be viewed as partially reduced cyclopentene-1,3-diones.
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Asymmetric Synthesis of Oxaziridines

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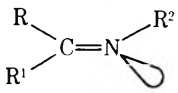
Oxidation of Schiff bases formed by the reaction of chiral (*R*)-(+)-α-phenylethylamine and carbonyl compound using *m*-chloroperbenzoic acid gives rise to the formation of nonracemic diastereomeric 3,3-disubstituted oxaziridines in a high optical yield. Oxidation of (*E*)-(*R*)-(−)-*N*-benzylidene-α-phenylethylamine yields a mixture of all four possible nonracemic diastereomers with predominance of *E* products.

The relatively small group of oxaziridines, containing the stable chiral N atom, is characterized by a high energy barrier for inversion, thus permitting the separation of enantiomers.[1-6]

Until now, optically active oxaziridines have been obtained by the oxidation of imines, using optically active peroxy acids.[2,3] Depending upon the substrate used, mixtures of compounds obtained represented nonracemic diastereomers or enantiomers with the presence of a small excess of one of them.[2,3] Such mixtures were usually separated by physical methods; in the case of a mixture of enantiomers, multiple recrystallizations afforded compounds which did not show a marked change of optical rotation after further recrystallizations.[4,6]

Two alternative mechanisms of imine oxidation have been postulated: (a) olefin type epoxidation (one step) involving nucleophilic reaction of π electrons of the C=N bond,[7,8] (b) Baeyer–Villiger (two step) type, through cleavage of π bonding followed by the elimination of one molecule of carboxylic acid used as peroxy acid.[9]

Chart I



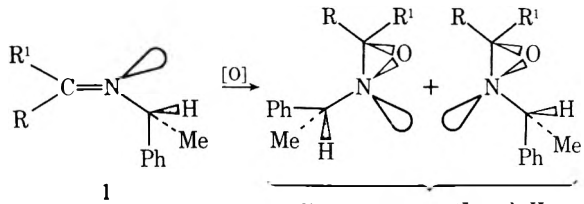
1

The next factor of influence in the course of reaction, is the kind and configuration of the imine used (Chart I).

Using imines derived from symmetrical ketones (1, R = R^1) a mixture of N enantiomers is obtained regardless of the mechanism. When aldimines or imines derived from unsymmetrical ketones are employed (1, R ≠ R^1) one can expect (a) in the case of the one-step mechanism two enantiomers (assuming that there is no inversion of the N atom in the intermediate stage and that the imine used was one of the isomers *Z* or *E*), (b) in the case of the two-step mechanism a mixture of four compounds, two enantiomers each of *Z* and *E*.

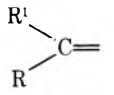
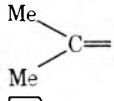
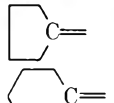
In our asymmetric synthesis of oxaziridines Schiff bases were used as substrates. These were obtained from (*R*)-(+)-α-phenylethylamine and a series of carbonyl compounds. We have observed that the oxidation of this type of imine by *m*-chloroperbenzoic acid yields a mixture of diastereomers with an excess of one of them.[10] The results obtained using ketimines of type 1 (R = R^1) and (*R*)-(+)-α-phenylethylamine are summarized in Scheme I.

Scheme I



1

diastereomers (I and II)

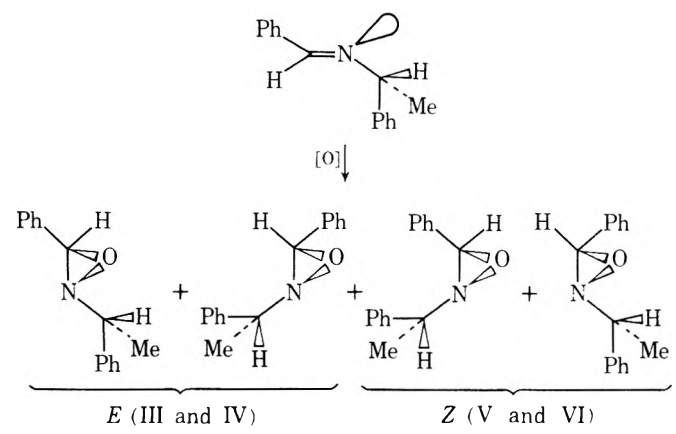
Starting 1	% diastereomers	
	I	II
	82	18
	87	13
	97	3

These results have been obtained by separation of nonracemic diastereomers through column chromatography (SiO_2) or HPLC (high performance liquid chromatography). The chemical yields have been determined by iodometric titration of the reaction mixture after removal of excess peroxy acid. The purity of the reaction products was determined by TLC and ^1H NMR spectroscopy.

In the case of the derivative of acetone (1, R = R^1 = Me), the ratio of I/II was also confirmed by integration of methyl signals in the ^1H NMR spectra. The signals from diastereotopic methyl groups originating from the presence of the acetone residue have the following value: I, 1.32 (s, 3, CH_3), 1.40 (s, 3, CH_3); II, 1.43 (s, 3, CH_3), 1.61 ppm (s, 3, CH_3). The signals from methyl group of residual amine are found: I, 1.47 (d, 3, CH_3), II, 1.32 ppm (d, 3, CH_3).

On the basis of our results one cannot assign configuration *RR* or *SR* to one of diastereomers I or II, since, so far as we could determine, no absolute configuration has as yet been determined for the N atom in oxaziridines. It has only been determined that the sign of the Cotton effect of the

Chart II



E (III and IV) *Z* (V and VI)

enantiomer product in excess agreed with the chiral peroxy acid used.[3,6]

In order to obtain more information in regard to the mechanism of imine oxidation we have used Schiff bases from benzaldehyde and (*R*)-(+)-α-phenylethylamine (1, R = H; R^1 = Ph). The resulting imine compound represent a pure *E* isomer (^1H NMR, TLC). This compound, oxidized as in former cases, gave a mixture of four nonracemic diastereomers, which were separated by column chromatography (Chart II).

The quantitative composition of the mixture was as follows.

Product (III, IV, V, VI)	*E* {*RRR*}	61.1%	(III)
	E {*SSR*}	22.2%	(IV)
	Z {*RSR*}	11.1%	(V)
	Z {*SRR*}	5.5%	(VI)

The composition of diastereomeric mixture *E* (III and IV) and *Z* (V and VI) could be confirmed by integration of signals produced by proton at C-3. The δ values (CCl_4, s) follow: III, 4.35, IV, 4.40 (*E*); V, 5.05, VI, 5.20 (*Z*).

The stability of the diastereomers was checked by heating their mixture in acetonitrile at 80° for ca. 60 hr. The samples of this solution investigated periodically did not show any quantitative change of the ^1H NMR signals of protons at C-3. We found only that after prolonged heating a thermal decomposition took place (titration of active oxygen).

The formation of four nonracemic stable diastereomers (III, IV, V, and VI) is not a convincing proof of a "two-step" mechanism.

We cannot exclude however, that in the cyclic intermediate postulated in the "one-step" mechanism[8] in which the free electron pair of nitrogen was engaged, an inversion of configuration on nitrogen takes place, which would lead to the additional formation of two diastereomers.

The "two-step" mechanism seems to be more probable. Its first step is the addition of peracid molecule to the C=N double bond with the formation of chiral center at C-3 (imine carbon atom). The preference of *R* or *S* attack depends on the chiral substituent (R) at nitrogen (Chart III).

Chart III

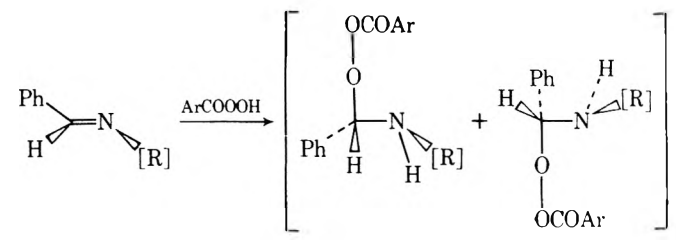
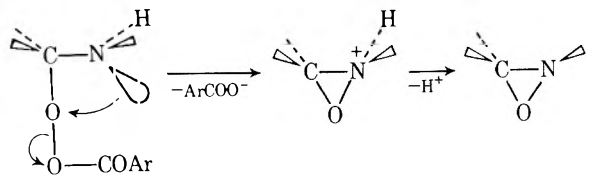


Chart IV



Thus formed two diastereomeric intermediates undergo elimination of the free acid, and this reaction requires an eclipsed configuration of the free electron pair at nitrogen with respect to oxygen atom in the peracid residue (Chart IV). Such an arrangement can occur in two ways: (a) rotation of the C–N bond or (b) inversion at nitrogen atom. The latter possibility leads consequently to the formation of two further diastereomers in the resulting reaction mixture.

In the case of an imine formed from a symmetric ketone, i.e., cyclohexanone, the addition of the peracid to the C=N double bond does not create a chiral center at C-3; however, the second reaction step involves a stereospecific intramolecular elimination of the acid and this particular reaction is responsible for the high stereospecificity observed in our experiments.

Experimental Section[13]

Schiff bases were prepared according to known procedures.[11,12] Active oxygen contents of oxaziridines were determined by iodometric titration with potassium iodide in a stirred mixture of dichloromethane, water, and glacial acetic acid.

Typical Preparation of Oxaziridine. A small excess of *m*-chloroperbenzoic acid (0.022 mol) in 40 ml of methylene chloride was added with stirring and cooling (0–5°C) to a solution of 0.02 mol of imine in 10 ml of methylene chloride. After the peroxy acid had been added, the reaction mixture was stirred for an additional 5 hr at 0–5°C. After that time the formed *m*-chlorobenzoic acid was removed by filtration. The filtrate was washed two times with a dilute solution of Na_2SO_3, then twice with a solution of Na_2CO_3, and finally with water. After drying over $MgSO_4$ (anhydrous), the solvent was evaporated and the residue was chromatographed over a column of SiO_2 using hexane–ethyl ether (9:1) as a solvent.

(*R*)-(+)-*N*-Isopropylidene-α-phenylethylamine (1, R = R¹ = Me): $[\alpha]_{436}^{22}$ +82.3° (*c* 1, $CHCl_3$); bp 60–62°C (0.9 mm); ir 1660 cm^{-1} (C=N); $n^{20}D$ 1.517; ^1H NMR 1.34 (d, 3, CH_3), 1.78 (s, 3, CH_3 at C=N), 1.97 (s, 3, CH_3 at C=N), 4.48 ppm (m, 1, CH).

(*R*)-(+)-*N*-Cyclopentylidene-α-phenylethylamine (1, R, R¹ = Tetramethylene): $[\alpha]_{436}^{22}$ +221.2° (*c* 1, $CHCl_3$); bp 93.5–94°C (0.7 mm); ir 1675 cm^{-1} (C=N); $n^{20}D$ 1.537; ^1H NMR 1.37 (d, 3, CH_3), 4.51 ppm (m, 1, CH at N).

(*R*)-(+)-*N*-Cyclohexylidene-α-phenylethylamine (1, R, R¹ = Pentamethylene): $[\alpha]_{436}^{22}$ +102.6° (*c* 1, $CHCl_3$); bp 102.5–104°C (0.8 mm); ir 1670 cm^{-1} (C=N); ^1H NMR 1.35 (d, 3, CH_3), 4.63 ppm (m, 1, CH at N).

(*R*)-(−)-*N*-Benzylidene-α-phenylethylamine (1, R = H; R¹ = Ph):[12] $[\alpha]^{20}D$ −83° (*c* 1.03, benzene); bp 115–116°C (0.5 mm); ir 1650 cm^{-1} (C=N); $n^{20}D$ 1.5881; ^1H NMR 1.48 (d, 3, CH_3), 4.38 (m, 1, CH at N), 8.15 ppm (s, 1, CH=N).

2-[(*R*)-α-Phenylethyl]-3,3-dimethyloxazirane. Diastereomer I: $[\alpha]_{436}^{22}$ +98.5° (*c* 1, $CHCl_3$); $n^{20}D$ 1.503; uv max (95% EtOH) 208 nm (ε 8675), 215 (5184), 242 (227), 248 (228), 252 (274.7), 258 (265), 264 (213.1), 268 (126.7); ^1H NMR 1.32 (s, 3, CH_3 at C-3), 1.40 (s, 3, CH_3 at C-3), 1.47 (d, 3, CH_3 at CHN), 3.43 ppm (m, 1, CH).

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.89; H, 8.72; N, 7.95; *m/e* 177.

Diastereomer II: $[\alpha]_{436}^{22}$ +271.9° (*c* 1, $CHCl_3$); $n^{20}D$ 1.508; uv max (95% EtOH) 207 nm (ε 8287), 211 (7432), 215 (4183), 247 (249), 252 (262), 257 (272), 264 (214), 268 (155.1); ^1H NMR 1.43 (s, 3, CH_3 at C-3), 1.61 (s, 3, CH_3 at C-3), 1.32 (d, 3, CH_3 at CHN), 3.4 ppm (m, 1, CH at N); *m/e* 177.

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.61; H, 8.69; N, 7.81.

2-[(*R*)-α-Phenylethyl]-3,3-tetramethyleneoxazirane. Diastereomer I: $[\alpha]_{436}^{22}$ +63.0° (*c* 1, $CHCl_3$); $n^{22}D$ 1.518; uv max (95% EtOH) 208 nm (ε 8063), 216 (4866), 242 (143.1), 248 (152), 253 (186), 259 (220.4), 264 (179.4), 268 (102); ^1H NMR 1.47 (d, 3, CH_3), 3.22 ppm (m, 1, CH at N); *m/e* 203.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.97; H, 8.45; N, 6.77.

Diastereomer II: $[\alpha]_{436}^{22}$ +295.4° (*c* 1, $CHCl_3$); $n^{22}D$ 1.522; uv max (95% EtOH) 208 nm (ε 8501), 211 (7911), 215 (4668), 247 (270), 251 (295), 258 (307), 264 (248.1), 268 (165.8); ^1H NMR 1.30 (d, 3, CH_3), 3.17 ppm (m, 1, CH at N); *m/e* 203.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.93; H, 8.72; N, 7.16.

2-[(*R*)-α-Phenylethyl]-3,3-pentamethyleneoxazirane. Diastereomer I: $[\alpha]_{436}^{22}$ +118.5° (*c* 1, $CHCl_3$); $n^{20}D$ 1.523; uv max (95% EtOH) 208 nm (ε 9000), 216 (5426.3), 241 (203.5), 248 (189), 252 (223), 258 (259), 264 (211), 268 (119); ^1H NMR 1.5 (d, 3, CH_3), 3.54 ppm (m, 1, CH at N); *m/e* 217.

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.17; H, 9.07; N, 6.47.

Diastereomer II: $[\alpha]_{436}^{22}$ +205.4° (*c* 1, $CHCl_3$); $n^{20}D$ 1.529; uv max (95% EtOH) 208 nm (ε 10401), 210 (9929), 214 (6273), 247 (240.5), 252 (260), 258 (271), 264 (200), 268 (103); ^1H NMR 1.3 (d, 3, CH_3), 3.54 (m, 1, CH at N); *m/e* 217.

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.68; H, 9.1; N, 6.64.

2-[(*R*)-α-Phenylethyl]-3-phenyloxazirane. Diastereomer III: $[\alpha]_{436}^{20}$ −238.2° (*c* 1.08, EtOH); oil; uv max (95% EtOH) 211 nm (ε 12400), 216 (11500), 247 (666), 253 (770), 258 (8. 45), 271 (535), 310 (230); ^1H NMR 1.58 (d, 3, CH_3), 3.14 (m, 1, CH at N), 4.35 ppm (s, 1, H-3); *m/e* 225.

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.40; H, 7.07; N, 6.07.

Diastereomer IV: $[\alpha]_{436}^{20}$ +188.4° (*c* 1.42, EtOH); mp 52–53°C (from hexane); uv max (95% EtOH) 209 nm (ε 14000), 211 (13730), 216 (12150), 247 (300), 253 (400), 259 (500), 260 (473), 264 (482), 272 (304); ^1H NMR 1.45 (d, 3, CH_3) 3.25 (m, 1, CH at N), 4.40 ppm (s, 1, H-3); *m/e* 225.

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.08; H, 6.90; N, 6.20.

Diastereomer V: $[\alpha]_{436}^{20}$ +350.9° (*c* 1.18, EtOH); oil; uv max (95% EtOH) 209 nm (ε 29000), 217 (21200), 247 (685), 252 (665), 259 (612), 264 (481), 271 (254); ^1H NMR 1.52 (d, 3, CH_3), 3.15 (m, 1, CH at N), 5.05 ppm (s, 1, H-3); *m/e* 225.

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.21; H, 7.07; N, 6.75.

Diastereomer VI: $[\alpha]_{436}^{20}$ +630.0° (*c* 0.94, EtOH); mp 98° (from hexane); uv max (95% EtOH) 207 nm (ε 27550), 211 (26056), 215 (21410), 252 (647), 259 (732.4), 264 (642.2), 271 (293); ^1H NMR 1.02 (d, 3, CH_3), 3.17 (m, 1, CH at N), 5.20 ppm (s, 1, H-3); *m/e* 225.

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.48; H, 6.68; N, 6.18.

Registry No.—I, R = R¹ = Me, 56424-40-9; I, R, R¹ = tetramethylene, 56424-41-0; I, R, R¹ = pentamethylene, 56424-42-1; I, R = H, R¹ = Ph, 56941-77-6; I, R = R¹ = Me, 56907-09-6; II, R = R¹ = Me, 56424-43-2; I, R, R¹ = tetramethylene, 56907-10-9; II, R, R¹ = tetramethylene, 56424-44-3; I, R, R¹ = pentamethylene, 56907-11-0; II, R, R¹ = pentamethylene, 56424-45-4; III, 56830-31-0; IV, 56907-12-1; V, 56907-13-2; VI, 56907-14-3.

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Notes

Base-Catalyzed Elimination Reactions of 4-Nitrobenzyl Fluoride

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Numerous studies of the reactions of 4-nitrobenzyl chloride and various derivatives thereof with alkali in mixed aqueous solvents have so far failed to determine unequivocally the mechanism of formation of 4,4′-dinitrostilbene (or derivatives thereof) under these conditions.[1-4] The reactions of the corresponding bromide and iodide analogs are reported to yield bis(4-nitrobenzyl) ether[5] but we are unaware of any similar studies of 4-nitrobenzyl fluoride, except the study of its reaction with sodium ethoxide in ethanol, in which an unidentified, high-melting product was obtained,[6] possibly the stilbene. In view of the considerable product sensitivity of these base-catalyzed reactions to the halide ion, it is of interest to study the reaction of 4-nitrobenzyl fluoride in an effort to provide evidence contributing toward a unifying, and acceptable, mechanistic scheme for these reactions. Accordingly we report here some results for reactions of the fluoride, together with product analyses for reactions of all four halides in the presence of *p*-dinitrobenzene. This reagent is well known as both a radical trap and an acceptor of one electron from a carbanion,[7] the latter role causing reactions to proceed via radical anion intermediates. Thus, these studies should indicate the probability, or otherwise, of the occurrence of a radical mechanism.

Reaction of 4-nitrobenzyl fluoride with excess sodium hydroxide in carefully purified aqueous dioxane 50% (v/v) under air gave *cis*- (40%) and *trans*-4,4′-dinitrostilbene epoxide (40%), ca. 5% *trans*-4,4′-dinitrostilbene, and traces of 4-nitrobenzyl alcohol and several other unidentified products. A similar reaction under nitrogen gave *cis*- (ca. 2%) and *trans*-4,4′-dinitrostilbene (20%), bis(4-nitrobenzyl) ether (24%), and a tar containing at least four other components (see Table I). These products may be contrasted with the *cis*- and *trans*-4,4′-dinitrostilbene obtained from the chloride and bis(4-nitrobenzyl) ether reported[5,8] from the bromide or iodide under air. The products from reactions of 4-nitrobenzyl fluoride thus differ markedly from those of the other halides and imply that the reaction proceeds via a different pathway or via more than one pathway. A possible alternative mechanism involves radical anion intermediates even though no product arising from the dimerization of 4-nitrobenzyl radicals was found. Thus, initial formation of the conjugate base, followed by electron transfer to either a neutral reactant molecule or to oxygen (eq 1–3), could initiate these reactions.

$$ArCH_2F + {}^-OH \rightleftharpoons Ar\bar{C}HF + H_2O \quad (1)$$

$$Ar\bar{C}HF + O_2 \longrightarrow ArCHF\cdot + O_2\cdot^- \quad (2)$$

$$Ar\bar{C}HF + ArCH_2F \longrightarrow Ar\dot{C}HF + ArCH_2F\cdot^- \quad (3)$$

$$ArCHF\cdot + O_2 \longrightarrow ArCHFO_2\cdot \xrightarrow{ArCH_2F} ArCHFO_2H + ArCHF\cdot \quad (4)$$

$$ArCHFO_2H + {}^-OH \xrightarrow{-H_2O} ArCHFO_2^- \longrightarrow ArCHO + \tfrac{1}{2}O_2 + F^- \quad (5)$$

$$ArCHO + Ar\bar{C}HF \longrightarrow ArCH(O^-)-CHFAr \longrightarrow ArCH(O)CHAr + F^- \quad (6)$$

Ar = 4-$O_2NC_6H_4$

If reaction of the fluoride proceeds via radical anion intermediates, then the addition of a radical-trapping agent, e.g., *p*-dinitrobenzene, should cause the reaction rate to decrease and competing reaction pathways to become evident (cf. the effect of *o*-dinitrobenzene on base-catalyzed elimination from 4-nitrobenzyldimethylsulfonium ion[9]). The similar addition of such a compound to the bromide or iodide should allow some reaction to occur via a radical anion pathway as a result of electron transfer from the α-halo carbanion to the added nitroaromatic[10] to give the stilbene and the corresponding epoxides, viz.

Table I
Percentage Yields of Products from Base-Catalyzed Reactions of 4-Nitrobenzyl Halides in Aqueous Dioxane (50% v/v)[d]

Registry no.	4-$O_2NC_6H_5CH_2X$ Product	X = F[a]		X = Cl		X = Br		X = I		X = F[c]	
		N_2	Air	N_2	Air	N_2	Air	N_2	Air	N_2	Air
619-93-2 (cis) 736-31-2 (trans)	4,4′-Dinitrostilbene (*cis*- and *trans*-)	22	5	43	26	33	17	28	12	26	13
14688-37-0	*cis*-4,4′-Dinitrostilbene epoxide		40		20		29		23		*b*
968-01-4	*trans*-4,4′-Dinitrostilbene epoxide		40		21		32		25		*b*
56679-04-0	Bis(4-nitrobenzyl) ether	24		5		6		14		52	47
619-73-8	4-Nitrobenzyl alcohol		*b*	9	*b*	13	*b*	16	*b*	15	21
2735-14-0	4,4′-Dinitrotolane	*b*		5		5		5			

[a] Reactions in the absence of *p*-dinitrobenzene. [aryl halide] = 1×10^{-2} *M*; [base] = 3×10^{-2} *M*. [b] Trace product. [c] [Aryl halide] = 1×10^{-2} *M*; [base] = 3×10^{-2} *M*. [d] [Aryl halide] = 1×10^{-2} *M*; [base] = 1×10^{-1} *M*; [*p*-dinitrobenzene] = 1×10^{-2} *M*.

$$ArCHX + ArNO_2 \longrightarrow ArCHX\cdot + ArNO_2\cdot^- \quad (7)$$

$$ArCH_2X + ArNO_2\cdot^- \longrightarrow ArCH_2X\cdot^- + ArNO_2 \quad (8)$$

$$ArCH_2X\cdot^- \longrightarrow X^- + ArCH_2\cdot \xrightarrow{ArCHX} ArCH_2CHXAr\cdot^- \quad (9)$$

$$ArCH_2CHXAr\cdot^- + ArNO_2 \longrightarrow ArCH_2CHXAr + ArNO_2\cdot^- \quad (10)$$

$$ArCH_2CHXAr + {}^-OH \longrightarrow ArCH{=}CHAr + H_2O + X^- \quad (11)$$

X = Cl, Br, or I

The results of reactions in the presence of *p*-dinitrobenzene are shown in Table I, from which the change in products obtained is immediately evident. Under nitrogen, 4,4′-dinitrostilbene is obtained from reactions of all four halides together with small amounts of 4-nitrobenzyl alcohol and 4,4′-dinitrotolane.[2] Low yields of bis(4-nitrobenzyl) ether are obtained from all compounds except the fluoride from which a large amount of this product is formed. Reactions under air gave large amounts of the *cis*- and *trans*-4,4′-dinitrostilbene epoxides but decreased amounts of 4,4′-dinitrostilbene from the chloride, bromide, and iodide.

The epoxide presumably arises via 4-nitrobenzaldehyde (eq 5 and 6). No evidence of 4,4′-dinitrobenzyl was obtained, suggesting that 4,4′-dinitrostilbene is only formed by oxidation of this intermediate if this oxidation is 100% efficient (cf. base-catalyzed oxidation of 4-nitrotoluene[10]). It is of interest to note that formation of the epoxides apparently occurs *only* at the surface of the solution.

The increasing strength of the carbon–halogen bond with decreasing atomic weight of the halogen increases the stability of the corresponding α-halo carbanions and shifts the equilibrium of eq 1 to the right. Reaction via the SN2 pathway, which involves attack on neutral reactant molecules, is thus progressively disfavored on going from iodine through to fluorine, as is reaction via the α-ElcB mechanism, which requires carbon–halogen bond breakage. Although the formation of radical anions from 4-nitrobenzyl and 4-nitrocumyl chlorides has been observed in the presence of 2-nitro-2-propyl carbanions, etc,[11] no evidence of reaction of 4-nitrobenzyl chloride via the radical anion is obtained except in the presence of *p*-dinitrobenzene. SN2 reaction via an ion pair intermediate[12] thus seems preferable to the α-ElcB mechanism for the chloride, whereas the poorer leaving group in the fluoride results in reaction via the radical anion mechanism. These results are thus in good accord with our conclusions from kinetic, etc., studies of derivatives of 4-nitrobenzyl chloride,[3,4] i.e., that reaction via a radical mechanism in the absence of radical initiators (e.g., peroxides) is unlikely.

Experimental Section

4-Nitrobenzyl fluoride (1.0877 g) was dissolved in dioxane (300 ml), sodium hydroxide solution (300 ml, 0.022 *N*) was added, and the reaction mixture was kept thermostatted at 35°C for 1 month. Yellow needles were precipitated and, after isolation, were shown to be *trans*-4,4′-dinitrostilbene oxide (40% based on substrate). The remaining solution was then acidified with concentrated hydrochloric acid and freeze dried. *cis*-4,4′-Dinitrostilbene epoxide (40%) and *trans*-4,4′-dinitrostilbene (5%) were isolated by preparative TLC using benzene as eluent. All compounds were identified by NMR, mass spectrometry, melting point, and mixture melting point with authentic samples.

Reactions of 4-nitrobenzyl chloride, bromide, and iodide with sodium hydroxide in the presence of *p*-dinitrobenzene in aqueous dioxane, under air or nitrogen, were perform ' at room temperature, and products were analyzed after 4–5 hr. 95% of the added *p*-dinitrobenzene was recovered unchanged.

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Registry No.—4-Nitrobenzyl fluoride, 500-11-8; sodium hydroxide, 1310-73-2; 4-nitrobenzyl chloride, 100-14-1; 4-nitrobenzyl bromide, 100-11-8; 4-nitrobenzyl iodide, 3145-86-6.

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The *p*-Nitrobenzyl System. IV.[1] Base-Induced Transformations in *p*-Nitrobenzyl Chloride, Bromide, Iodide, Tosylate, and Sulfonium Salts[2-4]

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As a part of a reinvestigation of the mechanisms of formation of *p,p′*-dinitrostilbene (**2**) from *p*-nitrobenzyl chloride (**1**),[5] we wish to report the products of base-induced reactions in several *p*-nitrobenzyl compounds. It has been repeatedly mentioned in the recent literature[6] that the product of reacting **1** with hydroxide ion in aqueous dioxane (eq 1) is almost exclusively *trans*-**2**. In view of doubts

$$\underset{\mathbf{1}}{ArCH_2Cl} + OH^- \longrightarrow \underset{\mathbf{2}}{ArCH{=}CHAr} \quad (1)$$

Ar = *p*-$NO_2C_6H_4$

of this information,[7] and in an attempt to elucidate the mechanism of this transformation, we carried out, in addition to kinetic and isotope effect measurements[4] to be published separately, a product analysis of the reactions of hydroxide ion with **1** and with *p*-nitrobenzyl bromide (**3**), iodide (**4**), and tosylate (**5**) in 50% aqueous dioxane. For comparative purposes,[8] we also reinvestigated the products of reacting *p*-nitrobenzyldimethylsulfonium bromide (**6**) and tosylate (**7**) with sodium hydroxide in aqueous solution. The results are shown in Tables I–III. It is quite evident from inspection of Table I that the reputed[5] *almost quantitative* yield of *trans*-**2** from the reaction of **1** with sodium hydroxide in 50% aqueous dioxane is in error. The reaction given in eq 1 yields a yellowish precipitate whose weight corresponds to 98% of that expected for a quantitative yield of **2**; however, TLC and its visible and uv spectra show that it contains the geometrical isomers of both **2** and *p,p′*-dinitrostilbene oxide (**8**) as well as smaller amounts of other compounds (Table I). On recrystallization of the crude product from nitrobenzene in the presence of a crystal of

Table I
Products and Yields of the Reaction of *p*-Nitrobenzyl Chloride with Sodium Hydroxide in Aqueous Dioxane (50% Water) at 25°

Entry no.	Reactants, *M* [$ArCH_2Cl$]	[NaOH]	Conditions	Yields, % 2[a,b]	8[a,b]	16[c]	12[c]	Others
1	0.01	0.10	Degassed	52[d]	43[e]	3	Trace	17[c] and *p*-nitrotolane,[a] trace
2	0.02	0.10	Oxygen		88[f]	5	2	*p*-Nitrobenzoic acid,[a] 4
3	0.01	0.10	*p*-DNB, 0.01 *M*	16	22	19	2	*p,p'*-Dinitrobibenzyl,[a,c] 11, 17[c]
4	0.01	0.10	Nitroxide, 0.001 *M* degassed	41	35	12	1	*p*-Nitrotolane,[a] trace
5	0.01	0.10	Nitroxide, 0.005 *M* degassed		34	49	6	

[a] Detected by TLC. [b] Quantitated by uv. [c] Determined by VPC. [d] *cis*-2, 27.8%; *trans*-2, 24.2%. [e] *cis*-8, 24.5%; *trans*-8, 18.5%. [f] *cis*-8, 51%; *trans*-8, 37%.

Table II
Products and Yields of the Reactions of *p*-Nitrobenzyl Dimethylsulfonium Tosylate and Bromide, 0.01 *M*, with Sodium Hydroxide, 0.1 *M*, in Water at 60°

Entry no.	Anion of sulfonium salt	Yields, % 2[a,b]	8[a,b]	Reaction conditions
6	OTs^-	31	52	No precautions to exclude air
7[c]	OTs^-	3	54	Saturated with O_2
8	Br^-	37	43	No precautions to exclude air
9	Br^-	4	59	Saturated with O_2

[a] Detected by TLC. [b] Quantitated by uv. [c] *p*-Nitrobenzyl alcohol (11%) and *p*-nitrotoluene (3%) were also detected.

iodine to isomerize *cis*-2 to *trans*-2,[8] only *trans*-2 is obtained. This is due to the fact that the other major product, viz. 8, is fairly soluble in nitrobenzene and remains in solution while only pure *trans*-2 crystallizes out. We tested this by mixing authentic samples of 2 and 8, dissolving in hot nitrobenzene, and cooling for crystallization. The crystalline material thus obtained was pure by TLC (silica), had undepressed melting point when mixed with pure *trans*-2, and had uv, NMR, and ir spectral characteristics identical with those of pure *trans*-2.

It is puzzling that the epoxide 8 is produced in thoroughly degassed solutions. Its formation may be accounted for by the reaction scheme shown in eq 2–6. The production of

$$\underset{\mathbf{1}}{ArCH_2Cl} + OH^- \rightleftharpoons \underset{\mathbf{9}}{\bar{A}rCHCl} + H_2O \quad (2)$$

$$\bar{A}rCHCl + ArCH_2Cl \longrightarrow \underset{\mathbf{10}}{\dot{A}rCHCl} + \underset{\mathbf{11}}{ArCH_2Cl^{\cdot -}} \quad (3)$$

$$\dot{A}rCHCl + H_2O \longrightarrow ArC(OH)HCl + H\cdot \quad (4)$$

$$ArC(OH)HCl + OH^- \longrightarrow \underset{\mathbf{12}}{ArCHO} + Cl^- + H_2O \quad (5)$$

$$ArCHO + \bar{A}rCHCl \longrightarrow \underset{\mathbf{8}}{ArCH(O)CHAr} + Cl^- \quad (6)$$

the carbanion 9 in the reaction medium has been proven by deuterium labeling.[5,9] The reaction of a radical, 10, with water (eq 4) to abstract a hydroxyl radical may seem strange; however, in the virtual absence of reduced products (Table I) eq 4 is necessary to account for the observed epoxide. An example of a similar hydroxyl abstraction is afforded by the oxidation of isobutyraldehyde by Fremy's salt in basic solution.[10] The hydrogen atom generated in eq 4 is presumably captured by unreacted 1 to give a transient radical anion[11] ($HArCH_2Cl^{\cdot -}$) which reacts with hydroxide

Table III
Products and Yields of the Reactions of *p*-Nitrobenzyl Bromide, Iodide, and Tosylate with Sodium Hydroxide[a] in 50% Aqueous Dioxane at 25°

Entry no.	*p*-Nitrobenzyl compd[b]	Yields, % 2[c]	8[c]	16[d]	Other[d]
10	Bromide	~1	10	67	18, 5; 12 and 17, traces
11	Iodide	Trace	20	76	12, 3
12	Tosylate	~4	20	52	12, 2; 17, trace

[a] [NaOH] = 0.1 *M*. [b] [$ArCH_2X$] = 0.01 *M*. [c] Determined by TLC. [d] Determined by VPC.

ion to give another radical anion, 11 in eq 3. The interception of the carbanion 9 by *p*-nitrobenzaldehyde (12) to give 8 (eq 6) is well documented.[5]

The possibility of intervention of radical anions in this system has been entertained previously.[11] We tested this possibility by conducting the reaction of 1 with hydroxide ion in the presence of *p*-dinitrobenzene (*p*-DNB), which is known to be a good electron acceptor, particularly from radical anions,[12] and in the presence of oxygen is reported to react with *p*-nitrobenzyl radical to give 12.[13] The presence of O_2 inhibits completely the formation of 2 but enhances the formation of 8, while *p*-DNB lowers the yields of both 2 and 8 to 16 and 22%, respectively (Table I). It is quite probable that the fates of the radical 10 and the radical anion 11 of eq 3 follow the scheme represented by eq 7–13.

$$\underset{\mathbf{11}}{ArCH_2Cl^{\cdot -}} + O_2 \longrightarrow \underset{\mathbf{1}}{ArCH_2Cl} + O_2^{\cdot -} \quad (7)$$

$$\underset{\mathbf{10}}{\dot{A}rCHCl} + O_2 \longrightarrow ArCH(O_2\cdot)Cl \quad (8)$$

$$ArCH(O_2\cdot)Cl + \bar{A}rCHCl \longrightarrow ArCH(O_2^-)Cl + \mathbf{10} \quad (9)$$

$$ArCH(O_2^-)Cl + H_2O \longrightarrow ArCH(O_2H)Cl + OH^- \quad (10)$$

$$ArCH(O_2H)Cl + Ar\bar{C}HCl^- \longrightarrow ArCH(O^-)Cl + ArCH(OH)Cl \quad (11)$$

$$ArCH(O^-)Cl \longrightarrow ArCHO + Cl^- \quad (12)$$

12

$$ArCH(OH)Cl + OH^- \longrightarrow 12 + Cl^- + H_2O \quad (13)$$

The above scheme serves to illustrate several points. The radical anion **11**, which may be invoked in stilbene formation,[11] is diverted back to **1** (eq 7). The radical **10** which, in the present scheme, is ultimately responsible for the production of the epoxide **8** via the aldehyde **12** (eq 6), is regenerated in what may be regarded as chain-propagation steps (eq 8 and 9). It is evident from eq 2, 3, 7, 8, and 9 that oxygen would divert **11** to give ultimately **8**. In the absence of oxygen it is possible that **11** is responsible for the production of **2** as indicated in the following scheme, eq **14**–**17**.

$$ArCH_2Cl\cdot^- \longrightarrow Ar\dot{C}H_2 + Cl^- \quad (14)$$

13

$$Ar\dot{C}H_2 + Ar\bar{C}HCl \longrightarrow ArCH_2CHClAr\cdot^- \quad (15)$$

14

$$ArCH_2CHClAr\cdot^- + OH^- \longrightarrow ArCH{=}CHAr\cdot^- + H_2O + Cl^- \quad (16)$$

$$ArCH{=}CHAr\cdot^- + 1 \longrightarrow ArCH{=}CHAr + ArCH_2Cl\cdot^- \quad (17)$$

2

Alternatively, **14** may react with **1** to give **15** which undergoes a β-elimination to **2** (eq 18, 19).

$$ArCH_2CHClAr\cdot^- + ArCH_2Cl \longrightarrow ArCH_2CHClAr + ArCH_2Cl\cdot^- \quad (18)$$

15

$$ArCH_2CHClAr + OH^- \longrightarrow ArCH{=}CHAr + H_2O + Cl^- \quad (19)$$

To test the presence of free radicals, the reaction between **1** and hydroxide ion in 50% aqueous dioxane was carried out in the presence of di-*tert*-butyl nitroxide, which is known to be a radical scavenger.[14] With added nitroxide, the yield of **2** is lowered while the amount of *p*-nitrobenzyl alcohol (**16**) is increased (Table I). This may reflect the scavenging of **13** by the nitroxide.

For comparison purposes, the products and yields of the reaction of the sulfonium salts **6** and **7** with hydroxide ion in aqueous solution are reported in Table II. Here, too, the products which were once thought to be exclusively **2** are actually mixtures of **2** and **8** as well as **16** and *p*-nitrotoluene (**17**) when no precautions to exclude oxygen are taken.

In Table III are reported the products and yields of the reactions of **3**, **4**, and **5** with sodium hydroxide in 50% aqueous dioxane. Previously, **3** and **4** were reported to give *p,p'*-dinitrobibenzyl ether (**18**) in quantitative yield.[15]

In summary, we wish first to call attention to the complexity of base-induced transformations of *p*-nitrobenzyl compounds and second to correct some of the errors which are perpetually relayed in the literature. We wish also to emphasize that although the present work suggests that radicals and radical anions may be involved in the **1** to **2** transformation, neither the carbene mechanism nor the alkylation–dehydrohalogenation mechanism can be excluded. Indeed, the three mechanisms may be operative simultaneously. We will report on the pros and cons of each of these mechanisms in the light of kinetic and isotope effect data.

Experimental Section

Qualitative analysis of the reaction products was done by TLC. Silica plates with a fluorescent indicator (Brinkmann silica gel HF-254) were used and were developed with benzene; standards were run alongside the unknown mixtures. VPC was used to quantitate the readily volatile components of products (Varian Aerograph 600-D with a flame ionization detector; 5% SE-30 6 ft × 0.125 in. column). Calibration curves, using *trans*-stilbene as an internal standard, were prepared for **1**, **12**, **16**, **17**, and *p*-DNB. Spectroscopic analyses (uv and visible on a Cary 14) were performed in DMF for the quantitation of the dinitrostilbenes[16] [*trans*-**2**, 368 nm (4.577); *cis*-**2**, 320 nm (4.193)] and the dinitrostilbene oxides [*trans*-**8**, 291 nm (4.371); *cis*-**8**, 277 nm (4.264)]. Mixtures of *cis*- and *trans*-**2** exhibited one maximum between 368 and 320 nm.[17] The amounts of the four components, *cis*- and *trans*-**2** and *cis*- and *trans*-**8**, were determined by solving simultaneous equations for the absorbances at 380, 340, 290, and 270 nm

$$A_{380} = 32300c_1 + 5350c_2 + 266c_3$$
$$A_{340} = 25200c_1 + 15000c_2 + 1840c_3 + 935c_4$$
$$A_{290} = 5700c_1 + 11750c_2 + 23500c_3 + 1600c_4$$
$$A_{270} = 4200c_1 + 8190c_2 + 14400c_3 + 17600c_4$$

where c_1, c_2, c_3, and c_4 refer to the concentrations in DMF of *trans*- and *cis*-**2** and *trans*- and *cis*-**8**, respectively.

Materials. The compounds used in this study were either commercially available and purified before using or prepared and purified by known procedures. The following compounds were used as chromatographic standards. Their melting points and spectral characteristics were in agreement with the literature: *cis*- and *trans*-**2**,[16] *cis*- and *trans*-**8**,[18] $ArCH_2CH_2Ar$,[19] $ArCH_2OCH_2Ar$,[15] ArC≡CAr,[20] **12**, **16**, and **17**.

Product Studies. All aqueous dioxane solutions were prepared from purified and freshly distilled dioxane and used immediately. Studies that involved degassed solutions were done on a vacuum line. Those studies involving the effect of O_2 were performed by saturating the solutions with O_2 and keeping the reaction mixture under an O_2 atmosphere. All experiments were conducted in 50% aqueous dioxane (v/v) except those with the sulfonium salts, where water was used as the solvent.

In a typical experiment, 50 ml of a 0.02 *M* solution of **1** in dioxane and 50 ml of a 0.20 *M* NaOH solution were degassed separately by a series of freeze–thaw cycles and then mixed under vacuum. After 24 hr, the reaction mixture was opened to atmospheric pressure, neutralized with dilute HCl, diluted with an equal volume of water, and stored in a refrigerator for 24 hr. The precipitate was isolated by filtration and dried; 0.132 of a yellow solid was obtained. This was analyzed by TLC and uv. The yields of **2** and **8** are given in Table I. The precipitate also contained a trace spot with the same R_f value as *p,p'*-dinitrotolane. A sample of this compound obtained by preparative TLC had *m/e* 268. The filtrate was extracted with chloroform. The organic layer was dried (Na_2SO_4), and the solvent removed on a rotary evaporator; the remaining solid (5 mg) was analyzed by TLC and shown to be **16**, with traces of **12** and **17**.

Registry No.—**1**, 100-14-1; *cis*-**2**, 619-93-2; *trans*-**2**, 736-31-2; **3**, 100-11-8; **4**, 3145-86-6; **5**, 1153-45-3; **6**, 14182-26-4; **7**, 19824-23-8; *cis*-**8**, 14688-37-0; *trans*-**8**, 968-01-4; **12**, 555-16-8; **16**, 619-73-8; sodium hydroxide, 1310-73-2; *p*-nitrotoluene, 99-99-0.

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Reductive Deoxygenation of Esters with Trichlorosilane[1]

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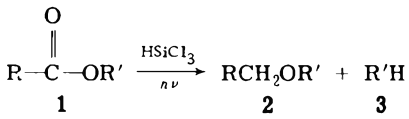
Trichlorosilane has been shown to be an efficient reagent for reducing simple aliphatic esters to the corresponding ethers under free-radical conditions.[2] We recently demonstrated the applicability of the reagent to the reduction of more complex bicyclic lactones and also the existence of significant selectivity when additional ester groupings were present.[3] We now wish to report that under the appropriate conditions trichlorosilane can be an effective reagent for the reductive deoxygenation of esters of nonprimary aliphatic alcohols.



1 2 3

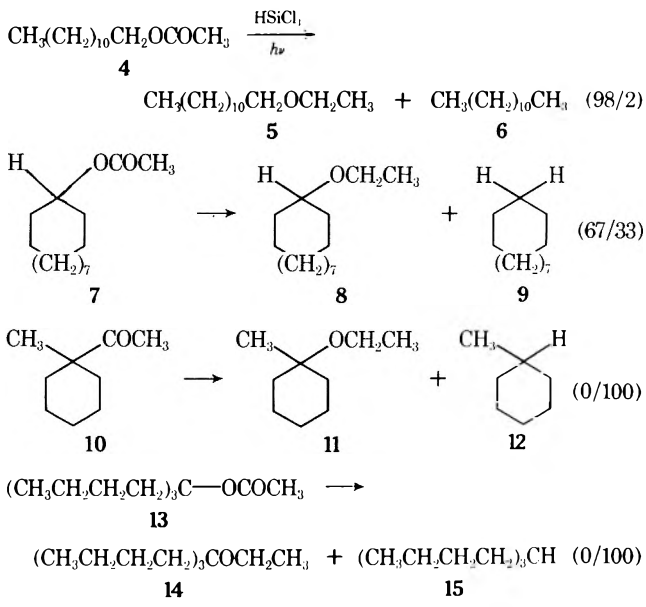
In general we find that for the reaction of a given ester **1** with trichlorosilane, two products, **2** and **3**, are formed competitively. Ether **2** is the result of a "normal" reaction with $HSiCl_3$ while **3** is the product of reductive deoxygenation. The relative amounts of **2** and **3** are most profoundly affected by the nature of R′. As shown in Scheme I for the acetates of several alcohols, irradiation with excess $HSiCl_3$ yields largely **2** for a primary acetate, exclusively **3** for a tertiary acetate, and a mixture of **2** and **3** for a secondary acetate.[4,5] These results are consistent with a reaction mechanism which involves radical **16** as a common intermediate for the formation of **2** and **3**, with the proportion of **16** which undergoes reductive deoxygenation being influenced by the stability of radical ·R′. Thus tertiary acetates give the highest proportion of reductive deoxygenation and primary acetates the lowest.

Table I
Reaction of 1-Adamantyl Esters with $HSiCl_3$

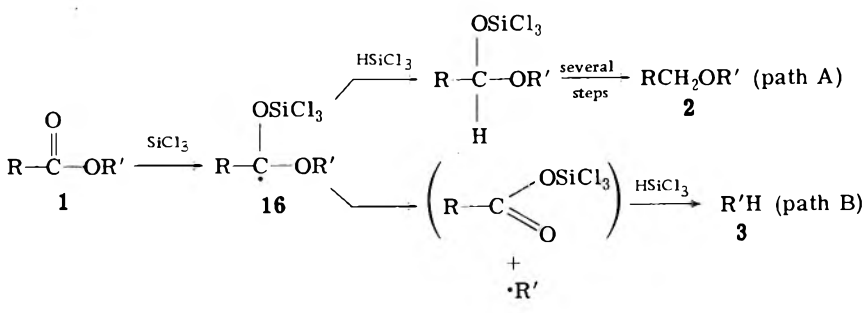
Ester	$HSiCl_3$/17[a]	THF/17[b]	% reaction	18/19[c]
17a[d]	8		100	42[f]/58[g]
17a	4		100	30/70
17a	4	24	100	18/82
17a	4	72	87	6/94
17a	2	72	58	2/98
17b[e]	8		100	12[h]/88
17b	4		100	3/97
17b	8	29	7	1/99

[a] Moles of $HSiCl_3$ per mole of ester. [b] Moles of THF per mole of ester. [c] Determined by GLC analysis. [d] Registry no., 19066-22-9. [e] Registry no., 56830-70-7. [f] Registry no., 6221-75-6. [g] Registry no., 281-23-2. [h] Registry no., 56830-71-8.

Scheme I



In an effort to determine if a judicious choice of reaction conditions would render the method preparatively useful in instances where ·R′ was of intermediate stability (i.e., secondary esters), several experiments were performed with esters of 1-adamantanol. The tertiary 1-adamantyl radical has been shown to be slightly more stable than a normal secondary radical,[6] and thus 1-adamantyl esters should provide a sensitive probe of the results of changes in reaction conditions. It was expected that one could most effectively maximize reductive deoxygenation by retarding the *bimolecular* second step of the ether-forming pathway (path A). For instance, a decrease in the $HSiCl_3$ concentration should retard path A to the benefit of path B. In addition, an increase in the steric bulk of the ester (pivalates vs. acetates) should have a similar effect. The results summarized in Table I are in general accord with these predictions. It is seen that either decreasing the amount of



$HSiCl_3$ or diluting the reaction medium with an inert solvent (THF) increases the proportion of reductive deoxygenation. A similar decrease is observed in going from 1-adamantyl acetate (**17a**) to 1-adamantyl pivalate (**17b**). At lower concentrations of $HSiCl_3$ the reaction does not go to completion, presumably because the radical chains become unproductively shortened.

$$\underset{\textbf{17a,b}}{\text{1-Ad-OCOCR}_2} \xrightarrow[h\nu]{HSiCl_3} \underset{\textbf{18a,b}}{\text{1-Ad-OCH}_2\text{CR}_3} + \underset{\textbf{19}}{\text{1-Ad-H}}$$

a, R = H

b, R = CH_3

It should be mentioned that the application of these trends to 1-dodecyl pivalate and cyclododecyl pivalate gives parallel results as compared to acetates **4** and **7**.[7]

In conclusion we have reported a new reaction of aliphatic esters with trichlorosilane, reductive deoxygenation. We have shown that the reaction is responsive to experimental changes in a predictable manner, and that it can be made to be preparatively useful for esters of secondary and tertiary alcohols. It should be pointed out that the high reactivity of $\cdot SiCl_3$ toward many functional groups[2] limits the generality of the method in some cases. We can see few examples where this reaction would be preparatively superior to other literature procedures for reductive deoxygenation,[8] except for the ease of preparation of the esters in question.

Experimental Section

The ir spectra were recorded on Perkin-Elmer 137 and 237 spectrophotometers. NMR spectra were determined on a Jeol MH-100 spectrometer and are reported in δ units downfield from Me_4Si. GLC analyses were performed on a Hewlett-Packard Model 700 laboratory gas chromatograph equipped with dual thermal conductivity detectors. A flow rate (He) of 55 ml/min through 6 ft × 0.25 in. columns (5% SE-30 on Chromosorb P) was employed. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich.

Preparation of Starting Materials. Dodecyl acetate (**4**),[9] cyclododecyl acetate (**7**),[10] 1-methylcyclohexyl acetate (**10**),[11] and 1-adamantyl acetate (**17a**)[12] were prepared by standard procedures.

5-*n*-Butyl-5-nonyl Acetate (13). A solution of 5.0 g (25 mmol) of 5-*n*-butyl-5-nonanol in 25 ml of anhydrous THF was added to a stirred suspension of 2.0 g (51 mmol) of KH (8.2 g of a 24.04% suspension) in 25 ml of dry THF under N_2. The mixture was stirred for 2 hr at room temperature and then cooled to 0°, whereupon 4.8 g (62 mmol) of acetyl chloride in 10 ml of dry THF was slowly added. The reaction mixture was stirred at 0° for 1 hr and at room temperature for 6 hr, and finally heated at reflux for 2 hr, whereupon it was poured into 500 ml of ice water and extracted with ether (3 × 100 ml). The combined organic extracts were washed with brine (2 × 50 ml), dried ($MgSO_4$), and concentrated. Two distillations gave 3.89 g (63%) of pure acetate, bp 67–76° (0.15 mm): ir (neat) 1749 cm^{-1} (C=O); NMR (CCl_4) δ 0.91 (t, J = 7 Hz, 9 H, $-CH_3$), 1.05–1.57 (broad, 12 H, $-CH_2-$), 1.57–1.88 (broad, 6 H, $-OCH_2-$), 1.91 (s, 3 H, $COCH_3$).

Anal. Calcd for $C_{15}H_{30}O_2$: C, 74.32; H, 12.47. Found: C, 74.49; H, 12.63.

1-Adamantyl Pivalate (17b). To a solution of 7.6 g (50 mmol) of 1-adamantanol in 75 ml of anhydrous THF under N_2 was slowly added 23 ml (55 mmol) of a 2.14 M hexane solution of *n*-butyllithium. After stirring the resulting suspension for 30 min at room temperature, a solution of 6.7 g (55 mmol) of pivaloyl chloride in 50 ml of anhydrous THF was added dropwise and the resulting red-orange mixture heated at reflux for 16 hr. To the cooled reaction mixture was added 100 ml of H_2O, the layers separated, and the aqueous phase extracted with ether (3 × 5 ml). The combined organic layers were washed with saturated $NaHCO_3$ (1 × 50 ml) and brine (1 × 50 ml), dried ($MgSO_4$), and concentrated. The crude product was chromatographed on silica gel, elution with benzene providing pure ester which was then distilled to give 7.3 g (62%) of viscous oil, bp 67–75° (0.05 mm). The oil solidified on standing: mp 25.5–27.0°; ir (neat) 1724 cm^{-1}; NMR (CCl_4) δ 1.10 [s, 9 H, $(CH_3)_3C-$], 1.61–1.79 (broad, 6 H, $-CH_2CO-$), 1.95–2.24 (broad, 9 H, $-CHCH_2-$).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.14; H, 10.21.

Reduction Products. Dodecane (**6**), cyclododecane (**9**), methylcyclohexane (**12**), 5-(*n*-butyl)nonane (**15**), and adamantane (**19**) were commercial samples. 1-Adamantyl ethyl ether (**18a**) was prepared according to the literature.[13] Dodecyl ethyl ether (**5**)[14] and cyclododecyl ethyl ether (**8**)[15] have been prepared previously but full characterization was not readily available in the literature. We have prepared them by standard (Williamson) methods and report pertinent physical data below.

Dodecyl Ethyl Ether (5): bp 97° (1.25 mm, Kugelrohr); NMR (CCl_4) δ 0.89 (t, J = 6 Hz, 3 H, $-CH_3$), 1.15 (t, J = 7.5 Hz, 3 H, $-CH_3$), 1.29 (broad s, 20 H, $-CH_2-$), 3.35 (q, J = 6 Hz, 2 H, $-CH_2O-$), 3.39 (q, J = 7.5 Hz, 2 H, $-OCH_2-$).

Anal. Calcd for $C_{14}H_{30}O$: C, 78.43; H, 14.10. Found: C, 78.15; H, 14.12.

Cyclodocecyl Ethyl Ether (8):[16] bp 95° (0.65 mm, Kugelrohr) [lit.[15] 117–119° (3 mm)]; NMR (CCl_4) δ 1.12 (t, J = 7 Hz, 3 H, $-CH_3$), 1.36 (broad s, 22 H, $-CH_2-$), 3.32 (m, unresolved, 1 H, CHO–), 3.36 (q, J = 7 Hz, 2 H, $-OCH_2-$).

Anal. Calcd for $C_{14}H_{28}O$: C, 79.18; H, 13.29. Found: C, 79.40; H, 13.48.

1-Adamantyl Neopentyl Ether (18b).[16] According to the general method of Pettit,[17] a solution of 0.375 g (0.01 mol) of $NaBH_4$ in 25 ml of anhydrous diglyme was placed in a three-neck 250-ml flask and cooled to 0° (ice bath) under a nitrogen atmosphere. To this was added over 20 min a solution of 1.19 g (0.005 mol) of 1-adamantyl pivalate and 21.25 g (0.15 mol) of freshly distilled boron trifluoride etherate in 50 ml of anhydrous THF. Stirring was continued for 1 hr at 0° and then an additional 1 hr at reflux whereupon the reaction mixture was cooled and quenched by the careful successive addition of 2 N HCl (25 ml) and water (50 ml). The layers were separated, the aqueous layer extracted with ether (3 × 50 ml), and the combined organic layers dried ($MgSO_4$) and concentrated. The residue (containing diglyme) was dissolved in 50 ml of petroleum ether and washed with water (3 × 25 ml), dried ($MgSO_4$), and again concentrated to give 0.843 g of crude product. GLC and NMR analysis showed the product to contain the desired ether, starting ester, and 1-adamantanol in the approximate ratio of 1:2:1. Chromatography (100 g of silica gel, benzene elution) afforded 0.212 g of ether (19%), homogeneous by GLC and TLC. The analytical sample was prepared by Kugelrohr distillation (85°, bath, 0.05 mmHg): NMR (CCl_4) δ 0.84 [s, 9 H, $-C(CH_3)_3$], 1.50–1.75 (broad, 12 H, $-CH_2-$), 2.00–2.50 (broad, 3 H, –CH–), 2.95 (s, 2 H, $-OCH_2-$).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.08; H, 11.94.

When this reaction was performed using $LiAlH_4$–boron trifluoride etherate,[17] the only observable product was 1-adamantanol plus a considerable amount of unreacted ester.

General Photolysis Procedure. The following experiment for the reaction of 1-adamantyl acetate with $HSiCl_3$ is typical. Other experiments were performed similarly with the molar ratios of $HSiCl_3$ and THF to starting ester being as indicated in Table I or ref 4.

A solution of 0.500 g (2.58 mmol) of 1-adamantyl acetate, 1.39 g (1.04 ml, 10.3 mmol) of $HSiCl_3$, 0.192 g (0.244 ml, 1.29 mmol) of di-*tert*-butyl peroxide, and 4.4 g (5.0 ml, 61.5 mmol) of anhydrous THF (doubly distilled from $LiAlH_4$) was placed in a Pyrex tube (ca. 14 mm i.d.) and degassed with three to eight freeze–pump–thaw cycles (0.01 mm). After sealing, the tube was irradiated for 5 hr at a distance of 12 mm from an Hanovia 450-W medium-pressure ultraviolet lamp. The resulting clear solution was diluted with 50 ml of CH_2Cl_2 and then the excess $HSiCl_3$ was destroyed by the careful addition (0°, stirring) of 10 ml of water and 2.5 ml of 10% NaOH solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 ml) and the combined organic layers washed with brine (50 ml) and dried ($MgSO_4$). Gas chromatographic (150°) analysis (standardized) of this dilute solution showed two peaks at 79 and 184 sec, respectively corresponding to adamantane (82%) and adamantyl ethyl ether (18%). Concentration of the organic material afforded 350 mg of crude product, which by NMR analysis was of the composition indicated above.

GLC data for the compounds from other experiments, which were conducted in a similar fashion, are as given: 1-dodecyl acetate (175°, 264 sec), 1-dodecyl ethyl ether (165 sec), dodecane (66 sec); cyclododecyl acetate (175°, 220 sec), cyclododecyl ethyl ether (171 sec), cyclododecane (97 sec); 1-methylcyclohexyl acetate (100°, 168

sec), 1-methylcyclohexane (74 sec); 5-butyl-5-nonyl acetate (150°, 209 sec), 5-butylnonane (88 sec); 1-adamantyl pivalate (180°, 261 sec), 1-adamantyl neopentyl ether (204 sec), adamantane (47 sec).

Registry No.—**4**, 112-66-3; **5**, 3482-63-1; **7**, 6221-92-7; **8**, 2986-53-0; **10**, 16737-30-7; **13**, 56830-72-9; **15**, 17312-63-9; trichlorosilane, 10025-78-2; 5-*n*-butyl-5-nonanol, 597-93-3; 1-adamantanol, 768-95-6; dodecane, 112-40-3; cyclododecane, 294-62-2; 1-methylcyclohexane, 108-87-2.

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Cuprous Chloride Catalyzed Dimerizations of β-Dicarbonyl Compounds via Their Dicarbanions

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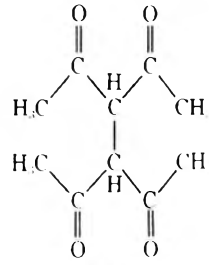
The use of dicarbanions from β-dicarbonyl compounds like β-diketones and β-keto esters in γ-alkylations and γ-acylations has become a common procedure.[1,2] The dicarbanions **2a–c** were investigated in an effort to dimerize them into bisacetylacetones (eq 1).

$$\underset{\mathbf{1}}{CH_3COCH_2COCH_3} \longrightarrow \underset{\mathbf{2a.\ M = M' = Na}\quad \mathbf{b.\ M = Na;\ M' = Li}\quad \mathbf{c.\ M = M' = Li}}{CH_3COCHMCOCH_2M'} \longrightarrow \begin{matrix} CH_3COCH_2COCH_2 \\ | \\ CH_3COCH_2COCH_2 \end{matrix} \quad (1)$$

Dimerization of 2,4-pentanedione (**1**) can lead to three possible compounds, **3**, **4**, and **5**.

The 3,3′ dimer or symmetrical tetraacetylethane **3** has been made by the self-condensation of the monoanion of 2,4-pentanedione in an ether solution of iodine.[3,4] The unsymmetrical 1,3′ dimer or 3-acetyloctane-2,5,7-trione, **4**, was obtained by Gritter and Patmore from copper acetylacetonate by a free-radical process.[5a,b] As for the 1,1′ dimer or decane-2,4,7,9-tetrone **5**, there is no record of such a compound in the chemical literature.



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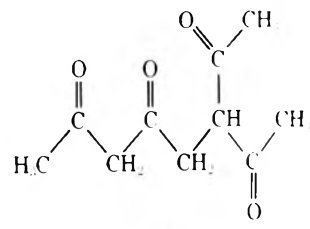

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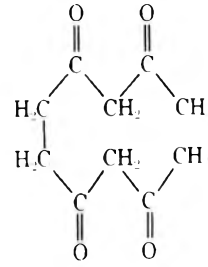
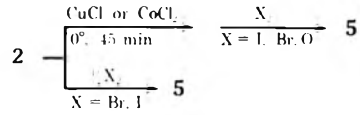


5

Table I provides a representative account of the attempts to obtain **5** by Scheme I. When cuprous chloride or

Scheme I



cobaltous chloride was used as a catalyst in the reaction between **2b** and iodine, the reaction proceeded very efficiently (entries 1–5). That the tan solid, mp 62–63°, obtained from the reactions has structure **5** is supported by several pieces of data. For example, this compound is enolic to $FeCl_3$ solution (brown-red color), and its ir and uv spectra are similar to those of **1**. The ^1H NMR spectrum of this solid has four proton centers, namely, at τ 8.02 (singlet) and 7.84 (singlet), $-C(=O)CH_3$ (6 H), 7.45 (singlet), $C(=O)CH_2CH_2C(=O)$ (4 H), 4.64 (singlet), $C(=O)CH=C(=O)$ (2 H), and a broad peak at −4.86 due to enolic protons (2 H). The mass spectrum (70 eV) of this material showed *m/e* 198 (M^+ ion). Elemental analysis is consistent with the formula $C_{10}H_{14}O_4$ (see Experimental Section).

Dilithioacetylacetone (**2c**, entry 6) did not undergo oxidative dimerization under the same conditions. Since **2c** was generated in liquid ammonia, which was then replaced by THF, traces of ammonia could have interfered rather than **2c** being inherently unreactive. The use of pyridine to solublize the cuprous chloride reduced the reaction period markedly, in addition to rendering the work-up procedure less tedious (entry 5).

The importance of the cuprous chloride or cobaltous chloride catalyst in these reactions as well as the conditions of the reactions is illustrated by entries 6–15. In these cases where the catalyst was not used, the conditions were changed, or other reagents that have been successful in coupling monoanions[3,4,6–9] were used with the dianions, no coupled product **5** could be isolated.

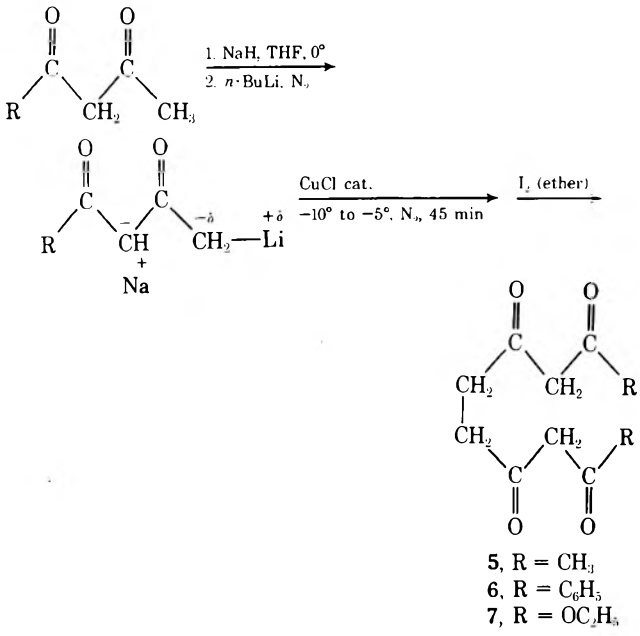
This procedure can be applied to other β-dicarbonyl compounds. As Scheme II illustrates, the method was successfully applied to the syntheses of 1,1′ dimers of benzo-

Table I
Results of the Dimerization Reactions of Acetylacetone via Dianions

No.	Dicarbanion	Conditions	X_2	Mole ratio of dianion:X_2[g]	Catalyst	% yield of 1,1 dimer
1	2b	THF, 0 → 25°, 24 hr, N_2	I_2	2:1	CuCl[a]	35–60
2	2b	THF, 0 → 25°, 24 hr, N_2	I_2	2:1	CuCl[c]	20–45
3	2b	THF, 0 → 25°, 6 hr, N_2	I_2	2:1	CoCl[d]	35
4	2b	THF, 0 → 25°, 22 hr, N_2	I_2	2:1	$CoCl_2$[e]	33
5	2b	THF, 0°, 2 hr, A	I_2	2:1	CuCl[f]	45
6	2a	NH_3, −33°, 1 hr	I_2	2:1		None
7	2a	NH_3, −33°, 1 hr	I_2	2:1	CuCl[a]	None
8	2c	THF, 0 → 25°, 24 hr, N_2	I_2	2:1	CuCl[a]	None
9	2b	THF, 0 → 24°, 24 hr, N_2	I_2	2:1		None
10	2b	THF, −63 → −30°, 0.5 hr, N_2	Br_2	2:1		None
11	2b	THF, 0 → 25°, 20 hr, N_2	Br_2	2:1	CuCl[a]	None
12	2b	THF, 0 → 25°, 24 hr, N_2		1:1[b]	$KMnO_4$	None
13	2b	THF, 0 → 25°, 24 hr, N_2		1:1[b]	$CuCl_2$	None
14	2b	THF, −110 → −50°, 1.5 hr, N_2	O_2	1:2[b]	CuCl	None
15	2b	THF, 0 → 25°, 12 hr, N_2; 63°, 2 hr, N_2			$CoCl_2$	None

[a] Catalytic amount of CuCl, 0.75 g. [b] Ratio of dianion to catalyst. [c] Stoichiometric amounts of CuCl (1:1 and 1:2). [d] Stoichiometric amount of $CoCl_2$ (4:1). [e] Catalytic amount of $CoCl_2$, 0.5 g (3.85 mmol). [f] 25 ml of pyridine added to dianion solution; catalytic amount of CuCl, 0.75 g. [g] All reactions were run on 0.05-molar scale except entry 9, which was run on 0.025-molar basis.

Scheme II



5, R = CH_3
6, R = C_6H_5
7, R = OC_2H_5

ylacetone and ethyl acetoacetate, namely **6** and **7**, in 75 and 50% yields, respectively. However, the sodiolithio dianion of phenylacetone, $PhC\bar{H}NaCOCH_2Li$, failed to undergo dimerization by this procedure.

Experimental Section

Infrared spectra were obtained with a Perkin-Elmer 257 grating infrared spectrophotometer using KBr pellets. The ^1H NMR spectra were obtained using a Varian Model A-60D spectrometer and samples dissolved in CCl_4 with Me_4Si as internal standard. The mass spectrum was recorded from a Bell & Howell instrument, Model 21-490.[11]

Melting points were determined using open capillary tubes in a Thomas-Hoover melting point apparatus. The melting points are uncorrected. Elemental analysis of the products was done by Galbraith Laboratories Inc., Knoxville, Tenn.

All the reactions involving organometallic compounds were run in three-necked round-bottom flasks equipped with serum-capped addition funnels in an atmosphere of dry nitrogen. Prior to the introduction of the reagents, the reaction vessel was thoroughly dried with a Bunsen burner flame while being purged with a stream of nitrogen. Tetrahydrofuran (THF) was refluxed over $LiAlH_4$ for 24 hr and distilled in a dry nitrogen atmosphere into vessels containing freshly drawn sodium ribbons. Commercially available anhydrous ether was stored over sodium ribbons. Cuprous chloride was freshly prepared and dried at 70° for 30 min. Anhydrous cobaltous chloride was kept in a vacuum oven at 150° for 24 hr and used immediately. *n*-Butyllithium (2.4 *M* in hexane) from Alfa Inorganics was used directly from the bottle.

Dimerization of 2b Using Cuprous Chloride as Catalyst and Iodine (Entry 1). A typical experimental procedure was as follows. A solution of 2,4-pentanedione (5.0 g, 0.05 mol) in dry THF (20 ml) was added dropwise to a stirred suspension of sodium hydride (1.2 g, 0.05 mol) in 30 ml of THF at 0° in a nitrogen atmosphere. The white sodium salt that was formed in 20 min was then treated with *n*-butyllithium in hexane (2.4 *M* solution) (29.0 ml, 0.05 mol). The *n*-butyllithium was added dropwise from a serum-capped addition funnel over 10–15 min. After the yellow solution had stirred for 15 min, the reaction flask was cooled to −10°. Freshly prepared dry cuprous chloride (0.75 g, 0.0076 mol) was added rapidly to the dianion solution and stirred for 45 min. A dark brown solution resulted. Prior to the addition of cuprous chloride about 30 ml of dry pyridine may be added to **2b** in order to increase the solubility of the inorganic salt (entry 5). A solution of iodine (6.35 g, 0.025 mol) in anhydrous ether (75 ml) was added over 10–15 min. The dark brown reaction mixture slowly acquired a pale yellowish-brown hue. The reaction mixture was stirred for 8–12 hr and allowed to warm to room temperature. It was cooled to 0°, poured into chopped ice (50 g), and acidified with cold concentrated hydrochloric acid to a pH of 2.0. The organic layer was separated and the aqueous phase was extracted with three 35-ml portions of ether in the presence of saturated ammonium chloride solution. The ethereal extract was washed with two 30-ml portions of 10% sodium thiosulfate solution, followed by washing with two 30-ml portions of saturated sodium chloride solution. Any insoluble material was removed by filtration through glass wool. The organic extract was dried over anhydrous Na_2SO_4.

The drying agent was removed by filtration and the filtrate on evaporation in a rotary evaporator at room temperature gave a yellowish-brown syrup (4.8 g). This was recrystallized from cyclohexane and methyl acetate to obtain 1.8–3.0 g (35–60%) of **5**, mp 60–62°, a pale yellow crystalline solid. An analytical sample was prepared by two recrystallizations from cyclohexane using Nuchar. The product was dried under vacuum at room temperature: mp 62–63°; ir (KBr) $\bar{\nu}_{max}$ 2960, 2900, 1670–1530 (broad), 1400, 1280, 1190, 1110, 1010, 905, 795, 760 cm^{-1}; uv λ_{max} (cylohexane) 227 nm (log ϵ 4.37).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.6; H, 7.07. Found: C, 60.36; H, 7.19.

The compound **5** was converted into its dipyrazole derivative, mp 198–200°.

Preparation of 1,6-Dibenzoyl-2,5-diketohexane (6). A solution of benzoylacetone (8.1 g, 0.05 mol) in THF (30 ml) was added dropwise to a stirred suspension of sodium hydride (1.2 g, 0.05 mol) and 75 ml of THF at 0° under a nitrogen atmosphere. A pale yellowish suspension of the monoanion was formed in 15 min.

About 28.0 ml of *n*-butyllithium (2.4 *M* solution in hexane) was then added dropwise over 15 min to form a dark green or greenish-blue solution, presumably the sodiolithio dianion of the β-diketone. The solution was then cooled to −5° and cuprous chloride (0.75 g, 0.0076 mol) was introduced rapidly into the flask. The mixture was stirred for 45 min as it turned dark brownish red. As described earlier, an iodine solution (6.35 g, 0.025 mol) in ether was added and the reaction mixture stirred for 8 hr at room temperature. The usual work-up procedure gave 7.2 g of an orange-yellow syrup which solidified into a yellow mass. This was recrystallized (ether and cyclohexane) to obtain 6.0 g (75%) of a pale yellow crystalline product, mp 83–85°. An analytical sample was obtained by recrystallization from ether at −63° as yellow needles: mp 89–90° [lit.[10] 92–95° (ethanol)]: ir (KBr) ν_{max} 3020, 1710–1620, 1400, 1290, 750 cm^{-1}; ^1H NMR (CCl_4) τ 7.21 [C(=O)CH_2CH_2C(=O), 4 H] [whereas for bezoylacetone -C(=O)CH_3 is seen as singlet at 7.92], 393 [s, -C(=O)CH=COH, 2 H], 2.67 (m) and 2.30 (m) (-C_6H_5, 10 H), and −5.5 (hump), enolic protons (2 H); uv λ_{max} (cyclohexane) 315, 248, and 216 nm (log ε 4.57, 3.6, and 4.32, respectively).

Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.60; H, 5.59. Found: C, 74.64; H, 5.77.

Preparation of Bis(ethyl acetoacetate) (7). The dianion of ethyl acetoacetate (0.05 mol) was generated by the procedure of Weiler et al. After cooling the yellowish-red solution to −5°, a cuprous chloride (0.75 g) was added and stirred for 45 min to obtain a dark solution. This organocopper reagent was then oxidized as before with iodine solution. The reaction mixture was stirred at 0° for 1–5 hr. The reaction mixture was poured onto chopped ice (30 g) and carefully neutralized with cold dilute 30% hydrochloric acid. The organic phase was separated and the aqueous layer was extracted with three 35-ml portions of ether. The ethereal solution was treated as before to obtain 6.8 g of a yellow-brown syrup.

This was triturated in petroleum ether (bp 35–60°) and ethyl acetate (10:1 v/v) and cooled to −63° (chloroform slush bath) as a white solid formed. The solid was suction filtered and air dried, 3.2 g (50%), mp 40–42°. An analytical sample was obtained by recrystallizations from petroleum ether and absolute ethanol at −63°: mp 47–48°; ir (KBr) ν_{max} 2990, 1750–1690 cm^{-1}; ^1H NMR (CCl_4) τ 8.8 (t, -OCH_2CH_3, 6 H), 7.20 [s, C(=O)CH_2CH_2C(=O), 4 H], 6.65 [s, C(=O)CH_2C(=O), 4 H], and 5.9 (q, -OCH_2CH_3, 4 H).

Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.82; H, 6.98. Found: C, 55.68; H, 7.10.

Generation of Dicarbanions 2a and 2c. The dianions were generated by the procedure of Hauser et al.[1b] from 5.0 g (0.05 mol) of 2,4-pentanedione and 2 molar equiv (0.1 mol) of MNH_2 (M = Na or Li).

Non-Copper-Catalyzed Reactions. The dianions were treated as indicated in Table I, entries 6–15. In each case a viscous oil which could not be crystallized to produce any 5 was obtained. Gas chromatography showed several components, including in several cases some 1.

Registry No.—**1**, 123-54-6; **2**, 56830-65-0; **3**, 56580-16-6; **4**, 56830-66-1; **5**, 56830-67-2; **6**, 56830-68-3; **7**, 56830-69-4; cuprous chloride, 7758-89-6; benzoylacetone, 93-91-4; ethyl acetoacetate, 141-97-9.

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(11) The authors thank Dr. James Pinson and Leonard Ingram for the mass spectrum.

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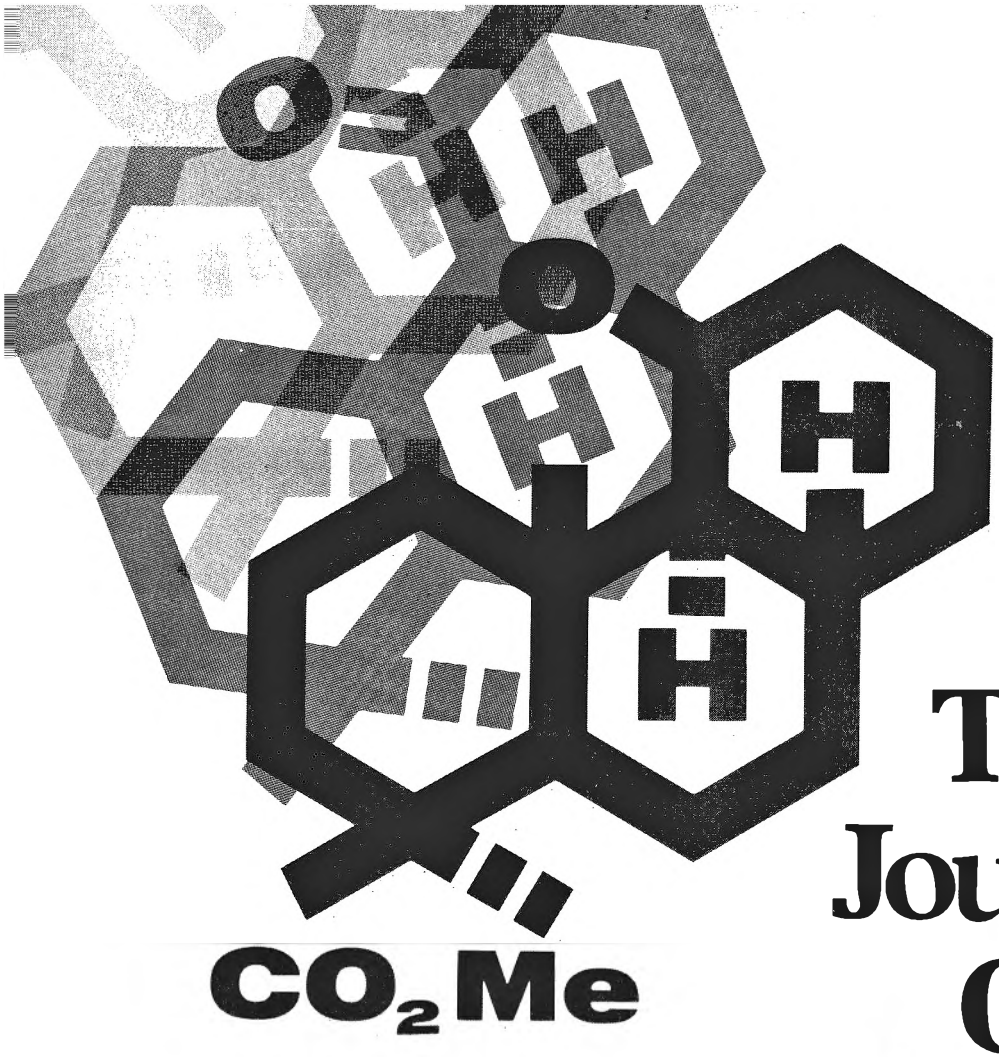

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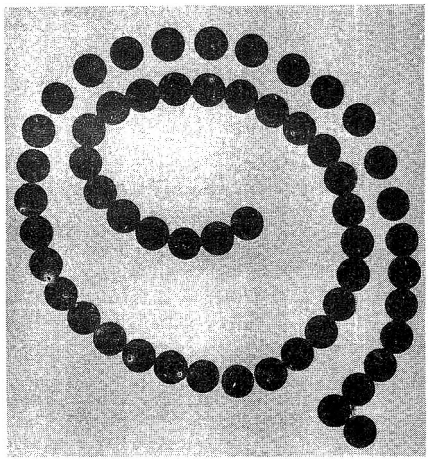

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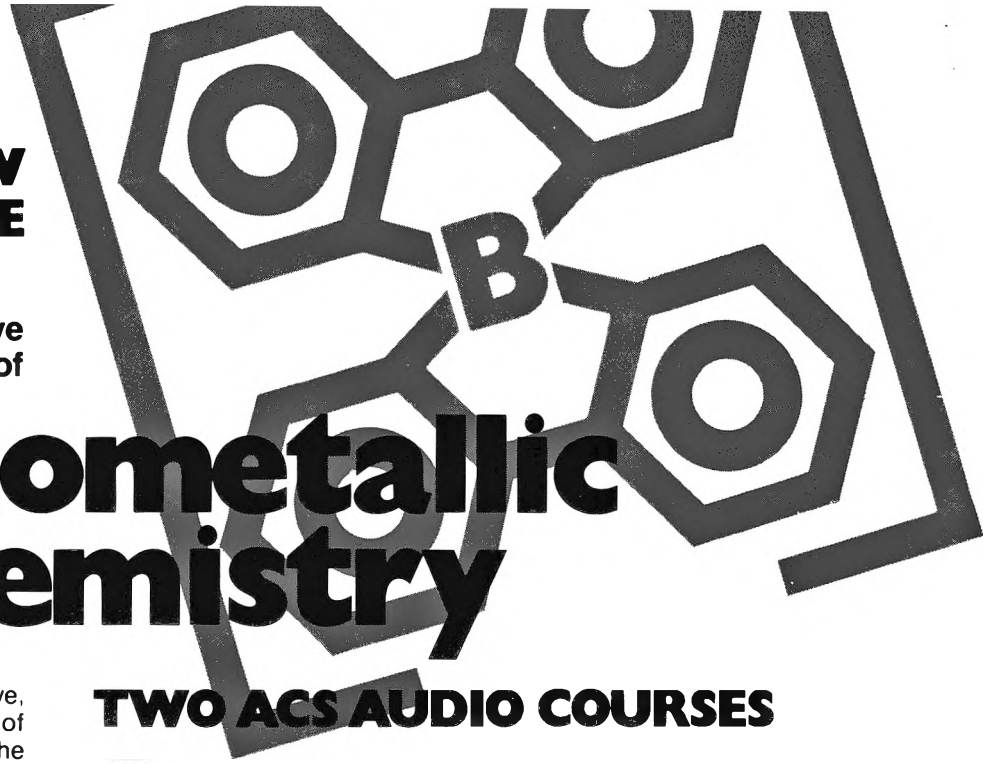

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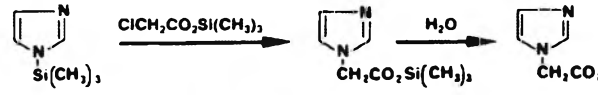
II. Synthetic Applications

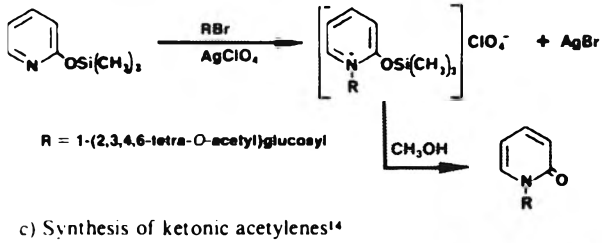
The importance of *tert*-butyldimethylsilyl ethers as hydroxyl protecting groups has been established by Corey and Venkateswarlu.[11] (See Aldrich ad on *tert*-butyldimethylsilyl chloride, *J. Org. Chem.*, October 31, 1975 issue.)

Other synthetic applications of silylated compounds are highlighted by the following examples. The trimethylsilyl derivatives described can be prepared by silylation with one of the following reagents: **BSA, BSTFA, TMCS (trimethylchlorosilane)** and **HMDS (hexamethyldisilazane).**

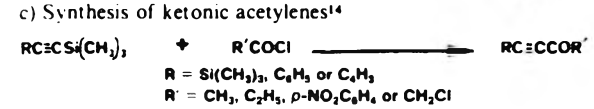
a) α-Halogenocarboxylic esters are inert towards free imidazole, but are very reactive towards silylated imidazole.[12]



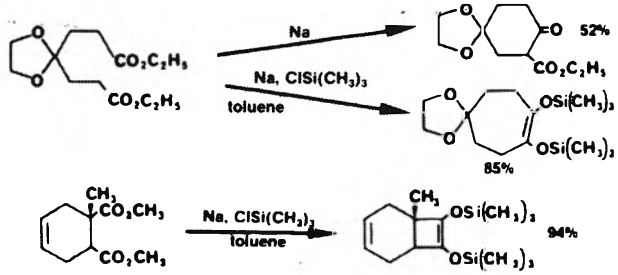
b) Acyl halogeno sugars react with O-silylated N-heterocycles to form N-glycosides.[13]



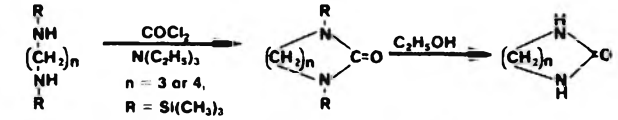
c) Synthesis of ketonic acetylenes[14]



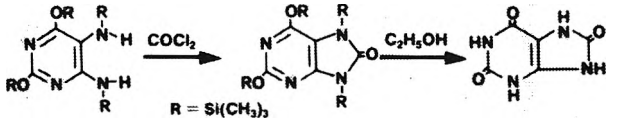
d) In acyloin condensations, the introduction of **TMCS** eliminates the Dieckmann and Claisen products, and the cyclization of 1,2-dicarboxylic esters gives good yields of the cyclobutane derivatives.[15]



e) Cyclic ureas cannot be prepared by cyclization of the free diamines with phosgene. However, silylated diamines undergo cyclization.[16]



Similarly, uric acid can be prepared from 2,6-bis-*O*-trimethylsilyl-4,5-bis(trimethylsilylamino)uracil.[16]



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