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VOLUME 42, NUMBER 25 DECEMBER 9, 1977

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DECEMBER 9, 1977

Role of Water in the Imidazole-Catalyzed Hydrolysis of *p*-Nitrotrifluoroacetanilide. A Study of Solvation in Acetonitrile–Water Mixtures[1]

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Solvation by water in the hydrolysis of *p*-nitrotrifluoroacetanilide has been studied through measurement of the rates of the imidazole-catalyzed hydrolysis as a function of water concentration in mixtures of acetonitrile and water. There is a complicated dependence on water with three apparently distinct regions of behavior: at $[H_2O] <$ [imidazole] = 1 M, linear dependence of rate constant on water concentration; at $[H_2O]$ from 1 to 10 M, linear dependence on $[H_2O]$ with a lower slope; and at $[H_2O] > 10$ M, approximately fourth order in water. These results are related to probable mechanisms.

A common observation in the crystallography of enzymes has been the low concentration of water at active sites, particularly after a model substrate is bound.[3] This appears to be an expected result of the evolution of enzymes because of the need for strong enzyme–substrate interactions which enable substrate to be held in an oriented, even strained, conformation. Water in the active site would interfere with oriented binding if it solvated those highly polar functionalities which make significant contributions to the total binding energy between enzyme and substrate.

Understanding of enzyme function has progressed far in recent years due to structural results from crystallography, enzymology, and mechanistic results from studies of the fundamental chemistry of the reaction which is catalyzed. Yet, there are still important gaps in our knowledge of enzyme function, partly due to incompleteness of the structural information[4] and partly due to our lack of understanding of the catalytic and inhibitory roles that water plays in the fundamental chemistry of the reaction. We expect that the enzyme must play the catalytic roles of water in the reaction and some of the catalytic power of enzymes may be due to exclusion of inhibitory effects of water. For example, a nucleophile might be expected to be more reactive when it is stripped of hydrogen bonds.

Therefore, it appears that an important area of fundamental chemistry, necessary for total understanding of enzyme function, is a knowledge of the role of water in reactions of biological importance. Because of the importance of enzymes which catalyze the cleavage of amide bonds, we have studied the imidazole-catalyzed hydrolysis of *p*-nitrotrifluoroacetanilide, p-$CF_3C(O)NHC_6H_4NO_2$ (pNTA) in acetonitrile–water at variable water concentrations. This amide, and closely related amides, have been previously studied in aqueous solution.[5-11] The results that we have found appear to be of interest both with regard to the roles of water in catalyzed hydrolysis of amides and with regard to the utility of this experimental method in studying the effects of water on chemical reactions.

Experimental Section

Materials. *p*-Nitrotrifluoroacetanilide (pNTA) was prepared from *p*-nitroaniline and trifluoroacetic anhydride,[12] and was recrystallized twice from ethanol–water, once from chloroform–hexane, and a final time from ethanol–water: mp 152.5–154 °C (lit.[12] 151.5–153 °C), IR 1745 cm^{-1} (C=O), UV (CH_3CN) 298 nm (ϵ 12 900), 219 nm (ϵ 10 700). **Imidazole** was recrystallized three times from benzene, mp 88.5–91.5 °C (lit.[13] 88–90). Perchloric acid (J. T. Baker "Analyzed") was determined by titration to be 70.74% $HClO_4$ (w/w). **Water** was distilled, boiled to remove CO_2, and stored under Ascarite. **1-Methylimidazole** was obtained from Aldrich Chemical Co. **Zinc perchlorate hexahydrate** was determined by EDTA titration to be 70.0% $Zn(ClO_4)_2$, i.e., $Zn(ClO_4)_2$-$6.3H_2O$. Acetonitrile was MCB "Spectroquality" grade which we analyzed by gas chromatography and showed to contain less than 10^{-3} M water and undetectable amounts of other impurities in chromatography on a Poropak column.[14]

Kinetic Method. Reactions were followed in acetonitrile–water mixtures on a Cary 16 spectrophotometer (thermostatted at 30.9 °C) by measuring the appearance of *p*-nitroaniline near 370 nm; the wavelength was adjusted to the λ_{max} which varies with the solvent. Buffers were prepared using imidazole and $HClO_4$. Solutions were prepared with all components except pNTA in a 10-mL volumetric flask, equilibrated in the constant-temperature bath, pNTA was added, and the solution was brought to the mark with additional solvent to give 10^{-4} M pNTA. We decided not to do these reactions at constant ionic strength because of the complications resulting from solvation of an additional solute.

Treatment of Data. For reactions with $t_{1/2}$ less than ca. 2 h, the experimental infinity point obtained after ca. 10 half-lives was used for the calculation of the rate constant by the least-squares method. However, pNTA reacts so slowly under many of our conditions that it was inaccurate to use the experimental infinity point. The rate

Table I. Dependence of the Rate Constant on Imidazole Concentration at a Constant Imidazolium Ion Concentration of 0.1 M at Different Water Concentrations

[Imidazole], M	[Imidazole]/[Imidazolium]	$10^6 k_{obsd}$, s^{-1}		
		$[H_2O]$ = 0.7 M	5.0 M	45 M
0.01	1:10	~0	0.13	5.7
0.033	1:3	0.1	0.47	13
0.10	1:1	0.32	1.4	51
0.30	3:1	1.1	4.5	200
1.00	10:1	4.4	16.0	520

Table II. Dependence of the Rate Constant on the Imidazolium Ion Concentration at a Constant Imidazole Concentration of 0.1 M at Different Water Concentrations

[Imidazolium], M	[Imidazolium]/[Imidazole]	$10^6 k_{obsd}$, s^{-1}		
		$[H_2O]$ = 0.7 M	5.0 M	45 M
0.01	1:10	0.20	1.1	94
0.033	1:3	0.28	1.2	59
0.10	1:1	0.32	1.4	51
0.30	3:1	0.28	1.6	51
1.00	10:1		1.8	41

constants for slower reactions were calculated using the theoretical infinity point which was measured using *p*-nitroaniline (recrystallized from ethanol–water) in the reaction mixtures and with the other product, trifluoroacetic acid. Duplicate determinations of the rate constant were made for two of our slowest reactions; for $k_{obsd} = 5.83 \times 10^{-7}$ s^{-1} and $k_{obsd} = 2.27 \times 10^{-6}$ s^{-1} the rate constants agreed within 9 and 6%, respectively.

Results

Product Identity. In the cases in which an infinity solution could be obtained, the UV spectrum of the solution is the same as that measured with *p*-nitroaniline, trifluoroacetic acid, and the reagents. The alternative product to trifluoroacetate, *N*-trifluoroacetylimidazole, is much more reactive than pNTA; *N*-trifluoroacetylimidazole hydrolyzed "instantaneously" at room temperature,[15] while pNTA hydrolyzed under similar conditions with a half-life of greater than 20 min.[11] While these observations do not preclude the acylimidazole as a reactive intermediate, previous results on this reaction[5-11] indicate water as the nucleophile in attack at the acyl carbon of pNTA. Our results (vide infra) demonstrate that at low water concentrations the reaction of pNTA requires one water molecule and, at $[H_2O]$ extrapolated to zero, the rate is indistinguishable from zero; this is strong evidence that water is the nucleophile especially since the rate of reaction of *p*-nitrophenyl acetate in similar media does not depend greatly on $[H_2O]$ at very low water concentrations and infrared spectra have demonstrated formation of an acyl imidazole.[14] Therefore, in the studies reported in this paper, we believe it is reasonable to conclude that water is the nucleophile and hydrolysis is the reaction.

Dependence of the Rate Constant on the Concentrations of Imidazole, Imidazolium Ion, and Hydroxide Ion. The dependence of the rate constant for the hydrolysis of pNTA on the concentration of imidazole at constant imidazolium concentration and its dependence on the concentration of imidazolium ion at constant imidazole concentration has been determined at 0.7, 5.0, and 45 M water (Tables I and II). The results indicate that the rate constant is dependent on the concentration of imidazole but essentially independent of the concentration of imidazolium ion in all three solvent systems, although there do appear to be salt effects (Table II). Figure 1 presents the results of the study of the dependence of the rate constant for hydrolysis of pNTA over a wide range of concentration of 10:1 imidazole/imidazolium ion in four solvent systems; in the light of Table II (no dependence on concentration of imidazolium ion), these results reflect the dependence on imidazole concentration. In 45 M water the rate constant increases linearly with the increase in imidazole concentration in agreement with the report[11] of the first-order imidazole dependence of the rate constant in water. However, in the four solvent systems displayed in Figure 1 the rate constants show a second-order component (eq 1). The scatter at low [imidazole] (Figure 1) is probably due to experimental error which is large because of the very slow rates (Table I).

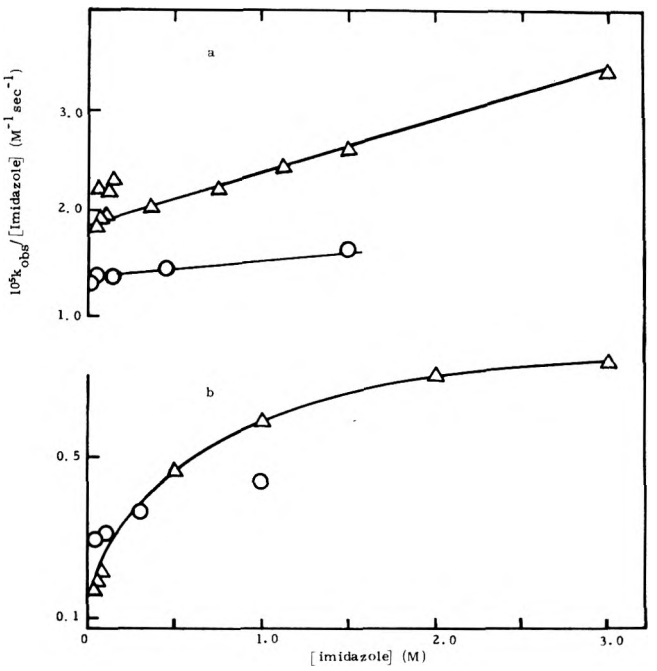


Figure 1. Plots of k_{obsd}/[Imidazole] vs. [Imidazole]: (a) 5 M water (○), 10 M water (△); (b) 0.7 M water (○), 1 M water (△).

$$k_{obsd} = k_1[\text{imidazole}] + k_2[\text{imidazole}]^2 \quad (1)$$

As shown by the linearity of the graphs (Figure 1a) of k_{obsd}/[Im] vs. [Im] in 5 M water, $k_1 = 1.4 \times 10^{-5}$ M^{-1} s^{-1} and $k_2 = 2.3 \times 10^{-6}$ M^{-2} s^{-1}. In 10 M water, $k_1 = 1.9 \times 10^{-5}$ M^{-1} s^{-1} and $k_2 = 7.7 \times 10^{-6}$ M^{-2} s^{-1}. However, the results in 0.7 and 1 M water (Figure 1b) show curvature (Figure 1); this is due to the fact that Figure 1b includes data both for water in excess of imidazole and for imidazole in excess of water as explained in the Discussion. In 45 M water, $k_1 = 5.3 \times 10^{-4}$ M^{-1} s^{-1}. All the results extrapolate to within experimental error of $k_{obsd} = 0$ at zero concentration of imidazole, indicating little or no contribution to the rate from hydroxide in these buffered systems. These results also indicate that at 1 M imidazole, the concentration used in most of our studies, the reaction is primarily first order in imidazole.

Dependence of the Rate Constant on the Concentration of Water. The dependence of the rate constant for the hydrolysis of pNTA in CH_3CN–H_2O on the concentration of water has been studied in three systems (Table III): 1.0 M imidazole/0.1 M imidazolium; 2.0 M imidazole/0.2 M imidazolium; and 1.0 M *N*-methylimidazole/0.17 *N*-methylimidazolium. The apparent pH of the 1.0 M imidazole/0.1 M imidazolium system varied by 0.6 pH unit over the solvent range we used, indicating considerable variation in pK_a with solvent.[16] Since the hydroxide-catalyzed rate is $\ll k_1$[imidazole], we consider this pH variation to be insignificant in our rate

Table III. Dependence of the Rate Constant on Water Concentration in Different Buffer Systems

	$10^6 k_{obsd}$, s^{-1}		
$[H_2O]$, M	[Imidazole] = 1.0 M [Imidazolium] = 0.1 M	2.0 M [Imidazole] = 0.2 M	[*N*-Methylimidazole] = 1.0 M [*N*-Methylimidazolium] = 0.17 M
0.12	1.0[a]		
0.23	1.8		
0.50	3.5	7.5	1.6
0.70	4.4		
0.75	4.5	10.5	
1.00	5.9	13.9	2.9
1.25	6.7	16.4	3.5
1.50	7.6	19.0	4.1
2.00		22.8	
2.50	10.4		6.8
3.00		29.0	
5.00	16.0	39.7	9.8
7.50	20.7		13.0
10.0	26.2	68.0	16.7
20.0	53.5		24.2
30.0	117		88.3
36.0	210		
40.0	294		237
42.0	357		
45.0	520		
48.0	750		
50.0			588

[a] From extrapolation of values determined at 0.5 M imidazole–0.05 M imidazolium and 0.1 M imidazole–0.01 M imidazolium.

studies. The rate constants in Table III are not corrected for ionization of pNTA to its unreactive anion.[11] We observe no UV absorbance due to the anion at or below 10 M water. Above 10 M water, spectral evidence was obtained for the anion of pNTA; consequently, in analyzing the data we corrected the rate constants (see below).

The dependence of the rate constant on water concentration in the 1.0 M imidazole/0.1 M imidazolium system is plotted in Figure 2. The plot appears separable into three regions: low, medium, and high water concentrations. We use eq 2–4 as a basis for interpretation of the results.

$$k_{obsd} = k_0 + k_1[H_2O] \quad (2)$$

For $[H_2O]$ = 0 to 1 M; k_0 = extrapolated intercept at $[H_2O]$ = 0; k_1 determined by dependence of k_{obsd} on $[H_2O]$ at $[H_2O]$ <1.1 M.

$$k_{obsd} = k_{1.1} + k_2[H_2O] \quad (3)$$

For $[H_2O]$ = 1 to 10 M; $k_{1.1}$ = intersection at 1.1 M H_2O of lines determining k_1 and k_2; k_2 determined by dependence of k_{obsd} on $[H_2O]$ at 1.1 M < $[H_2O]$ < 10 M.

$$k_{obsd} = k_{10} + k_3[H_2O]^n \quad (4)$$

For $[H_2O]$ = 10 to 55 M; k_{10} = intersection at 10 M H_2O of lines determining k_2 and k_3; k_3 and n determined by dependence of k_{obsd} on $[H_2O]$ at $[H_2O]$ > 10 M.

In the medium water concentration, ca. 2.5 to 10 M, the rate constant is linearly dependent on the water concentration (slope = $k_2 = 2.1 \times 10^{-6}$ M^{-1} s^{-1}), indicating that the reaction is first order in water in this region. In the low water region the rate constants at and below 0.5 M water show an initial linear dependence on water concentration (slope = $k_1 = 6.45 \times 10^{-6}$ M^{-1} s^{-1}; intercept = $k_0 = 2.8 \times 10^{-7}$ s^{-1}). The intercept, k_0, appears to be within experimental error of zero if one includes the possibility of water as an impurity in the acetonitrile or

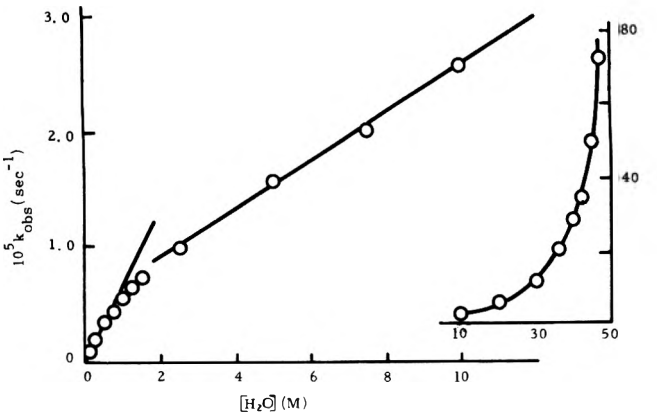


Figure 2. Plot of the rate constant vs. water concentration for 1.0 M imidazole/0.1 M imidazolium ion.

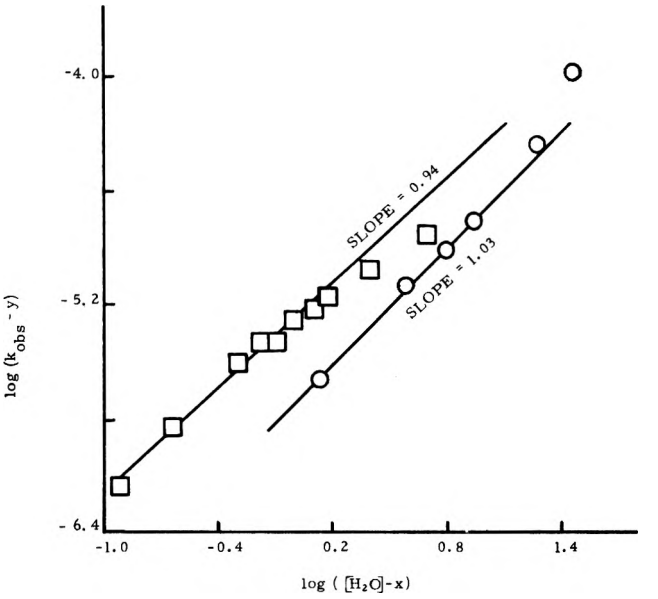


Figure 3. Plot of the log of the effective rate constant (1.0 M imidazole/0.1 M imidazolium) vs. the log of the effective water concentration for the low (□) and medium (○) water regions, (□) $x = 0$, $y = 0.3 \times 10^{-6}$ s^{-1}, (○) $x = 1$ M, $y = 7.7 \times 10^{-6}$ s^{-1}.

imidazole reagents. The two straight lines for low and medium $[H_2O]$ intersect at 1.1 M water and $k_{1.1} = 7.7 \times 10^{-6}$ s^{-1} (eq 3 and Figure 2).

We were concerned about more than one rate term making contributions in each of these regions of water concentration; that is, one might expect that $k_{obsd} = \Sigma k_i[H_2O]^{n_i}$. Therefore, we utilized a graphic determination of n_i for each region from the slope of the plot of log (k_{obsd} − other terms) vs. log $[H_2O]$ in that region. The upper line (□) of Figure 3 is such a plot for the low water region of Figure 2. The six points from 0.12 to 1.0 M describe a straight line with a nearly unit slope after subtraction of the intercept (using eq 2) from k_{obsd}, implying that the reaction is first order in water in that region. The lower line (○) of Figure 3 is a similar plot for the medium water region after the values for water concentration (1.1 M) and rate constant ($k_{1.1} = 7.7 \times 10^{-6}$ s^{-1}) at the intersection of the two lines in Figure 2 are subtracted from each point (eq 3). As expected from the linearity of the medium water region in Figure 2, the four points from 2.5 to 10 M water describe a straight line with unit slope, confirming the first-order dependence of the rate constant on water concentration in the medium water region.

The dependence of the rate constant on water concentration in the 2.0 M imidazole/0.2 M imidazolium system is plotted

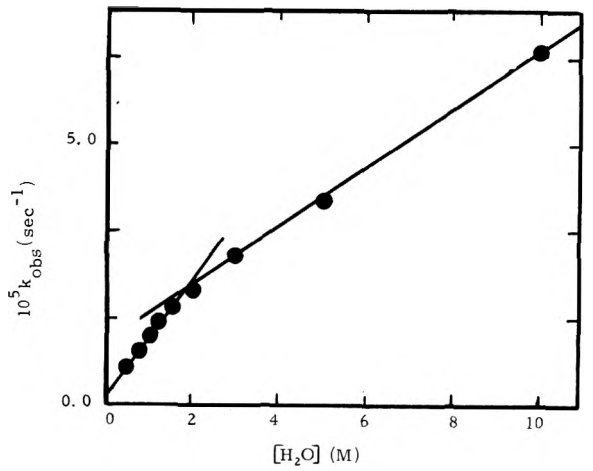


Figure 4. Plot of the rate constant for the 2.0 M imidazole/0.2 M imidazolium catalyzed hydrolysis of *p*-nitrotrifluoroacetanilide vs. water concentration.

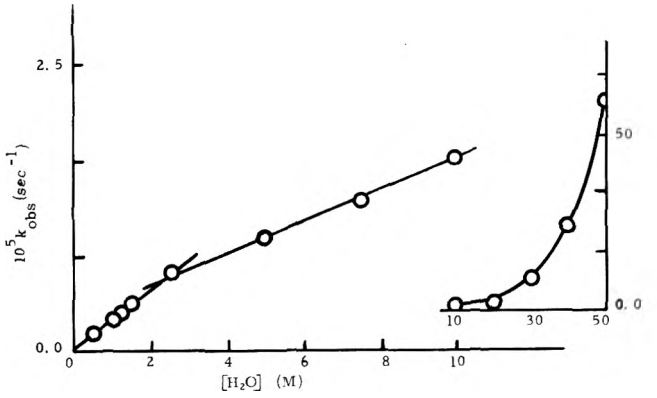


Figure 5. Plot of the rate constant for the 1.0 M *N*-methylimidazole/0.17 M *N*-methylimidazolium catalyzed hydrolysis of *p*-nitrotrifluoroacetanilide vs. water concentration.

in Figure 4. Just as in the 1.0 M imidazole/0.1 M imidazolium system (Figure 2), the plot shows two water dependence regions in the range studied. In the medium water region the three rate constants from 3.0 to 10.0 M water show a linear dependence on the water concentration ($k_2 = 5.6 \times 10^{-6}$ M^{-1} s^{-1}). In the low water region, the five rate constants at [H$_2$O] < 2 M show a linear dependence on water concentration ($k_1 = 11.6 \times 10^{-6}$ M^{-1} s^{-1}; intercept = $k_o = 1.9 \times 10^{-6}$ s^{-1}). The two lines intersect at 1.7 M water and $k = 21.5 \times 10^{-6}$ s^{-1}. The linearity of the dependence of the rate constant on water concentration in both the low and medium water regions of Figure 4 implies that the reaction is first order in water in both regions. This is confirmed by analysis of the data using graphs similar to Figure 3. In the low water region the five points from 0.5 to 1.5 M water describe a straight line with a slope of 1.01 after subtraction of the intercept from k_{obsd}. In the medium water region, after subtraction of the values for water concentration and rate constant at the intersection of the two lines in Figure 4 from each point, the three points from 3.0 to 10.0 M water describe a straight line with a slope of 1.00.

The dependence of the rate constant on water concentration in the 1.0 M *N*-methylimidazole/0.17 M *N*-methylimidazolium system is plotted in Figure 5. Just as in the 1.0 M imidazole/0.1 M imidazolium system (Figures 2 and 3), the plot shows three water dependence regions. In the medium water region the four rate constants from 2.5 to 10.0 M water show a linear dependence on water concentration ($k_2 = 1.3 \times 10^{-6}$ M^{-1} s^{-1}). In the low water region the four rate constants at and below 1.5 M show a linear dependence on water concentration ($k_1 = 2.5 \times 10^{-6}$ M^{-1} s^{-1}; intercept = $k_o = 3.2 \times 10^{-7}$ s^{-1}). The two lines intersect at 2.5 M water and $k = 6.7 \times 10^{-6}$ s^{-1}. The linearity of the dependence of the rate constant on water concentration in both the low and medium water regions of Figure 5 implies that the reaction is first order in water in both regions. This is confirmed by log-log analysis of the data. In the low water region the four points from 0.5 to 2.5 M water describe a straight line with a slope of 1.01 after subtraction of the intercept from k_{obsd}. In the medium water region, after subtraction of the values for water concentration and rate constant at the intersection of the two straight lines in Figure 5 from each point, the three points from 5.0 to 10.0 M water describe a straight line with a slope of 1.05.

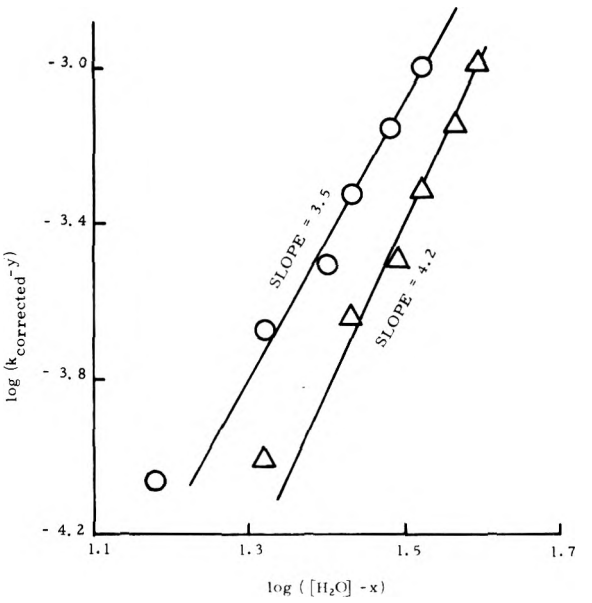


Figure 6. Plot of the rate constant (corrected for anion concentration) for the 1.0 M imidazole/0.1 M imidazolium catalyzed hydrolysis of *p*-nitrotrifluoroacetanilide vs. the log of the effective water concentration for the region of high [H$_2$O], (Δ) $x = 9$ M, $y = 2.4 \times 10^{-5}$ s^{-1}, (○) $x = 15$ M, $y = 3.65 \times 10^{-5}$ s^{-1}.

Using the values of k_1, k_2, and k_{10} (eq 2 and 3) for 1.0 M imidazole, we have determined the order of the reaction in water at high water concentration by the method of plotting log ($k_{obsd} - k_{10}$) vs. log [H$_2$O] (eq 4). However, a correction of k_{obsd} was required because, at concentrations of water greater than 10 M, we observed initial absorption in the electronic absorption spectra of our kinetic solutions due to the unreactive anionic form of *p*-nitrotrifluoroacetanilide. Since the anion is unreactive, we have corrected observed rate constants using eq 5, where the correction factor is calculated from the extinction coefficient of anion in pure water, the anion absorbance, and the ratio of the extinction coefficient of *p*-nitroaniline in water and the solvent. This resulted in correction factors as follows: 1.5 for the range 50 to 42 M water, 1.25 for 36 and 40 M water, 1.1 for 30 M water, and 1.02 for 20 M water. Equation 5 was applied in order to get corrected rate constants, which were used in the treatment based on eq 4 (see Figure 6).

$$k_{corr} = k_{obsd} \times \text{correction factor} \quad (5)$$

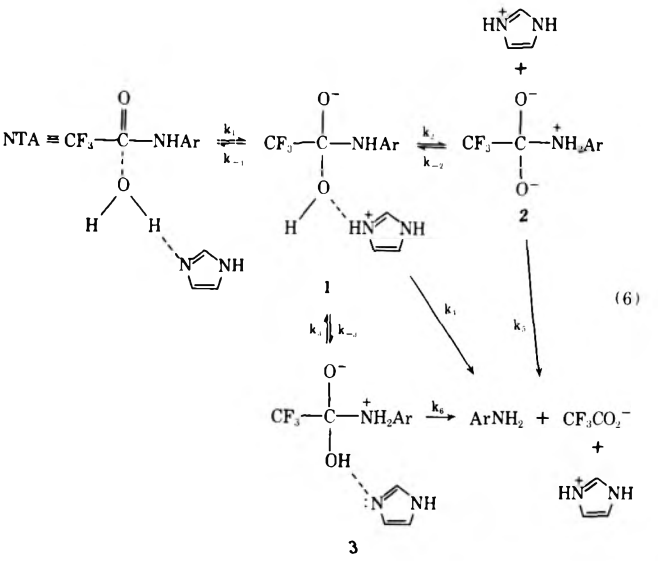
Although there is a problem in determining at what point the medium water region ends and the high water region begins and thus what values for the water concentration and rate constant should be subtracted from each point in order to apply eq 4 to the data, Figure 6 indicates, by subtracting rate constant and water concentration values which seem to be high and low limits for the transition points, that in the high water region the imidazole-catalyzed reaction is fourth order in water. This does not mean that lower and higher order

water terms are nonexistent; at the lower ends of the lines in Figure 6, the deviations of the lowest points indicate contributions from terms lower than fourth order in water. However, the excellent fit of the other points indicates that the predominant contribution to the rate is fourth order in the high region of water concentration. We find similar results when we analyze the *N*-methylimidazole data in the same way. Using the rate constants in Table III, the data from 30 to 48 M yield $k_3 = 3.3 \times 10^{-10}$ M^{-4} s^{-1} for the reaction carried out at 1 M imidazole and 0.1 M imidazolium ion.

Discussion

General Comments. It appears that the results are well enough defined to attempt empirical correlations leading to understanding the catalytic and inhibitory roles of water in this reaction, the hydrolysis of an amide—therefore, a reaction of biological importance. However, we emphasize at the beginning of the discussion that, although these results are encouraging, this research is only a beginning on the very difficult problem of elucidating the effects of water on a molecule along a reaction coordinate. One concern with such studies of solvation is that the activity of each component of the system should be known at each solvent composition in order to rigorously analyze observations. However, we believe that this is not necessary for progress on the problem of solvation because: (1) There has been great progress made in an empirical understanding of acid-catalyzed reactions in strongly acidic solutions.[17] This progress has been made largely on an empirical basis in media which change much more drastically than the mixed solvents we have employed. (2) Our cosolvent with water, acetonitrile, has major advantages: (a) It has a high dielectric constant and the dipole moment, $\mu = 4.0$, is even larger than that of water, $\mu = 1.9$, so association, ion pairing, aggregation and nonspecific solvent effects should be minimal. (b) Specific hydrogen-bonding and proton-transfer effects in these media should be entirely due to the water, not the acetonitrile, because acetonitrile has no protons which can compete in proton donation with water protons and acetonitrile appears to be 10^8 less basic than water (pK_a for $CH_3CNH^+ = -10$).[18] Nevertheless, the hypotheses in this discussion must be regarded as tentative until more research is done.

We need to consider our results in terms of mechanism for three regions of water concentration which differ considerably; the low, medium, and high water regions may be characterized approximately by powers of ten differences in water concentration: 0.5, 5, and 50 M. Of particular concern is the question of the location of the transition state along the reaction coordinate in each region, since our solvation numbers indicate the extent of solvation of *transition state over ground state*. The scheme shown in eq 6 will serve as the basis for our discussion. The dependence on water and imidazole (see Results) indicates that both molecules play essential roles. Water as a nucleophile is indicated by the negligible rate at $[H_2O] = 0$ as distinct from the imidazole-catalyzed reaction of *p*-nitrophenyl acetate which has been shown to proceed through an acylimidazole and gives a significant rate at $[H_2O] = 0$. The role of imidazole is demonstrated in Table I and Figure 1a,b. The complicated dependence of k_{obsd} on [imidazole] in Figure 1b is expected from the results (Table III and Figures 2, 4, and 5) which demonstrate the importance of the imidazole/water ratio; one water molecule is essential for reaction and there is a decreased dependence on $[H_2O]$ as the imidazole/water ratio changes from greater than one to less than one (Figure 2). In Figure 1a the imidazole/water ratio is always considerably greater than one and the water concentrations are in the well-behaved, medium range of water concentration, but in Figure 1b there are data for $[H_2O]$ both greater than and less than [imidazole], so the curved dependence is not surprising.



Both Figure 1a and 1b indicate some contribution to the rate by a term second order in imidazole. Although this is a minor contribution to the total rate, this indicates to us that the rate-determining step is not addition to the carbonyl group using the analogy to reactions of aryl esters.[19] In addition, previous research on the hydrolysis of amides leads one to expect rate-determining cleavage of the C–N bond.[20] The fourth order dependence on water appears to be additional evidence for this rate-determining step. Therefore, we suggest the following analysis of the roles of water in this reaction.

(1) The Low $[H_2O]$ Region, 0.1–1 M. The strong, first-order dependence on $[H_2O]$ certainly appears to the water molecule that is the nucleophile. Although k_4, k_5, and k_6 could contribute to the formation of product, the need for a good leaving group makes k_5 and k_6 most likely, especially in low water concentrations where the activity of an amide anion would increase dramatically. Because the reaction is predominantly first order in imidazole, either k_1 is rate determining in the k_6 pathway or k_6 must involve imidazole as a base, abstracting the OH proton in the transition state. Because there is a significant second-order contribution from imidazole, we suggest that the second imidazole may act as a base to remove the O–H proton as the imidazolium ion formed in k_1 donates a proton to N. However, other hypotheses are possible, such as two imidazoles hydrogen bonded to one nucleophilic water with k_1 rate determining.

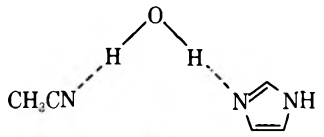
(2) The Medium $[H_2O]$ Region, 1–10 M. We suggest that the second water molecule (the first being the nucleophile) is involved in the proton transfer required for 1 → products. Grunwald and co-workers[21] have found that one water molecule is needed for proton transfer similar to that required for 1 → 2. Even in the region of $[H_2O]$ = 1 to 10 M, it should be difficult to eliminate amide anion from 1; however, cleavage of 2 to give *p*-nitroaniline should be a facile process particularly since it also generates the resonance-stabilized $CF_3CO_2^-$ ion with increased C–O bond strengths. The charged form of the reactive intermediate, 2, is not unprecedented.[5,22] Therefore, proton transfer is critical and would appear to be the most critical function for a water molecule involved in solvation.

It is possible that the increased rate of reaction in the region of $[H_2O]$ = 1 to 10 M is a bulk solvent effect, but the well-behaved first-order behavior in this region (Figures 2, 3), rather than some curved dependence, leads us to believe that there is a specific, proton-transfer role for a water molecule which leads to this preferred pathway in this region of $[H_2O]$

concentration. We will comment on the availability of water molecules below.

(3) The High H_2O Region: Our results demonstrate that the reaction is predominantly fourth order in water (Figure 6) in addition to the two water molecules implicated by the first-order dependence on water in the low and medium ranges of $[H_2O]$. Since Figure 6 is based on solvation changes beyond 10 M water, it appears that the latter two water molecules are already in the ground state in the high water region. Since one water is the nucleophile, this leads to a total solvation number of 5. The solvation results indicate a highly solvated transition state which we suggest closely resembles the highly reactive intermediate **2**, which decomposes rapidly to products (k_5 very fast).[5] Therefore, we suggest that solvation of **2** is a suitable model for solvation of the transition state when water is readily available and that the high degree of hydration when water is readily available appears to be associated with hydrogen bonding to the O^- atoms of **2**.

In summary, we suggest that the structure of the transition state is always near **2** but may vary in structure, solvation, and energy depending on the availability of water. It is noteworthy that three regions of water composition found experimentally to have differing solvation for the reaction are also distinguishable in the relationship of $[H_2O]$ to concentrations of other components: (1) In the low water region, $[H_2O]$ < [imidazole] so that as $[H_2O]$ increases the concentration of **5** increases. The intersection of the k_1 and k_2 lines in Figure 2 is within experimental error of the water concentration required to solvate all imidazole as in **5** and to solvate each imidazolium ion with two water molecules as proton acceptors in hydrogen bonds. (2) The medium $[H_2O]$ region, 1–10 M water, is the region in which all the water should be predominantly present as **5** or **6**. (3) In the high $[H_2O]$ region, there will be free OH groups and hydrogen bonds between water molecules.



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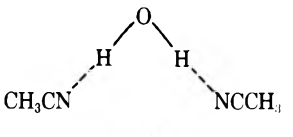

6

The above discussion demonstrates ways that solvation studies such as the one reported here will be useful in our understanding of solvation, structures of transition states, and solvent structure. As our studies of hydration in acyl transfer reactions proceed, we expect to be able to draw general conclusions which will substantiate these suggestions or will enable us to modify them and which will enable us to draw firm conclusions about the need for functional groups on enzymes to replace critical water molecules in order to lower activation barriers.

Acknowledgment. We thank Gail Saxton for useful discussions and assistance.

Registry No.—pNTA, 404-27-3; acetonitrile, 75-05-8; imidazole, 288-32-4; water, 7732-18-5.

References and Notes

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On the Photochemistry of 1-Oxaspiro[2.*n*]alkan-5-ones

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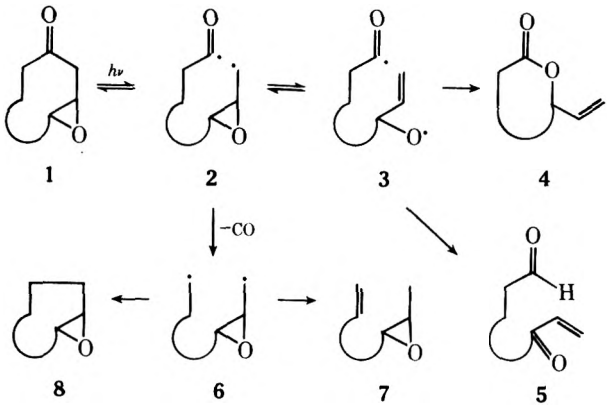
Irradiation of an ether solution of 4,4-dimethyl-1-oxaspiro[2.4]heptan-5-one gives 4-isopropylidenepentanolide and 2-isopropylidenepentane-1,5-dial in yields of 65 and 5%, respectively. Irradiation of 4,4,7,7-tetramethyl-1-oxaspiro[2.5]octan-5-one under comparable conditions affords 3,3-dimethyl-5-isopropylidenehexanolide and 4,4-dimethyl-2-isopropylidenehexane-1,6-dial in yields of 45 and 20%, respectively. The photoproducts resulting from these reactions are readily accounted for by the general scheme we have previously advanced for the photochemistry of β,γ-epoxy cyclic ketones. These results suggest that the photochemistry previously reported for a 1-oxaspiro[2.3]-hexan-5-one, though typical of that for other cyclobutanones, is not characteristic of 1-oxaspiro[2.*n*]alkan-5-ones.

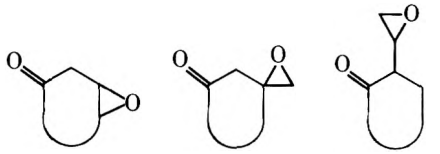
Recently we have suggested a general scheme to account for the photochemistry of β,γ-epoxy *cyclic* ketones.[2] It is proposed that irradiation of a β,γ-epoxy cyclic ketone **1** (Scheme I) initially leads to Norrish type I bond cleavage and the formation of an apparent diradical species **2** which undergoes subsequent ring opening to give the acyl alkoxy diradical **3**. Unless specific substituent and/or skeletal constraints are present, product formation proceeds from **3** by

Scheme I



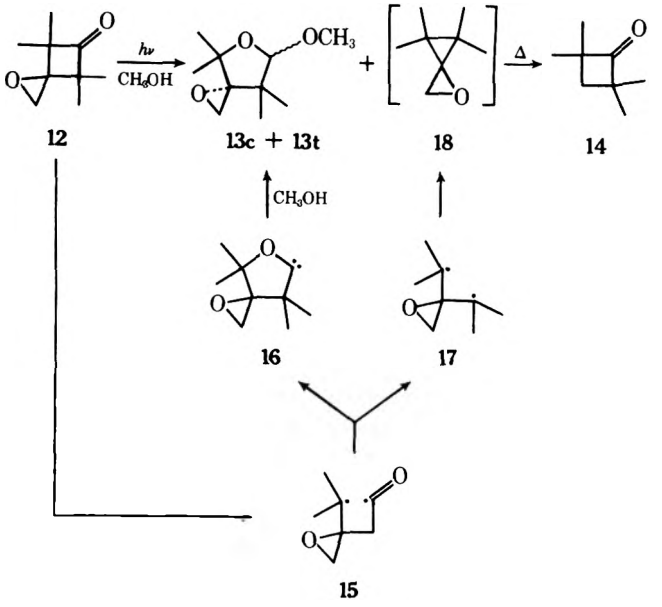
competitive ring closure to give lactone **4** and hydrogen transfer to provide aldehyde **5**. If the formation of either **4** or **5** is prevented, then the other product predominates. If the formation of both **4** and **5** is precluded, then decarbonylation occurs to give diradical **6** which undergoes disproportionation to provide **7** and/or ring closure to afford **8**.

There are three possible skeletal arrangements for a β,γ-epoxy cyclic ketone. The epoxide moiety may have two points in common with the carbon ring containing the carbonyl functional group (**9**, bicyclic), one point in common (**10**, spiro), or no points in common (**11**, exocyclic). Although the photochemistry of β,γ-epoxy cyclic ketones of types **9**[2,3] and **11**[4]



have received significant attention, the photochemistry of only one spiroepoxy cyclic ketone has been reported. Irradiation of a solution of 4,4,6,6-tetramethyl-1-oxaspiro[2.3]hexan-5-one (**12**) in dry methanol gives *cis*-acetal **13c**, *trans*-acetal **13t**, and 2,2,3,3-tetramethylcyclobutanone (**14**) in yields of 55, 31, and 12–14%, respectively.[5] These products are readily accounted for by a mechanism characteristic for the photochemistry of cyclobutanones.[6] Thus, irradiation of **12** (Scheme II) leads to Norrish type I bond cleavage and affords acyl alkyl diradical **15**. Subsequent or concerted rearrangement and rebonding of **15** provides oxacarbene **16** which is trapped by

Scheme II



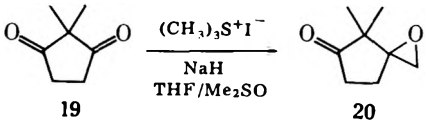
methanol to give acetals **13c** and **13t**. Alternatively, diradical **15** can lose carbon monoxide to generate diradical **17**. Ring closure of **17** would give oxaspiropentane **18** which presumably undergoes a thermal rearrangement to provide **14**.[5]

It is evident that the photoproducts obtained from irradiation of the 1-oxaspiro[2.3]hexan-5-one **12** are clearly *not* those which would have been predicted by our general scheme for the photochemistry of β,γ-epoxy cyclic ketones. In order to determine if the photochemistry of **12** is simply that which is typical of other cyclobutanones or whether it is characteristic of 1-oxaspiro[2.*n*]alkan-5-ones, we have synthesized and examined the photochemistry of a 1-oxaspiro[2.4]heptan-5-one and a 1-oxaspiro[2.5]octan-5-one.

Results and Discussion

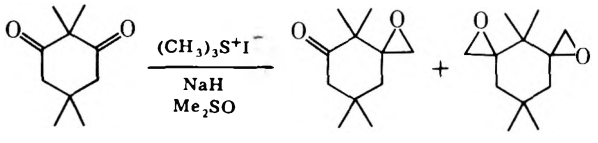
Synthesis. Previously we have noted that it appears that in order for product formation to be significant in the photochemistry of most β,γ-epoxy cyclic ketones the α-carbon of the β,γ-epoxy ketone moiety must be substituted with either two alkyl groups or one exceptionally good radical-stabilizing group, e.g., phenyl or cyclopropyl.[2] Consequently, for this study we prepared 4,4-dimethyl-1-oxaspiro[2.*n*]alkan-5-ones.

Treatment of 2,2-dimethylcyclopentane-1,3-dione[7] (**19**) with ca. 0.5 equiv of dimethylsulfonium methylide[8] proceeded with 81% conversion of **19** to give 4,4-dimethyl-1-oxaspiro[2.4]-heptan-5-one (**20**) in 39% yield. The structure of **20** follows

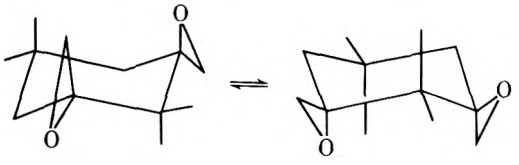


from its mode of formation and spectral characteristics which include an infrared carbonyl absorption at 1742 cm^{-1} and methyl singlets at δ 1.03 and 0.93 in its ^1H NMR spectrum.

4,4,7,7-Tetramethyl-1-oxaspiro[2.5]octan-5-one (**22**) was prepared by an analogous reaction. Treatment of 2,2,5,5-tetramethylcyclohexane-1,3-dione[9] (**21**) with 1 equiv of dimethylsulfonium methylide proceeded with nearly complete conversion of **21** to provide a mixture of **22** and 4,4,9,9-tetramethyl-1,6-dioxadispiro[2.1.2.3]decane (**23**) in yields of 21 and



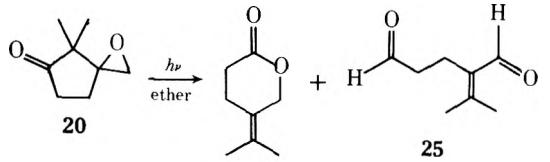
2%, respectively. When epoxy ketone **22** was submitted to the same reaction conditions, it was cleanly converted to diepoxide **23**. The structures of **22** and **23** follow from their analytical data, spectral characteristics, and mode of formation. Of particular interest is the ^1H NMR spectrum of **23** in which the C-4 and C-9 *gem*-dimethyls give rise to singlets at δ 1.03 and 0.87, respectively, the C-8 and C-10 methylene protons lead to a singlet at δ 1.55, and the C-1 and C-7 methylene protons afford two-proton doublets (J = 4.7 Hz) at δ 2.73 and 2.37.



This spectrum is only consistent with the oxygens in **23** being in axial–equatorial positions and **23** undergoing a conformational equilibrium process which is sufficiently rapid at ambient temperature on the ^1H NMR time scale so that corresponding groups are homotopic.

Photochemistry. Irradiation of an ether solution of 1-

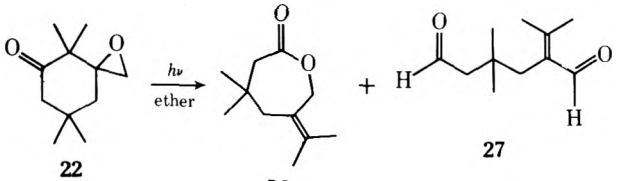
oxaspiro[2.4]heptan-5-one **20** through a Corex filter with a Hanovia L 450-W lamp afforded 4-isopropylidenepentanolide (**24**) and 2-isopropylidenepentane-1,5-dial (**25**) in yields of 65 and 5%, respectively. Consistent with the structure assignment, the infrared spectrum of lactone **24** contains a carbonyl absorption at 1740 cm^{-1} and the ^1H NMR spectrum of **24**



20 **24** **25**

consists of a broad singlet at δ 4.86 for the C-5 methylene protons, a broad singlet at δ 2.59 for the C-2 and C-3 methylene protons, and a broad singlet at δ 1.69 for the allylic methyls. Dialdehyde **25** shows carbonyl absorptions in the infrared at 1722 (nonconjugated aldehyde) and 1661 cm^{-1} (conjugated aldehyde) and a carbon–carbon double bond stretch at 1631 cm^{-1}. The ^1H NMR spectrum of **25** contains a one-proton singlet at δ 10.12 and a one-proton multiplet at δ 9.76 for the conjugated and nonconjugated aldehydic protons, respectively, a broad singlet at δ 2.53 for the C-3 and C-4 methylene protons, and singlets at δ 2.19 and 1.99 for the allylic methyls which are *Z* and *E* to the carbonyl, respectively. Extended irradiation of an ether solution of lactone **24** under identical photolysis conditions led to no significant photodecomposition.

The photochemistry of 1-oxaspiro[2.5]octan-5-one **22** parallels that of β,γ-epoxy ketone **20.** Irradiation of an ether solution of **22** through a Corex filter gave 3,3-dimethyl-5-isopropylidenehexanolide (**26**) and 4,4-dimethyl-2-isopropylidenehexane-1,6-dial (**27**) in yields of 45 and 20%, respectively. The structures of **26** and **27** follow from their analytical data and spectral characteristics. Consistent with these assignments, the infrared carbonyl absorption of **26** occurs at 1724 cm^{-1}, whereas dialdehyde **27** shows carbonyl absorptions

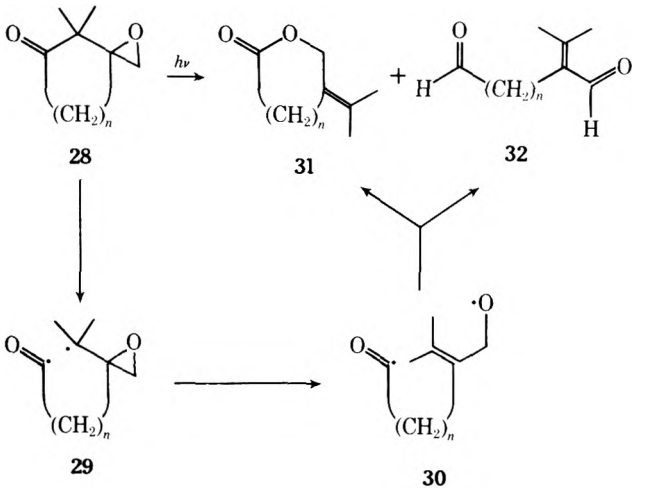


22 **26** **27**

at 1716 and 1665 cm^{-1}. The ^1H NMR spectra of **26** and **27** are strikingly similar to those already discussed in detail for lactone **24** and dialdehyde **25,** respectively.

The photoproducts obtained from **20** and **22** can readily be accounted for by a common mechanism (Scheme III). Thus,

Scheme III



28 **31** **32** **29** **30**

irradiation of a 1-oxaspiro[2.*n*]alkan-5-one (**28**) gives initial Norrish type I bond cleavage and provides diradical species **29** which ring opens to afford acyl alkoxy diradical **30.** Product formation proceeds from **30** by competitive ring closure to give lactone **31** and hydrogen transfer to provide dialdehyde **32.** It is apparent that this scheme parallels that which we have previously suggested as being general for unencumbered β,γ-epoxy cyclic ketones (see Scheme I).[2] Consequently, it would appear that the photochemistry of 4,4,6,6-tetramethyl-1-oxaspiro[2.3]hexan-5-one (**12**),[5] though typical of that for other cyclobutanones,[6] is not characteristic of 1-oxaspiro[2.*n*]alkan-5-ones.

Experimental Section

General. Infrared spectra were obtained on Perkin-Elmer 180 or 337 spectrophotometers and proton magnetic resonance spectra were recorded with Varian A-60A or Perkin-Elmer R-12B 60-MHz spectrometers. Apparent splittings are given in all cases. Unless noted otherwise, yields were obtained by integration of appropriate signals in the ^1H NMR spectrum of the crude reaction product(s) vs. the signal of a predetermined amount of added standard (generally trichloroethylene) and are regarded as being accurate to ca. ±10%. Elemental analyses were performed by Micro-Analysis Inc., Wilmington, Del.

4,4-Dimethyl-1-oxaspiro[2.4]heptan-5-one (20). A 57% mineral oil dispersion of sodium hydride (0.480 g, 0.0114 mol) was washed three times with petroleum ether. The resulting powder was aspirated dry and flushed with dry nitrogen. Dimethyl sulfoxide (150 mL, distilled from calcium hydride) was added, and the stirred mixture was heated at 70–75 °C until hydrogen evolution ceased. The resulting solution was cooled to room temperature, and tetrahydrofuran (200 mL, distilled from lithium aluminum hydride) was added. The reaction mixture was then cooled in an ice bath and a solution of trimethylsulfonium iodide (1.80 g, 0.0088 mol) in 20 mL of dry dimethyl sulfoxide was introduced. The reaction mixture was maintained at 0 °C and a solution of 2,2-dimethylcyclopentane-1,3-dione (**19,** 2.0 g, 0.016 mol) in 200 mL of dry dimethyl sulfoxide and 200 mL of dry tetrahydrofuran was added dropwise over 1.5 h. The resulting mixture was stirred under nitrogen at 0 °C for 2 h and then at room temperature overnight. At this point, the reaction was quenched with water (300 mL) and extracted with ether (five 100-mL portions), and the combined ether extracts were dried over anhydrous potassium carbonate. Evaporation of the solvent at reduced pressure gave an oil. GLC analysis (10 ft × 0.25 in. SE-30 column, 160 °C) of the residue showed that the reaction had proceeded with 81% conversion of **19** to give a single product in 39% yield. The product was purified by GLC (above conditions) to give **20** as an oil: δ_{Me_4Si} ($CDCl_3$) 2.82 (s, 2 H), 2.68–1.78 (br m, 4 H), 1.03 (s, 3 H), and 0.93 (s, 3 H); ν ($CHCl_3$) 3025, 2980, 2940, 1742, 1495, 1460, 1405, 1375, 1300, 1070, and 925 cm^{-1}.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.31; H, 8.63.

4,4,7,7-Tetramethyl-1-oxaspiro[2.5]octan-5-one (22). Epoxy ketone **22** was prepared by a procedure analogous to that employed for **19** → **20** with the following alterations. A solution of trimethylsulfonium iodide (3.69 g, 0.0178 mol) in 15 mL of dry dimethyl sulfoxide was added to an ice-cooled tetrahydrofuran solution of the ylide prepared from sodium hydride (1.00 g, 0.024 mol) and dimethyl sulfoxide (150 mL). After 2 min, a solution of 2,2,4,4-tetramethylcyclohexane-1,3-dione (3.00 g, 0.0178 mol) in 15 mL of dry dimethyl sulfoxide was added and the resulting mixture was stirred under nitrogen at 0 °C for 2 h and then at room temperature overnight. A common workup procedure was employed. GLC analysis (10 ft × 0.25 in. SE-30 column, 175 °C) of the oily reaction residue indicated the presence of three components with retention times of 6.9, 10.7, and 14.0 min which were obtained in yields of 1.4, 21.0, and 2.0%, respectively. The reaction products were purified by GLC (above conditions) to give unreacted **21** (t_R 6.9 min), **22** (t_R 10.7 min) [mp 58–62 °C; δ_{Me_4Si} ($CDCl_3$) 2.74 (d, J = 4.5 Hz, 1 H), 2.41 (d, J = 4.5 Hz, 1 H), 2.35 (m, 2 H), 1.76 (m, 2 H), 1.08 (s, 3 H), 1.03 (br s, 6 H), and 0.95 (s, 3 H); ν ($CHCl_3$) 2965, 1710, 1470, 1375, 1280, and 1080 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.69; H, 9.98.], and **4,4,9,9-tetramethyl-1,6-dioxadispiro[2.1.2.3]decane (23,** t_R 14.0 min) as an *oil [ν ($CHCl_3$) 3010, 2985, 2960, 2935, 1470, 1370, and 960 cm^{-1}.* Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.66; H, 10.36.].

Photolysis of 20. A solution of 198 mg of **20** in 15 mL of diethyl ether was irradiated through a Corex filter with a Hanovia L 450-W high pressure mercury lamp. Monitoring the photolysis by GLC (5

ft × 0.25 in. FFAP column, 160 °C) showed a gradual disappearance of **20** and the concomitant appearance of two photoproducts. The reaction was essentially complete after irradiation for 80 min. Evaporation of the solvent at reduced pressure gave a yellow oil. Purification of the photoproducts by GLC (above conditions) provided **4-isopropylidenepentanolide (24)** as an oil [ν ($CHCl_3$) 3015, 2925, 1740, 1445, 1375, 1340, 1290, 1255, 1140, and 1035 cm^{-1}. Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.28; H, 8.44.] and **2-isopropylidenepentane-1,5-dial (25)** as an oil [ν ($CHCl_3$) 3025, 1722, 1661, 1631, 1375, and 1160 cm^{-1}.]

Analysis of the crude photolysate by ^1H NMR showed that **24** and **25** were obtained in yields of ca. 65 and 5%, respectively.

Photolysis of 22. A solution of 205 mg of **22** in 12 mL of diethyl ether was irradiated through a Corex filter with a Hanovia L 450-W high-pressure mercury lamp. Monitoring the photolysis by GLC (5 ft × 0.25 in. Carbowax column, 175 °C) indicated a gradual disappearance of **22** with the concomitant formation of two photoproducts. After irradiation for 2 h, ca. 95% of **22** had reacted. Evaporation of the solvent at reduced pressure provided a yellow oil. Purification of the photoproducts by GLC (above conditions) gave **3,3-dimethyl-5-isopropylidenehexanolide (26)** as an oil [δ_{Me_4Si} ($CDCl_3$) 4.57 (s, 2 H), 2.49 (s, 2 H), 2.22 (s, 2 H), 1.77 (s, 3 H), 1.71 (s, 3 H), and 1.01 (s, 6 H); ν ($CHCl_3$) 2970, 1724, 1380, 1315, 1280, 1115, and 1025 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.32; H, 9.67.] and **4,4-dimethyl-2-isopropylidenehexane-1,6-dial (27)** as an oil [δ_{Me_4Si} ($CDCl_3$) 10.09 (s, 1 H), 9.76 (m, 1 H), 2.40 (br s, 2 H), 2.20 (m, 5 H), 1.97 (m, 3 H), and 0.99 (s, 6 H); ν ($CHCl_3$) 3025, 2965, 2880, 1716, 1665, 1635, 1380, 1190, and 1155 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.40; H, 9.76.].

Analysis of the crude photolysate by ^1H NMR showed that **26** and **27** were obtained in yields of 45 and 20%, respectively.

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Registry No.—**19,** 3883-58-7; **20,** 63704-11-0; **21,** 702-50-1; **22,** 63704-12-1; **23,** 63704-13-2; **24,** 63704-14-3; **25,** 63704-15-4; **26,** 63704-16-5; **27,** 63704-17-6.

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Formation of Carbonium Ions from Electrooxidation of Alkyl Bromides

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Primary, secondary, and tertiary bromoalkanes were potentiostatically oxidized at platinum gauze. The anolyte was acetonitrile–lithium perchlorate or tetraethylammonium fluoborate and the reference electrode Ag/0.1 M $AgNO_3$. Carbon–bromine bond cleavage, leading to the formation of *N*-alkylacetamides, was observed to be the exclusive route of these oxidations. Each of the oxidations of 2-bromopropane, 2-bromobutane, *tert*-butyl bromide, and neopentyl bromide yielded a sole amide, whereas 1-bromobutane, 1-bromopentane, 1-bromohexane, 1-bromo-2-methylpropane, 1-bromo-3-methylbutane, 2-bromopentane and 3-bromohexane gave mixtures of amides. A mechanism involving an initial electron transfer from the nonbonding orbital of the bromine is proposed. This intermediate is thought to undergo attack by the nucleophilic solvent and/or undergo carbon–bromine bond breaking to generate highly energetic carbonium ions, which react with the acetonitrile directly or after rearrangement.

The anodic oxidation of aliphatic halides has been studied on relatively few systems to date. Iodoalkanes and haloadamantanes were studied by several groups.[1,2] However, the electrochemical oxidation of simple alkyl bromides, with the sole exception of bromoadamantyl derivatives, has been unsuccessful. Preliminary study has recently demonstrated that covalently bound bromine makes the selective electrooxidation of organic bromides feasible in acetonitrile solution.[3] Carbon–bromine bond cleavage was found to occur exclusively, resulting in the formation of carbonium ion intermediates which reacted to form *N*-alkylacetamide products. This paper reports the results of a comprehensive study on anodic oxidation of a variety of primary, secondary, and tertiary bromoalkanes. The nature of the products and gross mechanistic features of the oxidation process are discussed.

Results

Preparative electrolyses were performed potentiostatically in a three-compartment cell at room temperature. Acetonitrile–lithium perchlorate or tetraethylammonium flouborate were used in both anode and cathode compartments. The solvent was routinely distilled from phosphorus pentoxide before use. The background current in all experiments was ~0.5 mA/cm^2 at 2.35 V. Initial currents with added substrates were 10–100 times the background, depending on the nature of the substrate. Coulometry was accomplished with an electronic counter. The coulometric data reported are uncorrected for background current, but if the coulometry were corrected (assuming that the current due to background oxidation was that which was determined without added substrate) the *n* values would be lowered by less than 0.1. In the electrooxidations of primary alkylbromides, the anode potential was pulsed to about 0.5 V for 1 s every 20 s. This resulted in higher currents and more rapid oxidations. For secondary bromoalkanes only an occasional pulsing was needed. The work-up included concentration of the anolyte followed by extraction with chloroform, methylene chloride, and water. Evaporation of the organic solvents after drying over anhydrous magnesium sulfate usually gave oily acetamido derivatives. The products reported in Table I were isolated after preparative GLC collection and identified by standard spectroscopic techniques and by comparison with authentic samples.

Table I. Voltammetric Data[a] and Oxidation Products

Substrate	Registry no.	Electrolyte[b]	mF consumed	Current yield, %[c]	Products[d]
$(CH_3)_3CBr$	507-19-7	A	4.0	83	$(CH_3)_3CNHCOCH_3$ (1) (98%)
$(CH_3)_2CHBr$	75-26-3	A	3.6	41	$(CH_3)_2CHNHCOCH_3$ (2) (92%)
		B	3.2	70	2 (95%)
$CH_3CH(Br)CH_2CH_3$	78-76-2	A	4.0	31	$CH_3CH(NHCOCH_3)CH_2CH_3$ (3) (95%)
		B	4.0	50	3 (98%)
$(CH_3)_3CCH_2Br$	630-17-1	B	4.6	33	$(CH_3)_2C(NHCOCH_3)CH_2CH_3$ (4) (43%) CH_3CONH_2 (5) (14%)
$(CH_3)_2CH(CH_2)_2Br$	107-82-4	B	4.0	28	4 (16%) $(CH_3)_2CHCH(NHCOCH_3)CH_3$ (6) (25%) $(CH_3)_2CHCH_2CH_2NHCOCH_3$ (7) (53%)
$(CH_3)_2CHCH_2Br$	78-77-3	B	4.4	50	1 (56%) + 3 (3%) $(CH_3)_2CHCH_2NHCOCH_3$ (8) (1%) 5 (15%)
n-C_4H_9Br	109-65-9	B	4.6	40	3 (67%) n-$C_4H_9(NHCOCH_3)$ (9) (33%)
n-$C_5H_{11}Br$	110-53-2	B	4.0	40	1-$C_5H_{11}(NHCOCH_3)$ (10) (30%) 2-$C_5H_{11}(NHCOCH_3)$ (11) (33%) 3-$C_5H_{11}(NHCOCH_3)$ (12) (33%)
2-$C_5H_{11}Br$	107-81-3	B	4.0	51	11 (33%) + 12 (67%)
n-$C_6H_{13}Br$	111-25-1	B	5.1	54	1-$C_6H_{13}(NHCOCH_3)$ (13) (27%) 2-$C_6H_{13}(NHCOCH_3)$ (14) (41%) 3-$C_6H_{13}(NHCOCH_3)$ (15) (31%)
3-$C_6H_{13}Br$	3377-87-5	B	4.0	40	14 (12%) + 15 (88%)

[a] All E_p values were in the range of 2.5–2.8 V vs. Ag|$AgNO_3$ 0.1 M in CH_3CN except for *tert*-butyl bromide (2.4 V). Electrooxidations were carried out at controlled potential of 2.35 V; 20 mmol of alkyl bromide in 10 mL CH_3CN was used in each experiment. [b] The electrolyte concentration was 0.5 M (A, tetraethylammonium fluoborate; B, $LiClO_4$). [c] Current yields are based on 2 e/mol. [d] Percentages shown express product distributions of isolated materials. On this basis the current yield is treated as 100%. In the oxidations of neopentyl bromide, 1-bromo-2-methylpropane, and 1-bromo-3-methylbutane, unidentified materials were also present in the product mixtures.

Table II. The Effect of Concentration on the Yield of 2 in the Anodic Oxidation[a] of Isopropyl Bromide at 2.35 V vs. Ag|$AgNO_3$ 0.1 M

[*i*-PrBr]	Current yield, %[b]
0.025	8
0.1	10
0.5	20
1.6[c]	45

[a] In all runs, tetraethylammonium fluoborate (0.2 M) was used as an electrolyte. [b] Yields are based on isolated products after passing 4 mF in each experiment, assuming 2 e/mol. [c] At concentrations higher than 1.6 M two phases were formed due to a limited solubility of certain bromoalkanes. Therefore current yield comparisons for all compounds listed in Table I are with substrate concentration of 1.6 M.

Cyclic voltammograms were recorded for each compound using tetrabutylammonium fluoborate as an electrolyte. Each bromoalkane shows one anodic peak in the range 2.5–2.8 V vs. Ag/Ag^+ at 0.2 V/s scan rate. *tert*-Butyl bromide and all secondary bromides gave a reasonably well-defined wave whereas primary bromoalkanes gave ill-defined ones. The anodic peak positions were dependent on sweep rate and there was no evidence of a reversible cathodic peak even at sweep rates of 60 V/s.

N-Alkylacetamido products which resulted from carbonium ion fragments are listed in Table I. The oxidations of *tert*-butyl bromide, 2-bromobutane, and 2-bromopropane each gave a sole amide derivative, while other primary and secondary bromides yielded mixtures of acetamidated products, due to one or more hydride shifts (e.g., from the oxidation of *n*-bromoalkanes) or a methyl shift (in the oxidation of neopentyl bromide) or both shifts (in the case of 1-bromo-2-methylpropane).

Table III. The Effect of Electrolytes on the Yields of 2 and 3[a]

Substrate	Concn, M	Supporting electrolyte	Current yield, %[c]
2-Bromobutane	1.6	TEAF	31
	1.6	$LiClO_4$	50
	1.6	TEAP[b]	41
	1.6	NH_4BF_4	22
2-bromopropane	0.5	TEAF	20
	0.5	$LiClO_4$	41

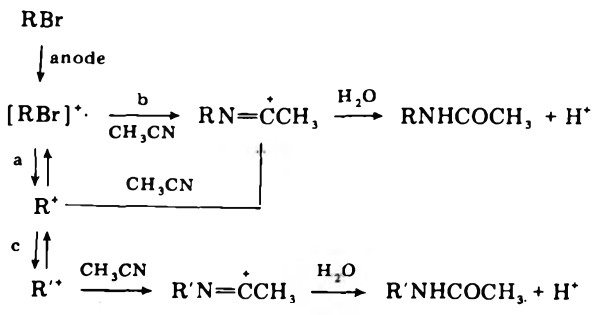
[a] All experiments were carried out potentiostatically at 2.35 V vs. Ag|$AgNO_3$ 0.1 M, at room temperature. Electrolyses were stopped after utilizing 4 mF. [b] TEAP = tetraethylammonium perchlorate. [c] Based on 2 e/mol calculation.

Several sets of experiments were conducted in order to optimize the product yields. The dependence of current yields on the concentration of the substrate is illustrated in Table II for the oxidation of 2-bromopropane. It shows clearly that the more concentrated the solution, the higher the current yield achieved. According to these results all preparative oxidations were carried out at a substrate concentration of 1.6 M.

The effect of the *n* value on the yield for the oxidation of *tert*-butyl bromide has been studied. When $n = 3$ or 4 the product mixture was contaminated with unidentified materials other than *N*-(*tert*-butyl)acetamide. However, when $n \leq 2$ the desired amide was obtained in over 95% purity. As a consequence of these results, the calculated current yields for all the electrooxidations presented in Table I are based on 2 e/mol.

Table III illustrates the influence of several supporting electrolytes on the extent of carbon–bromine bond breaking in the case of oxidation of 2-bromobutane and 2-bromopropane. For both substrates, higher yields of the corresponding

Scheme I



amides were achieved with lithium perchlorate. Thus, this electrolyte was employed in most preparative electrolyses described in this work.

Regarding the yields obtained from the experiments described above it seems reasonable to assume that the oxidation of alkyl bromides competes with oxidation of products and/or intermediates. Consequently, the reactions were arbitrarily discontinued when ~10% of the charge calculated for a two-electron process had been utilized. This procedure was used in order to avoid further oxidation of the products.[4a]

Discussion

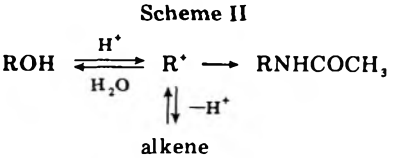
Table I illustrates that the cleavage of the carbon–bromine bond in the anodic oxidation of bromoalkanes is the sole process which appears to occur in the entire range of the substrates studied. This is in contrast to the behavior of secondary bromoadamantanes.[2a] This high selectivity is particularly noteworthy in the case of isobutyl bromide and 1-bromo-2-methylbutane, where tertiary hydrogens are present and for which no products due to C–H breaking were detected.

On the basis of an earlier argument[3] it seems likely that in the electrooxidation of simple alkyl bromides an initial electron is removed from the nonbonding orbital of the bromine (Scheme I) followed either by C–Br cleavage to generate a carbonium ion (path a), possibly a highly energetic one, and/or S_N2 type displacement on an initially formed cation radical (path b).[1b,4b] The carbonium ion, R^+, can undergo a reversible rearrangement (path c) to the isomeric carbonium ion (R'^+) and then react with the nucleophilic solvent to give amides different from those obtained via paths a and b. In support of the pathways in Scheme I, products **11** and **12**, for instance, from the oxidations of 1- and 2-bromopentanes, point to carbonium ion rearrangements (there is clear precedent for carbonium ion precursors in acetonitrile[2b]), whereas products **9**, **10**, and **13** point to an S_N2 type mechanism. It is clear, however, that the above results could be attributed to both cation radical and carbonium ion intermediates as well.

As is evidenced by the product distribution for 1-bromoalkanes (Table I), the isomerizations normally tend from primary to secondary and from secondary to tertiary alkyl products, that is, in the direction of the more stable carbonium ion. However, the oxidation of another primary alkyl bromide, 1-bromo-3-methylbutane, for instance, yielded a mixture of three amides derived from primary, secondary, and tertiary carbonium ions. This fact implies (assuming an S_N1 mechanism) that the rearrangement of the carbonium ion by hydride migration occurs in competition with the direct addition of the nucleophilic solvent acetonitrile to the carbonium ion.

Table I also indicates that carbonium ions "prefer" to rearrange toward the center of the molecule. This trend was observed for the oxidations of several compounds, e.g., 2-bromopentane and 1- and 3-bromohexanes. The rationale for this tendency may be attributed to a slightly greater inductive effect which the ethyl group exerts in comparison to the methyl group.[5] Consequently, a carbonium ion substituted with two ethyl groups is more stable than that substituted with one ethyl and one methyl group.

Scheme II



The carbonium ion intermediates might have been expected to produce alkenes and/or alcohols in addition to the acetamide, as demonstrated in Scheme II.

As we noted previously,[3] no olefins or alcohols were detected in the product mixtures of the various oxidized bromoalkanes (e.g., no dibromide from the formation of isobutylene or *tert*-butyl alcohol was observed from the oxidation of *tert*-butyl bromide). If one discounts the possibility of modifying the reactivity of a cation with a highly positively charged anode, i.e., adsorbed cations, one is then left with the proposition that the alkene, if formed, is converted to acetamide in a Ritter reaction.[6a] This is quite probable near the anode surface at which a high acid concentration must exist. Such acid-catalyzed processes converting alcohol or alkene to acetamide are not uncommon under these conditions.[7] Furthermore, aliphatic alcohols and olefins are known to oxidize below[8] the potential applied for the oxidation of bromoalkanes and such a possibility could also explain their absence.

In order to investigate the influence of acid on the formation of products, one would have expected that anodic oxidation of alkyl bromides in a basic medium would result in a decrease in the yield of *N*-alkylacetamides. Indeed, when 2-bromobutane was oxidized in the presence of an excess of anhydrous Na_2CO_3, under the same oxidation conditions described in Table I, the yield of **3** went down from 50% (without the presence of Na_2CO_3) to 32%. It is unlikely that all of this difference in yield is due to experimental error and therefore it seems that at least some of the 18% difference "belongs" to other products which, unfortunately, were difficult to identify under the conditions studied, for the reasons described in the preceding paragraph.

Mechanisms involving intramolecular remote abstration of hydrogen, by an $RBr^{+}\cdot$ type of intermediate, as found in mass spectroscopy of alkyl halides[9] and similarly in electrooxidation of ketones,[10] are ruled out since no bifunctional alkanes (e.g., acetamidated bromoalkane, biacetamidated products, etc.) were observed, as one would have expected from such a process. A mechanism involving intermolecular hydrogen abstration is also ruled out for the same reasons. However, intermolecular interaction between a neutral alkyl bromide and an oxidized molecule could be involved.

The fate of the bromine is not clear at present. However, neither Br_2 nor products containing bromine functionality were observed. The possibility of the formation of "Br^+" intermediate and its role as an electrophile (as demonstrated by Miller et al.[1b] in the case of "I^+") is under investigation.

Summary

This work has demonstrated not only the high selectivity of the heterolysis of the carbon–bromine bond but also the selectivity of the type of products isolated. Although the detailed mechanism of carbonium ion formation has not been elucidated, it most reasonably arises from a fleeting bromoalkyl cation radical initially generated by the electrochemical process. In fact, all of the data presented here for alkyl bromide oxidations can be rationalized in terms of an initial one-electron transfer from the highest filled molecular orbital of the organic bromide to the electrode. In subsequent steps bromoalkyl cations undergo scission of the carbon bromine bond to form carbonium ions and oxidizable bromine.

These carbonium ions are responsible for the *N*-alkylacetamide products. Attack on nitriles by carbonium ions has ample precedent in the literature[6b] and, indeed, the formation of only rearranged *N*-*tert*-pentylacetamide from oxidation of neopentyl bromide, for example, requires a mechanism involving carbonium ions. This mechanism bears a striking resemblance to that for the decomposition of alkyldiazonium ions.[11] The latter are highly unstable and decompose to alkyl carbonium ions.

Experimental Section

Preparative Oxidations. For all experiments listed in Table I, the electrolysis cell consisted of a 20-mL water-jacketed flat-bottomed glass cylinder with a four-neck flat flange lid equipped with a platinum gauze as anode, a flat stainless steel spatule as a cathode, an Ag|0.1 M $AgNO_3$ in MeCN reference electrode with a fine fritted cylinder at one end, and a magnetic stirrer bar. The separation of the anode cell and the cathode cell was achieved by a medium fritted cylinder at one end of the cathode. In some preparative oxidations, especially with primary bromoalkanes, the anode potential was pulsed to ~0 V for 1 s each 25 s. This was generally unnecessary, however, and had no discernible effect on the product. The potential was set at 2.35 V and the reactions were arbitrarily terminated, usually after passage of ~4 mF/mol of added substrate. The workup procedure consisted of evaporation of much of the acetonitrile (*Caution:* not to dryness. If perchlorate electrolyte is used the anolyte contains perchloric acid!), addition of water, and extraction twice with chloroform and twice with methylene chloride. The combined organic layers were washed once with water and then dried over anhydrous magnesium sulfate. After filtration and evaporation to an oil the product mixtures were isolated by preparative gas chromatography (GLC), using a 10% SE-30 column, 2 m × 0.25 in., on Chromosorb W. The products isolated (Table I) were characterized by NMR and GLC comparisons with authentic samples.

In electrolysis experiments at lower substrate concentrations (Table II) a different type of three-compartment cell was used which has been described elsewhere.[12]

Cyclic Voltammetry. Voltammograms were recorded for each bromoalkane in twice-distilled acetonitrile. The cell volume was 10 mL and the electrolyte was tetrabutylammonium fluoborate. The Ag|0.1 M $AgNO_3$ reference electrode was separated from the working electrode by a glass frit. The auxiliary electrode was a platinum sheet (10 × 20 mm), and the working electrode was a platinum wire sealed in glass and ground smooth making a small platinum button. All the voltammograms showed no cathodic peak corresponding to reduction of an initially formed cation radical.

Instrumentation. A Perkin-Elmer IR spectrometer Model 137 and Varian XL100 NMR spectrometer were used for structure determination. Gas-liquid chromatography (GLC) analyses were performed by Varian Aerograph Model 920 gas chromatograph equipped with a thermal conductivity detector. The potentiostat employed is a Princeton Applied Research Model 173. Coulometry during preparative electrolysis was performed with a counter constructed from an Acromag integratortotalizer. A Universal Programmer Model 175 from Princeton Applied Research was used as a function generator to pulse the anode potential during preparative oxidations and to determine scan rates during cyclic voltammetry measurements. The recorder employed during these cyclic experiments is a Model 26000 A4 X-Y recorder from Bryans.

Materials. Acetonitrile (Fluka 99.5%) was purified by distillation from phosphorus pentoxide under nitrogen and stored over 4A molecular sieves. Anhydrous lithium perchlorate (Alfa Products) was used without any further treatment. Tetraalkylammonium fluoborates and perchlorate were purchased from Fluka AG and used without further purification. All bromoalkanes were commercial samples (Aldrich and BDH Labs).

Authentic Samples. *N*-Alkylacetamide derivatives (Table I) were prepared by two procedures described elsewhere.[1a] The availability of the starting material determined the method of choice. Thus, aminoalkanes were treated with acetic anhydride and tertiary alcohols were reacted with H_2SO_4 in acetonitrile. The NMR data for all products listed in Table I are in accordance with the literature and the elemental analyses of all the *N*-alkylacetamide products were satisfactory. The amides show characteristic absorptions in the IR in the regions 1650, 1670, and 3300 cm^{-1}.

Acknowledgment. The author is thankful to Dr. A. Pross for helpful discussions.

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Reactions and Crystal and Molecular Structure of an Unsymmetrical Spirosulfurane: Manifestations of Hypervalent Bond Polarization in a Sulfurane[1]

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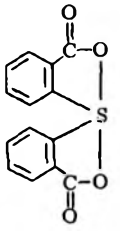
The regiospecificity evidenced in several of its reactions is correlated with the x-ray structure of unsymmetrically substituted diaryldialkoxyspirosulfurane **6**. Most impressive is the large difference (0.24 Å) between the lengths of the S–O bonds, 1.713 (2) and 1.955 (2) Å, from which we infer a high degree of polarization in the hypervalent O–S–O bond. The estimated S–O bond orders are 0.96 and 0.37, respectively. The crystals of **6** are monoclinic, the space group is $P2_1/c$, and there are four molecules in a unit cell of dimensions a = 11.201 (1), b = 14.253 (2), c = 11.768 (2) Å, β = 114.08 (1)°. The structure was refined to an R factor of 0.047. Reactions of **6** with methyl fluorosulfonate and trifluoromethanesulfonic acid reflect the relative nucleophilicities and basicities of the oxygens of **6**. The oxygen nearer the CF_3 substituents is more basic and more nucleophilic than that more distant from these electron-withdrawing groups, in a striking demonstration of the polarizability of the three-center four-electron bond. These chemical reactivities are consistent with what might be predicted from the x-ray data if one assumes the S and O separated by 1.955 Å to be essentially zwitterionic. The relevance of this work to earlier work on sulfuranes with polarized hypervalent bonds is discussed.

The x-ray structures of a number of symmetrically substituted sulfuranes, including **1** and **2**, have been reported.[2-6] A prominent feature of all these structures is the longer than usual S–O single bonds, identical in length to each other



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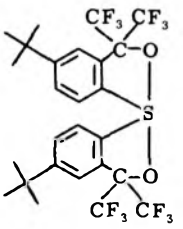
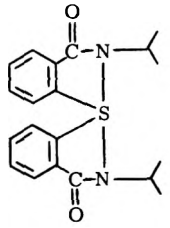


2

within experimental error. For example, the S–O bond lengths of **1** are both 1.83 Å,[2] and in **2** the S–O bond lengths are 1.82 and 1.83 Å.[3] Diazasulfurane **3** has S–N bond lengths of 1.899 and 1.897 Å.[6] Identical or nearly identical hypervalent bond lengths are expected for sulfuranes with identical apical ligands.

Evidence for the polarizability of the hypervalent bond in sulfuranes has recently been discussed.[7] The carbonyl-stretching frequency is found to be very responsive to variations in substituents (L, X, Y) in sulfuranes of type **4** and **5**.



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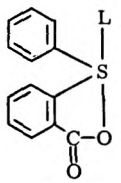

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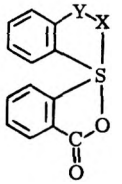
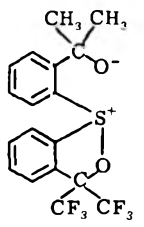


5

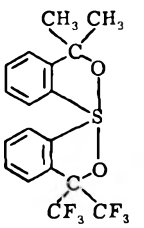
This has been postulated to be a result of the variable level of negative charge on the acyloxy group, reflecting a greater or lesser resemblance to a carboxylate anion in its carbonyl-stretching frequency.

If sulfuranes with unsymmetrical apical substitution patterns have strongly polarized hypervalent bonds, then this should cause a significant difference in their bond lengths; i.e., the more electronegative apical ligand should have a longer S–X bond length and the less electronegative ligand should have a smaller S–X bond length.

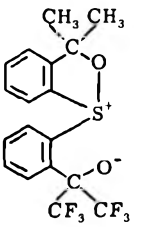
We herein report the x-ray structure for unsymmetrical



6a



6



6b

sulfurane **6** which reveals a large difference in S–O bond lengths. The three-center four-electron hypervalent bond[8] is not badly represented by resonance structures such as **6a** and **6b**. We might expect **6b** to contribute more to the structure than **6a** as a result of the inductive electron withdrawal of the CF_3 substituents. This expected polarization of the hypervalent three-center bond should be reflected in reactivity and in bond lengths. This work was undertaken to probe these predictions.

Experimental Section

General. Chemical shifts for protons are reported on the δ scale, ppm downfield from the Me_4Si internal standard; fluorine chemical shifts are reported on the ϕ scale, ppm upfield from the $CFCl_3$ internal standard. The ^1H NMR and ^{19}F NMR integral ratios are rounded to the nearest whole number of nuclei. Melting points are uncorrected. Elemental analyses of new compounds are within 0.4% of theoretical values, unless otherwise noted.

Alkylation of 6 with Methyl Fluorosulfonate. Sulfurane **6** (81 mg, 0.198 mmol), synthesized by the published[9] method, was dissolved in ca. 1 mL of dry $CDCl_3$ and methyl fluorosulfonate (22.6 mg, 16 μL, 0.198 mmol) was added. The reaction, followed at 25 °C by ^1H NMR (disappearance of methyl singlet of $MeOSO_2F$), was complete after 12.5 days. The ^1H NMR spectrum of this solution showed methyl singlets at δ 2.04, 2.15, and 4.38 (OCH_3) for sulfonium salt **8**. Another small singlet (ca. 9% of the total OCH_3 singlet at **8** at 75% reaction completion) was seen at δ 3.98 which might be due to the methoxy group of sulfonium salt **7**. The solution was extracted with aqueous NaOH to give (^1H NMR) ca. 80% sulfoxide **9** and ca. 20% of an unidentified product. Chromatography on silica gel (6.2 g) with $CHCl_3$ gave 16.4 mg (20.3%) of sulfurane **6** and 66.1 mg (75.8%, 95% based on conversion) of sulfoxide **9**, mp 166–167 °C; ^{1}NMR (100 MHz, $CDCl_3$) δ 1.74 (s, 3, CH_3), 1.79 (s, 3, CH_3), 3.61 (m, 3, OCH_3, coupling to CF_3 groups, J_{HF} = 1.1 Hz), 4.54 (br s, 1, OH), 6.78 (br d, 1, ArH), 6.95–7.14 (m, 1, ArH), 7.20–7.40 (m, 2, ArH), 7.54–7.84 (m, 3, ArH), 8.28–8.46 (m, 1, ArH); ^{19}F NMR ($CDCl_3$) ϕ 68.13 (q, 3, CF_3, J_{FF} = 8.5 Hz), 70.64 (q, 3, CF_3, J_{FF} = 8.5 Hz); mass spectrum (70 eV) m/e (rel intensity) 440 (6.0, $M^{+\cdot}$), 425 (34.4, $M^{+\cdot} - CH_3$), 409 (3.9, $M^{+\cdot} - OCH_3$), 379 (7.2), 289 (4.0), 265 (4.2), 239 (4.7), 205 (12.8), 149 (44.6), 91 (15.6), 77 (17.0), 43 (100).

Anal. ($C_{19}H_{18}F_6O_3S$) C, H.

Reaction of Unsymmetrical Spirosulfurane 6 with Trifluoromethanesulfonic Acid. To a solution of sulfurane 6 (230 mg, 0.563 mmol) in 25 mL of ether was added 51 μL (86.2 mg, 0.574 mmol) of trifluoromethanesulfonic acid at 25 °C. In a few seconds a white precipitate formed. The mixture was stirred for 15 min and filtered. The crystals were washed with ether to give 256 mg (81.4%) of crystalline sulfonium triflate 12: mp 200–202 °C; IR (KBr) 3450 (w, br, OH), 3000 (w), 1475 (w), 1447 (w), 1320–1120 (s, five or more strong peaks), 1030 (m), 975 (m), 965 (m), 948 (m), 831 (m), 765 (m), 704 (m), 640 (m); ^{1}H NMR (220 MHz, CH_2Cl_2) δ 1.932 (s, 3, CH_3), 2.205 (s, 3, CH_3), 7.468 (d, 1, ArH, J = 8 Hz), 7.627 (t, 1, ArH, J = 8 Hz), 7.705–7.932 (m, 5, ArH), 8.09 (d, 1, ArH, J = 8 Hz), 11.40 (br s, 1, OH); ^{19}F NMR (90 MHz, CH_2Cl_2) φ 73.51 (q, 3, CF_3, J_{FF} = 8.5 Hz), 74.73 (q, 3, CF_3, J_{FF} = 8.5 Hz), 78.9 (s, 3, $^-OSO_2CF_3$).

Anal. ($C_{19}H_{15}F_9O_5S_2$) C, H, F, S.

Treatment of Sulfurane 6 with HCl. (a) Sulfurane 6 (132.2 mg, 0.32 mmol), dissolved in 3 mL of CH_2Cl_2, was shaken with 1 mL of concentrated HCl. The CH_2Cl_2 layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The CH_2Cl_2 extracts were combined and dried ($MgSO_4$), and solvent was removed, leaving a white solid (120 mg, 91.8% recovered) identified as 6 by melting point and ^{1}H NMR: ^{1}H NMR of 6 ($CDCl_3$) δ 1.62 (s, 3, CH_3), 1.80 (s, 3, CH_3) 7.15–7.80 (m, 6, ArH), 8.15–8.47 (m, 2, ArH, protons ortho to S).

(b) A solution of sulfurane 6 (242 mg, 0.59 mmol) in 10 mL of dry ether was saturated with HCl gas. No precipitate formed. The ether was removed by N_2 stream and the product was analyzed by ^{1}H NMR ($CDCl_3$): δ 1.83 (s, 3, CH_3), 2.10 (s, 3, CH_3), 7.40–7.87 (m, 6, ArH), 7.93–8.14 (m, 1, ArH), 8.35 (d, 1, ArH, J = 8 Hz). The product was recrystallized from $CHCl_3$–hexane (181 mg, 75% recovered) and was identified as 6 (^{1}H NMR).

(c) A solution of 6 in $CDCl_3$, saturated with HCl, gave the following ^{1}H NMR: δ 1.92 (s, 3, CH_3), 2.22 (s, 3, CH_3), 7.43–8.06 (m, 7, ArH), 8.30 (d, 1, ArH, J = 8 Hz), 9.13 (s, 2.2, HCl, excess). The downfield shifts of the methyl groups in the presence of HCl suggest some sort of interaction with HCl but no chlorosulfurane (14) could be isolated.

X-Ray Crystallography of Spirosulfurane 6. Crystals of 6 were grown by slowly evaporating a chloroform solution of 6. No special precautions were needed to protect the crystal from moisture.

Crystal Data for 6: $C_{18}H_{14}F_6O_2S$ mol wt = 408.4; monoclinic, a = 11.201 (1), b = 14.253 (2), c = 11.768 (2) Å, β = 114.08 (1)°, V = 1715.4 Å, Z = 4, ρ_c = 1.58 g/cm^3, μ(CuK$_\alpha$) = 23.6 cm^{-1}, F(000) = 832, systematic absences for $0k0$ when $k = 2n + 1$ and for $h0l$ when $l = 2n + 1$ establish the space groups as $P2_1/c$. The cell dimensions were obtained by a least-squares fit to the automatically centered setting for 15 reflections on a Syntex $P2_1$ diffractometer equipped with a graphite monochromator, λ(CuK$_\alpha$) = 1.54178 Å.

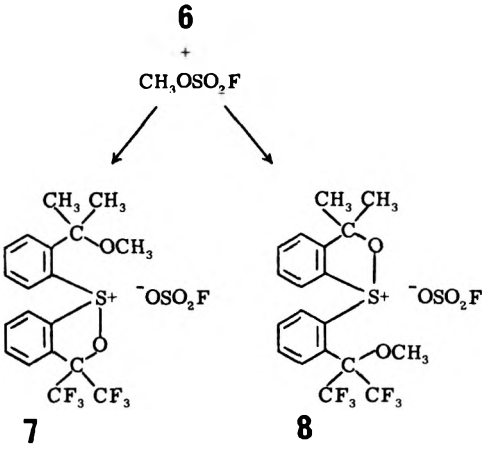
Solution and Refinement of the Structure of 6. A crystal with dimensions ca. 0.4 × 0.3 × 0.2 mm was used for data collection. The data collection was performed in the 2θ:θ scan mode. The variable scan option was employed (2.0–10.0°/min) with the total background time/scan time set at 0.25. Three standards from different parts of the reciprocal space were monitored every 50 reflections. Examination of these reflections showed no crystal deterioration. The hkl and $\bar{h}kl$ octants were collected out to 2θ = 126° (sin θ/λ = 0.588). Out of the possible 3075 unique reflections collected, 2556 were observed using a 2σ criterion based on counting statistics. The data were corrected for Lorentz and polarization effects, but not for absorption; the maximum and minimum transmission factors were estimated to be 0.45 to 0.62.[10]

The structure was solved by direct methods using the programs supplied by Syntex.[11] The hydrogens were located from difference maps. Full-matrix, least-squares refinement of positional and anisotropic thermal parameters for the nonhydrogen and of positional and isotropic thermal parameters for the hydrogen atoms converged with values for R and R_w of 0.047 and 0.057, respectively.[12] The final value of $[\Sigma w(|F_{obsd}| - |F_{calcd}|)^2/(m - n)]^{1/2}$, where m is the number of observations and n is the number of variables, was 1.91. The scattering curves were taken from the analytical expression used in the "International Tables for X-Ray Crystallography".[13] A final difference map showed a peak, 60% of an average hydrogen, between C(18) and C(16); the rest were less than 50% of an average hydrogen. The final values of the atomic coordinates[14] are given in Table I.

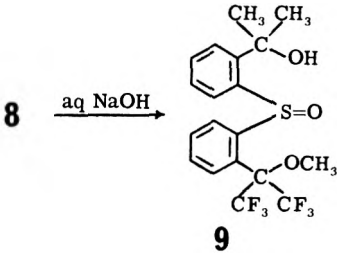
Results

The synthesis and some properties of spirosulfurane 6 have been reported.[9] It is found to be inert toward hot aqueous acid or base, a property which it shares with sulfurane 2.[15] Pyrolysis of 6 occurs only at temperatures above ca. 350 °C, which reflects an unusually high thermal stability for 6, compared to other spirosulfuranes[9,16] substituted with less electronegative ligands. Sulfurane 6 is only weakly basic as evidenced by interactions with a chiral alcohol and with Eu(fod)$_3$.[9] The oxidation of 6 to the sulfurane oxide has also been reported.[17] Oxidation is the only reaction seen for 2.[15]

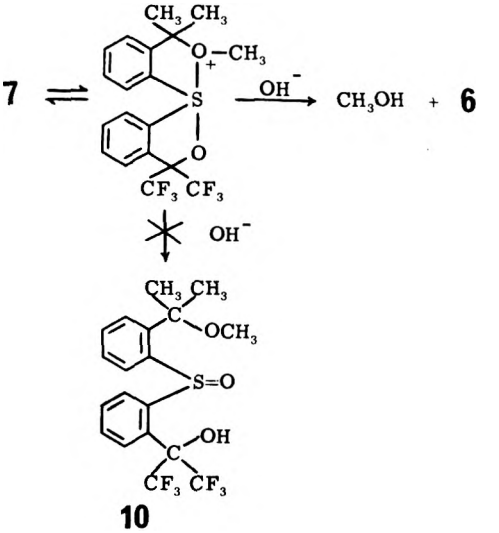
Scheme I



The alkylation of 6 with methyl fluorosulfonate provides insight into the relative nucleophilicities of the two oxygens of 6. Two possible methylation products are sulfonium salts 7 and 8 (Scheme I). The addition of 1 equiv of methyl fluorosulfonate to a chloroform solution of 6 at 25 °C initially gives sulfonium salt 8 as the only detectable product. The ^{1}H NMR spectrum of 8 shows two methyl singlets at δ 2.04 and 2.15. The methoxy signal is a broad multiplet (J_{HF} = 1.1 Hz) at δ 4.38. Upon treatment with aqueous NaOH, sulfonium salt 8 is converted to sulfoxide alcohol 9. During the course of the



methylation, another singlet at δ 3.98 begins to grow until, when the reaction is 75% complete, the new singlet is ca. 9% of the area of the methoxyl singlet of 8. We suspect that this singlet might be the methoxyl peak of sulfonium salt 7. Our failure to isolate the corresponding sulfoxide 10 upon hydrolysis of the reaction mixture may be the result of de-



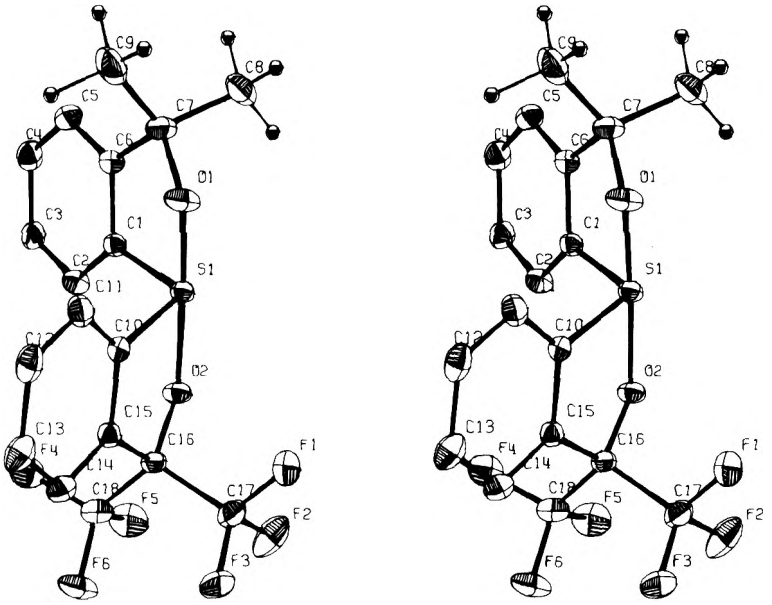
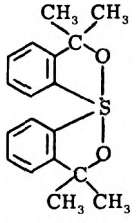


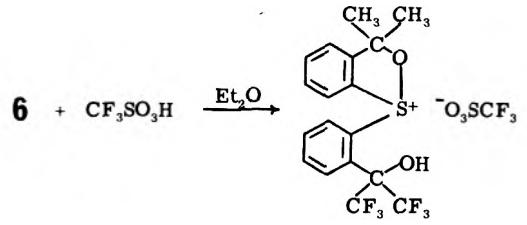
Figure 1. Stereoscopic view of spirosulfurane **6**.

methylation of **7** to regenerate **6** under these conditions. The ether function in **9** is probably less prone to demethylation because the electron-withdrawing trifluoromethyl groups lower the Lewis basicity of the adjacent oxygen and hence decrease the importance of S–O bonding analogous to that giving oxonium character to **7** in the pictured route to **6**. In any case, methylation on the perfluoroalkoxy oxygen is the kinetically preferred reaction. Clearly, the oxygen adjacent to the CF_3 groups is the more nucleophilic of the two. It is interesting to note that methylation[9] of spirosulfurane **11** is much slower than methylation of **6** (12.5 days for **6** vs. 11 h for **11**).[18]



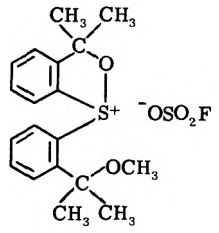
11

The addition of trifluoromethanesulfonic (triflic) acid to an ether solution of **6** gave a precipitate of sulfonium triflate **12**. The structure assigned to **12** is based on chemical-shift



12

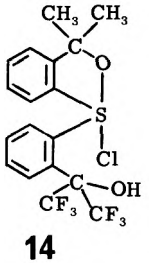
comparisons of the methyl groups of **12** with sulfonium salts **8** (δ 2.04 and 2.15) and **13** (δ 1.78, 1.87, 1.98, and 2.17).[9] The methyl peaks of **12** at δ 1.93 and 2.21 are similar in chemical shifts to those of **8** and to two of the peaks of **13** (δ 1.98 and 2.17), and very different from the chemical shifts of the *gem*-dimethyl peaks for the ether function of **13** (δ 1.78 and 1.87) and of the *gem*-dimethyl peaks for the product of hydrolysis of **8**, sulfoxide **9** (δ 1.74 and 1.79), which serve as models for the isomer of **12** which would result from protonation at the other oxygen.



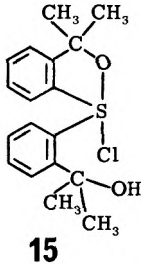
13

Since **12** is the product of a rapid protonation equilibrium, one expects both O-protonated species to be present in a solution of **12**. The chemical-shift arguments presented above suggest that the equilibrium strongly favors protonation on the fluoroalkoxy oxygen. The more basic site is, therefore, the same as the more nucleophilic site which was methylated in the reaction forming **8**.

An attempt to prepare chlorosulfurane **14** by the procedure[9] used to prepare chlorosulfurane **15** failed. However, when a

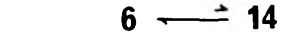


14



15

$CDCl_3$ solution of **6** is saturated with HCl the methyl groups shift downfield. A similar shift is also seen in **15**.[9] The interaction of **6** with HCl appears to be quite weak with the equilibrium lying in the direction of **6**.



The final coordinates for spirosulfurane **6** are listed in Table I.[14] The important bond lengths and bond angles of **6** are found in Tables II and III.[14] The important bond lengths and bond angles of **2** and **6** are compared in Table IV.[14] Figure 1 shows a stereoscopic view of the molecular structure of **6** and Figure 2 shows its crystal structure.

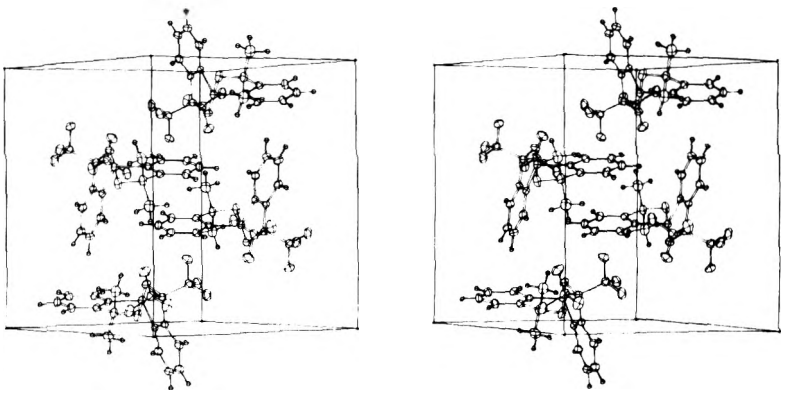


Figure 2. Stereoscopic view of the crystal structure of **6**.

Discussion

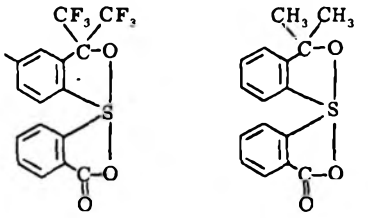
Unsymmetrical spirosulfurane **6** has approximate trigonal bipyramidal geometry about sulfur, like the geometry seen for other sulfuranes.[2-6] The most striking feature of **6** is the large difference in the lengths of the S–O bonds (*a*, 1.713 (2); *b*, 1.955 (2) Å; see Table IV). Their difference (0.24 Å) reflects polarization of the hypervalent O–S–O bond resulting from the difference in electronegativities of the apical ligands. The average S–O bond length of **6** (1.83 Å) is nearly equal to the S–O bond lengths of sulfurane **2** (1.825 Å). The short S–O distance in **6** is only slightly longer than a normal S–O bond (1.70 Å),[19] whereas the other S–O bond distance is 0.26 Å longer. Respective bond orders of 0.96 and 0.37 are calculated for these bonds, using the Pauling[20] correlation of bond order with bond length. The only other significant difference between the bond lengths and bond angles of **2** and **6** are the C–O bonds of **6** (*e*, 1.436; and *f*, 1.369; Table IV) which differ by 0.07 Å. This difference may be in part ascribed to the electronegativity differences of the alkoxy ligands, since bond *f* in **6** is slightly shorter than the average C–O bond length of **2** with the shorter C–O bond in **6** being associated with a longer S–O bond to the same oxygen atom.

The C–S–C angles of **2** and **6** are identical. This is somewhat surprising because the C–S–C angle of **6** might have been expected to be larger than that of **2**, in view of a previously noted trend[4,21] which relates a decrease in the electronegativity of the apical ligands to an increase in the angle. On going from **2** to **6** one apical ligand decreases in electronegativity. The large difference in the S–O bond lengths does not affect the O–S–O angle of **6**, which is nearly equal to that of **2**.

The x-ray structure of **6** shows that the hypervalent O–S–O bond in sulfur is strongly distorted by the introduction of structural features expected to result in polarization of this three-center bond. The fluoroalkoxy ligand in **6** is significantly more electronegative than the unfluorinated alkoxy ligand. Electron density is removed from the dimethylalkoxy ligand toward the fluoroalkoxy ligand. The observations of a long S–O bond *b* and a short S–O bond *a* in **6** are consistent with the idea that resonance structure **6b** is quite important in describing the resonance hybrid which is **6**.

The overall effect of the CF_3 groups is to decrease the basicity and nucleophilicity of **6** compared to the unfluorinated analogue **11**. The inductive electron-withdrawing effect of this substitution of CF_3 for CH_3 is shown by the results of this paper to be greater at the oxygen more remote from the CF_3 substituent of **6** than at the adjacent oxygen. The reactions of **6** with methyl fluorosulfonate and triflic acid occur preferentially at the oxygen of the fluoroalkoxy group consistent with the postulated large contribution of resonance structure **6b**. Electrophilic attack at the fluoroalkoxy oxygen places the positive charge of the product alkoxysulfonium ion adjacent to the less electronegative alkoxy group in **8** and **12**. The resemblance of the transition state for methylation to the product can be used to rationalize the greater nucleophilicity of the oxygen nearer the CF_3 substituents.

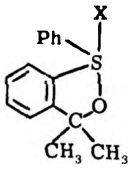
The carbonyl-stretching frequencies of sulfuranes **1**, **16**, and **17** are 1724, 1708, and 1647 cm^{-1}. The hypervalent bond is symmetrically substituted in sulfurane **1**. The lower carbonyl-stretching frequency seen (**16**) has been interpreted[7]



16 **17**

in terms of an increase in carboxylate anion character for **16** in relation to **1**. In **16** there is more electron density on the acyloxy ligand than on the fluoroalkoxy ligand. The acyloxy ligand is effectively more electronegative than the fluoroalkoxy ligand. The considerably lower carbonyl-stretching frequency seen in **17** points to an even higher degree of carboxylate anion character in this unsymmetrical sulfurane, a result of the lesser electronegativity of the alkoxy ligand compared to the fluoroalkoxy ligand.

Chemical shift evidence for polarization of the hypervalent bond has been reported[7] for monocyclic sulfuranes of structure **18**. The average of the peak positions for the two methyl

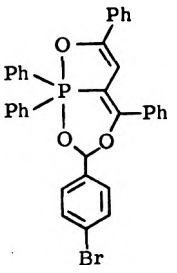


18

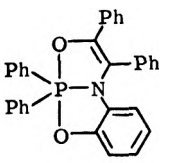
groups shift to lower field with increasing electronegativity of X. Extension of this argument to bicyclic sulfuranes is possible. The average positions of the methyl groups of **11**, **6**, and **17** are δ 1.62, 1.74, and 1.82. The increasing downfield shift parallels the expected order of increasing polarization of the O–S–O bond.

The order of increasing polarization of the hypervalent bond for known spirosulfuranes is inferred from an examination of both infrared and ^1H NMR evidence, to be as follows: **1**, **2**, **11** (symmetrical) < **16** < **6** < **17**.

Similar distortions of the hypervalent bond are reported for phosphoranes. The crystal structures of unsymmetrical phosphoranes **19** and **20** have been determined.[22,23] The P–O



19



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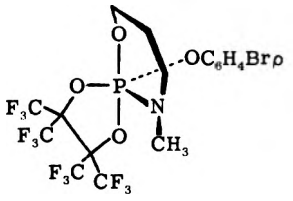
bond lengths of **19** differ by 0.05 Å and those of **20** by 0.06 Å. The differences in apical bond lengths are not nearly as large as those found in **6** (0.24). Compound **21** provides an even



21

closer analogue of **6** in that one apical substituent is an α,α-bis(trifluoromethyl)alkoxy group and the other an "ordinary" alkoxy group. The difference in the two apical P–O bond lengths[24] is 0.10 (1) Å, a deviation from the ideal TBP geometry, with equal bond lengths, which is in the same direction as the deviation from ideality seen for **6**, but less than half as large. The smaller differences in P–O bond lengths seen for **19**, **20**, and **21** reflect a smaller polarizability, or at least a smaller deformability, of a hypervalent bond with a central phosphorus than is seen for one with a central sulfur. A similar reduction in polarizability is reflected in carbonyl-stretching frequencies of iodinanes[25] when compared to sulfuranes. Further work will be required to probe the generality of this observation and to establish a probable rationalization.

Acknowledgment. This work was supported in part by a grant to J.C.M. from the National Cancer Institute (CA 13963). The x-ray work was carried out using equipment purchased under the terms of our National Science Foundation Major Equipment Chemistry Department Grant (MPS 75-05911).

Registry No.—**2**, 38195-99-2; **6**, 63731-54-4; **8**, 63731-56-6; **9**, 63731-57-7; **12**, 63765-59-3; **13**, 63731-59-9; methyl fluorosulfonate, 421-20-5; trifluoromethanesulfonic acid, 14993-13-6.

Supplementary Material Available: A listing of final thermal parameters (Table I), complete bond lengths and angles (Tables II and III), and a comparison of bond lengths and angles (Table IV) (6 pages). Ordering information is given on any current masthead page.

References and Notes

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(11) The structure was solved by a version of the MULTAN program, G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971), that has been incorporated into the SYNTEX EXTL system, based on the Data General ECLIPSE Computer. All crystallographic calculations were carried out on this system.
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Reactions of Some New Diaryldialkoxyspirosulfuranes. The Barrier to Cuneal Inversion of Configuration at Sulfuranyl Sulfur in Diastereomeric Spirosulfuranes[1,2]

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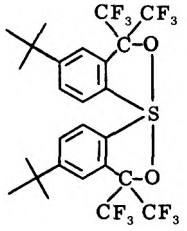
The syntheses of diaryldialkoxyspirosulfuranes **8**, **11**, **15**, and **17** are reported, including the first example of a pair of diastereomeric spirosulfuranes (**17a** and **17b**) which may be interconverted by cuneal inversion at sulfur(IV). Hydrolyses of these compounds are compared with each other and with those of related species. The most studied of these sulfuranes, 3,3,3′,3′-tetramethyl-1,1′-spiro[3*H*-2,1-benzoxathiole] (**8**), undergoes a wide variety of reactions, including reactions with hydrogen halides to form halosulfuranes and with strong acids to form alkoxysulfonium salts. For both classes of products, ^{1}H NMR spectra show evidence for an intramolecular degenerate ligand-exchange process. Low-temperature ^{1}H NMR studies on one of these adducts confirms this interpretation. The pyrolytic fragmentation reactions of **8**, **11**, and **15** show facile dehydration for **8** and intramolecular disproportionation for **11** and reveal a great thermal stability for **15**. The reactivity (and basicity) of these spirosulfuranes is decreased by increasing electronegativity of apical ligands. The configurational stability of **17** has been determined by measuring the rate of isomerization of *exo*-**17a** to *endo*-**17b**. The rate constant ($k_1 = 3 \times 10^{-6}$ s^{-1}) for this process at 84 °C corresponds to a lower limit of $\Delta G^*_{84°C} = 30$ kcal mol^{-1} for cuneal inversion of configuration (inversion through a planar transition state) at sulfuranyl sulfur. Possible alternative interconversion mechanisms are discussed.

The number of reported examples of spirosulfuranes has grown rapidly.[2-9] However, there have been relatively few reports concerning the reactions of these new compounds.[4,6,9] Martin and Perozzi report[6] that bicyclic spirosulfuranes are much less reactive than acyclic sulfuranes, with monocyclic sulfuranes showing intermediate reactivities. For example, spirosulfurane **1** is reported to be completely inert toward acid or base hydrolysis and unreactive toward a number of reagents, whereas its acyclic analogue **2** is extremely reactive.[6]



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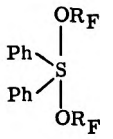
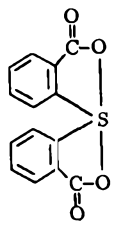


2, (OR_F = $OC(CF_3)_2Ph$)

Kalman and Kapovits[4] reported only one reaction (hydrolysis) for spirosulfurane **3**. Some reactions of tetrakis(alkoxysulfurane)[3] **4** and several spirotris(alkoxysulfuranes) have been reported.[9]



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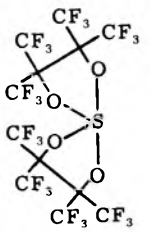


4

In the past few years, considerable interest has centered around the determination of inversion barriers of sulfonium salts.[10-14] Only recently has this interest been extended to sulfuranes[9a,15,16] and selenuranes.[17]

We report here the synthesis and reactions of several new spirobicyclic sulfuranes. The results are compared and contrasted with those for previously reported sulfuranes, with the goal of evaluating the influences of changes in electronegativity of apical ligands and of *gem*-dialkyl substitution on the stability of spirosulfuranes. We also describe the isolation of a pair of diastereomeric sulfuranes with a chiral center at the sulfuranyl sulfur and a determination of the barrier to interconversion of the two by a process involving, at least formally, inversion at sulfur.

Experimental Section

General. Proton chemical shifts are reported on the δ scale, ppm downfield from tetramethylsilane internal standard; fluorine chemical shifts are reported on the ϕ scale, ppm upfield from fluorotrichloromethane internal standard. The ^{1}H NMR and ^{19}F NMR integral ratios are uncorrected.

Solvents and Reagents. Chloroform-*d* and methylene chloride were dried by passage through a column of Woelm basic alumina (activated at 150 °C for 24 h). Ether and tetrahydrofuran (THF) were dried by several additions of sodium wire over several days until further additions caused no further hydrogen evolution. Pyridine-d_5 was obtained in sealed ampules from Merck.

2,2′-Dicarboxydiphenyl Sulfide Diethyl Ester (5). 2,2′-Dicarboxydiphenyl sulfide[18] (4.77 g, 17.4 mmol) and 20 mL of thionyl chloride were combined and boiled overnight. Excess thionyl chloride was removed by high vacuum. The residue was dissolved in 50 mL of benzene and added to a solution of 10 mL of absolute ethanol and 20 mL of pyridine. After 5 min the solvents were removed by vacuum. The residue was dissolved in ether, and the ether solution was extracted with dilute aqueous HCl, dilute aqueous NaOH, and water. The ether solution was dried ($MgSO_4$) and the solvent removed, leaving 4.27 g (74.2%) of diester **5**: mp 64.5–65.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 6, CH_3), 4.35 (q, 4, CH_2), 7.12–7.67 (m, 6, Ar**H**), 7.80–8.17 (m, 2, Ar**H**); mass spectrum (70 eV) *m/e* (rel intensity) 330 (100, M^+·), 239 (19.0), 213 (69.2), 184 (25.6), 137 (10.8), 136 (19.3), 29 (17.4).

Bis[2-(1-hydroxy-1-methylethyl)phenyl] Sulfide (6). Diethyl ester **5** (20.0 g, 0.061 mol) was dissolved in 100 mL of dry ether and added dropwise with stirring to 100 mL of 2.9 M CH_3MgBr (0.29 mol) in ether. After 2 h of boiling the solution was added to a dilute HCl–ice mixture. The ether layer was extracted with dilute aqueous KOH and water and dried (Na_2SO_4), and solvent was removed, leaving a light yellow oil, which upon trituration with pentane gave a light-yellow solid. The solid was recrystallized from ether–pentane to give 15.95 g (87.2%) of white crystalline product: mp 113.5–114.5 °C; IR ($CHCl_3$) 3465 (m, br, OH), 3000 (s), 1466 (s), 1430 (s), 1384 (s), 1364 (s), 1165 (s), 1036 (m), 947 (s), 855 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.76 (s, 12, CH_3), 3.37 (s, 2, OH), 7.00–7.63 (m, 8, Ar**H**); mass spectrum (70 eV) *m/e* (rel intensity) 302 (14.1, M^+·), 284 (3.0, M^+· − H_2O), 266 (10.9, M^+· − $2H_2O$), 251 (42.6, M^+· − $2H_2O$ and CH_3), 227 (15.5), 211 (16.5), 149 (100), 134 (58.1), 115 (33.7), 77 (27.3).

Anal. ($C_{18}H_{22}O_2S$) C, H, S.

1-Chloro-1-[2-(1-hydroxy-1-methylethyl)phenyl]-3,3-dimethyl[3*H*-2,1-benzoxathiole] (7). *tert*-Butyl hypochlorite (1.08 g, 10.0 mmol, 1.13 mL) was added slowly by syringe to a stirred solution of diol **6** (3.01 g, 10.0 mmol) in 50 mL of ether at 0 °C. After 15

min the white precipitate was filtered and washed with ether to give 2.94 g (87%) of 7. This material was recrystallized from CH_2Cl_2–hexane: mp 174.5–177 °C; IR ($CHCl_3$) 3390 (w, br, OH), 2968 (s), 1475 (m), 1443 (m), 1391 (w), 1372 (m), 1302 (w), 1245 (m), 1185 (w), 1152 (m), 1129 (w), 840 (s), 793 (m), 675 cm^{-1} (m); ^1H NMR (CD_2Cl_2) δ 1.86 (s, 6, CH_3), 1.94 (s, 6, CH_3), 7.34–7.75 (m, 6, ArH), 8.20 (br s, 2, ArH, protons ortho to S); mass spectrum (70 eV) *m/e* (rel intensity) no molecular ion, 300 (0.4, $M^+ \cdot$ – HCl), 285 (100, $M^+ \cdot$ – HCl and CH_3), 167 (20.6), 149 (14.1), 91 (10.3), 43 (18.3).

Anal. ($C_{18}H_{21}ClO_2S$) C, H, Cl, S.

3,3,3′,3′-Tetramethyl-1,1′-spiro[3*H*-2,1-benzoxathiole] (8). A sample of 4.08 g (12.1 mmol) of chlorosulfurane **7** was added to a mixture of ether and dilute aqueous KOH in a separatory funnel and shaken until no solid remained. The layers were separated, the ether layer was dried (Na_2SO_4), and the solvent was removed. The white solid remaining was recrystallized from ether–pentane to give 2.98 g (82%) of sulfurane **8**: mp 155–155.5 °C; IR (CCl_4) 2972 (s), 1467 (m), 1443 (s), 1376 (m), 1358 (s), 1287 (m), 1253 (m), 1160 (s), 1032 (m), 956 (s), 882 (s), 628 (s), 540 cm^{-1} (m); ^1H NMR (CD_2Cl_2) δ 1.53 (s, 6, CH_3), 1.63 (s, 6, CH_3), 7.10–7.58 (m, 6, ArH), 8.24–8.42 (m, 2, ArH, protons ortho to S); mass spectrum (70 eV) *m/e* (rel intensity) 300 (0.9, $M^+ \cdot$), 285 (100, $M^+ \cdot$ – CH_3), 167 (22.8), 149 (13.0), 135 (9.9), 43 (18.3).

Anal. ($C_{18}H_{20}O_2S$) C, H, S.

Bis[2-(hydroxymethyl)phenyl] Sulfide (9). Diester **5** (23.48 g, 0.071 mol), in 150 mL of dry ether, was added dropwise to a suspension of $LiAlH_4$ (5 g, 0.13 mol, excess) in 300 mL of dry ether under N_2. After 2 h of boiling, the mixture was carefully added to a dilute aqueous HCl–ice mixture. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether solutions were dried (Na_2SO_4), the solvent was removed, and the product was recrystallized from ether–hexane to give 17.13 g (98%) of diol **9**: mp 109–110 °C; IR ($CHCl_3$) 3630 (m, OH), 2940 (s), 1740 (w), 1470 (m), 1446 (m), 1389 (w), 1032 (m), 1010 (m), 795 (m), 670 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 2.10 (s, 2, OH), 4.76 (s, 4, CH_2), 7.05–7.64 (m, 8, ArH); mass spectrum (70 eV) *m/e* (rel intensity) 246 (100, $M^+ \cdot$), 228 (91.0, $M^+ \cdot$ – H_2O), 213 (61.0), 197 (52.9), 195 (94.6), 184 (31.3), 165 (33.8), 136 (52.5), 91 (47.8), 77 (67.3).

Anal. ($C_{14}H_{14}O_2S$) C, H, S.

1-Chloro-1-(2-hydroxymethyl)phenyl[3*H*-2,1-benzoxathiole] (10). *tert*-Butyl hypochlorite (0.55 g, 5.06 mmol, 0.547 mL) was added by syringe to a stirred solution of diol **9** (1.245 g, 5.06 mmol) in 30 mL of dry THF at 0 °C. After 15 min of stirring the precipitate was filtered, washed with ether, and dried (vacuum) to give 1.01 g (71%) of chlorosulfurane **10**: mp 90–92 °C; IR (KBr) 3430 (s, br, OH), 3140–2800 (s), 1464 (m), 1446 (m), 1218 (m), 1205 (m), 1032 (m), 931 (s), 769 (s), 730 (m), 548 cm^{-1} (m); mass spectrum (70 eV) *m/e* (rel intensity) no molecular ion, 244 (23.4, $M^+ \cdot$ – HCl), 243 (100, $M^+ \cdot$ – HCl and H), 215 (50.6), 197 (96.5), 184 (44.1), 137 (91.8), 109 (47.2), 91 (27.3), 77 (32.9).

Anal. ($C_{14}H_{13}ClO_2S$) C, H, Cl, S.

1,1′-Spiro[3*H*-2,1-benzoxathiole] (11). Method A. Triethylamine (1.89 g, 18.7 mmol) was added to a stirred suspension of 5.29 g (18.7 mmol) of chlorosulfurane **10** in 250 mL of dry ether in an inert atmosphere box. After stirring for 5 days at 25 °C, the mixture was filtered and the filtrate was cooled to −78 °C. After 3 h the deposited crystals were filtered and washed with ether to give 1.18 g (26%) of sulfurane **11**: mp 158–161 °C (sealed tube); IR ($CHCl_3$) 3015 (s), 2853 (m), 1470 (m), 1452 (m), 1258 (w), 1141 (s), 652 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 5.100 and 5.195 (AB pattern, 4, CH_2, J = 14 Hz), 7.14–7.50 (m, 6, ArH), 7.95–8.14 (m, 2, ArH, protons ortho to S); mass spectrum (70 eV) *m/e* (rel intensity) 244 (30.4, $M^+ \cdot$), 243 (100, $M^+ \cdot$ – H), 226 (22.7, $M^+ \cdot$ – H_2O), 215 (48.1), 197 (99.1, $M^+ \cdot$ – CH_3O_2), 184 (28.9), 165 (23.0), 237 (82.0), 109 (39.1), 91 (20.9), 77 (27.9).

Anal. ($C_{14}H_{12}O_2S$) C, H, S.

Method B. About 1 g (~0.025 mol) of potassium hydride was added to a mixture of 3.88 g (0.0138 mol) of chlorosulfurane **10** in 150 mL of dry THF in an inert atmosphere box. Hydrogen evolution occurred, and after 1 h the mixture was filtered. The solvent was removed leaving yellowish crystalline **11**, 2.33 g (69%).

2-Bromo-2′-carboxydiphenyl Sulfide. 2-Bromothiophenol[19] (28.7 g, 0.152 mol) and 2-iodobenzoic acid (37.7 g, 0.152 mol) were dissolved in 300 mL of water containing about 20 g of potassium hydroxide and 0.5 g of copper bronze. The solution was boiled 8 h and filtered while hot. After cooling to 25 °C, the solution was acidified with concentrated HCl. The precipitate was filtered, washed with water and air dried to give 45.0 g (95.8%) of the acid: mp 184–185 °C; IR (KBr) 3440 (s, OH), 3000 (s, br), 1682 (s, C=O), 1587 (w), 1560 (w), 1462 (m), 1416 (m), 1312 (m), 1290 (m), 1270 (s), 1258 (s), 1149 (m), 1056 (m), 1040 (m), 1020 (m), 750 cm^{-1} (s); ^1H NMR (Me_2SO-d_6) δ 6.60–6.83 (m, 1, ArH), 7.10–8.10 (m, 7, ArH), 13.1 (br s, 1, OH); mass spectrum (70 eV) *m/e* (rel intensity) 310 (71.4, $M^+ \cdot$ ^{81}Br), 308 (69.6, $M^+ \cdot$ ^{79}Br) 229 (45.6, $M^+ \cdot$ – Br), 212 (10.2, $M^+ \cdot$ – Br and OH), 185 (22.6), 184 (55.2), 183 (20.8), 139 (22.2), 137 (100), 136 (32.0), 108 (20.4), 69 (12.7).

Anal. ($C_{13}H_9BrO_2S$) C, H, Br, S.

2-Bromo-2′-carboxydiphenyl Sulfide Ethyl Ester (12). 2-Bromo-2′-carboxydiphenyl sulfide (34 g, 0.11 mol) was dissolved in excess thionyl chloride and refluxed for 5.5 h. The excess $SOCl_2$ was removed in vacuum, leaving a red solid. The solid acid chloride was dissolved in benzene and added to a solution of EtOH and pyridine. After a few minutes of swirling, the mixture was stripped of solvent and the residue was dissolved in ether and extracted with dilute aqueous HCl, dilute aqueous NaOH, and water. The ether layer was dried ($MgSO_4$) and ether removed, leaving an amber oil which crystallized after 1 day: 32.3 g (87%); mp 59–63 °C; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3, CH_3), 4.37 (q, 2, CH_2), 6.75–7.15 (m, 8, ArH); mass spectrum (70 eV) *m/e* (rel intensity) 338 (82.3, $M^+ \cdot$ ^{81}Br), 336 (79.1, $M^+ \cdot$ ^{79}Br), 293 (9.8, $M^+ \cdot$ ^{81}Br – OEt), 291 (10.5, $M^+ \cdot$ ^{79}Br – OEt) 257 (32.3, $M^+ \cdot$ – Br) 229 (100), 212 (70.8, $M^+ \cdot$ – OEt and Br), 184 (84.8), 139 (32.6), 137 (32.7), 108 (21.9).

Anal. ($C_{15}H_{13}BrO_2S$) C, H, Br, S.

2-Bromo-2′-(1-hydroxy-1-methylethyl)diphenyl Sulfide (13). Ester **12** (15.8 g, 0.047 mol) was dissolved in 150 mL of dry ether and added dropwise to a stirred solution of 50 mL of 2.86 M CH_3MgBr in ether (0.14 mol) to maintain gentle reflux. After this addition, the solution was stirred for 30 min at room temperature, and then quenched with saturated aqueous NH_4Cl. The ether layer was extracted with aqueous HCl and water and dried ($MgSO_4$), and ether was removed to give 13.7 g (90.4%) of **13** as a light yellow viscous oil: IR (neat) 3450 (s, OH), 3100–2900 (s), 1580 (s), 1450 (s), 1360 (s), 1250 (s), 1170 (s), 1140 (s), 1110 (s), 1050 (s), 1043 (s), 1023 (s), 955 (s), 860 (s), 755 (s), 710 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.71 (s, 6, CH_3), 3.36 (br s, 1, OH), 6.76–7.83 (m, 8, ArH); mass spectrum (70 eV) *m/e* (rel intensity) 324 (63.4, $M^+ \cdot$ ^{81}Br), 322 (63.9, $M^+ \cdot$ ^{79}Br), 309 (50.6, $M^+ \cdot$ ^{81}Br – CH_3), 307 (50.0, $M^+ \cdot$ ^{79}Br – CH_3), 228 (29.0, $M^+ \cdot$ – Br and CH_3), 213 (27.8, $M^+ \cdot$ – Br and $2CH_3$), 210 (42.8), 185 (11.3), 184 (22.3), 151 (100), 149 (12.6), 108 (15.6), 59 (17.2), 43 (63.1).

Anal. ($C_{15}H_{15}BrOS$), C, H, Br, S.

2-(1-Hydroxy-1-methylethyl)-2′-(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)diphenyl Sulfide (14). Bromo alcohol **13** (4.52 g, 13.98 mmol), in 150 mL of dry ether in a flask equipped with a dry ice condenser, was cooled to 0 °C, 15 mL of *n*-butyllithium in hexane (ca. 2.1 M, 31.5 mmol, slight excess) was added by syringe, and the solution was stirred for 0.5 h at 25 °C. Hexafluoroacetone was bubbled in (7 mL, 9.8 g, excess), and the mixture was stirred for 10 min and added to a saturated NH_4Cl ice–water solution. Ether was added and the mixture was shaken. The ether layer was washed with water and dried ($MgSO_4$) and solvent was removed, leaving 6.25 g of red oil. The oil was chromatographed on a column of silica gel (50-cm long, 4.5-cm diameter) using chloroform as eluent. The fraction containing diol **14** (2.18 g) was rechromatographed on another silica gel column (26 × 3 cm) using 1:1 ether–hexane as eluent and again on a 2-in. column of silica gel containing activated charcoal with 1:1 ether–hexane: 1.844 g (32.1%) of light yellow solid; mp 99.5–103 °C; IR ($CHCl_3$) 3600 (w, free OH), 3250 (m, hydrogen bonded OH), 3000 (w), 1472 (w), 1437 (w), 1387 (w), 1370 (w), 1300–1170 (four or five strong bands, CF_3 stretch), 1152 (m), 1114 (m), 1040 (w), 965 (m), 952 (m), 931 (m), 715 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 1.78 (s, 6, CH_3), 2.76 (s, 1, disappears with D_2O shake, OH), 6.90–7.66 (m, 7, ArH), 7.80 (br, 1, ArH, proton ortho to carbon bearing $2CF_3$), 7.92 (s, 1, disappears with D_2O shake, OH); ^{19}F NMR ($CDCl_3$) ϕ 74.52 (s, 6, CF_3); mass spectrum (70 eV) *m/e* (rel intensity) 410 (46.6, $M^+ \cdot$), 395 (32.7 $M^+ \cdot$ – CH_3), 377 (6.4, $M^+ \cdot$ – CH_3 and H_2), 210 (20.0), 151 (49.0), 149 (27.3), 128 (9.4), 59 (10.4), 43 (100).

Anal. ($C_{18}H_{16}F_6O_2S$) C, H, F, S.

Another method used to prepare **14** using activated magnesium[20] resulted in purer material, but yields were quite variable.

3,3-Bis(trifluoromethyl)-3′,3′-dimethyl-1,1′-spiro[3*H*-2,1-benzoxathiole] (15). Diol **14** (1.70 g, 4.1 mmol) was dissolved in 50 mL of ether and cooled to 0 °C. *tert*-Butyl hypochlorite (0.45 g, 0.47 mL, 4.1 mmol) was added dropwise with stirring. A very small amount of white precipitate was noted. After 1 h, the ether solution was extracted with dilute aqueous NaOH and dried ($MgSO_4$), and solvent was removed to give a white solid. The crude product was recrystallized from CH_2Cl_2–ether–hexane to give 1.1 g (65.6%) of white, crystalline sulfurane **15**: mp 167.5–168.5 °C; IR ($CDCl_3$) 3000 (w), 1470 (w), 1448 (w), 1296 (m), 1267 (m), 1210 (s), 1167 (m), 1150 (s), 1131 (m), 1054 (w), 970 (m), 954 (m), 877 (w), 660 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.65 (s, 3, CH_3), 1.83 (s, 3, CH_3), 7.23–8.00 (m, 6, ArH), 8.27–8.67 (m, 2, ArH, protons ortho to S); mass spectrum (70 eV) *m/e*

(rel intensity) 408 (0.5, $M^{+}\cdot$), 393 (100, $M^{+}\cdot - CH_3$), 339 (16.2, $M^{+}\cdot - CF_3$), 213 (6.0), 212 (4.9), 205 (8.6), 184 (7.2), 151 (12.7), 149 (11.4), 91 (12.3), 43 (23.7).

Anal. ($C_{18}H_{14}F_6O_2S$) C, H, F, S.

2-(1-Hydroxy-1-methylethyl)-2′-(1-hydroxy-1-methylpropyl)diphenyl Sulfide (16). Bromo alcohol **13** (10.7 g, 33.1 mmol) in 200 mL of dry ether was cooled to 0 °C and 45 mL of *n*-butyllithium in hexane (ca. 2.1 M, 94.5 mmol, excess) was added by syringe. After stirring the mixture at 25 °C for 0.75 h, methyl ethyl ketone (10 mL, excess) was added. The mixture was stirred for 15 min and added to a saturated NH_4Cl ice–water solution. An ether extract was washed with water and dried ($MgSO_4$), and solvent was removed to give 15.04 g of yellow liquid. This was chromatographed on a column of silica gel (96-cm long by 3-cm diameter) using chloroform as eluent. The fraction of diol **16** (4.38 g) was treated with activated charcoal and passed through a short column of silica gel containing some activated charcoal to give a light yellow oil: 4.02 g (38.4%); ^1H NMR ($CDCl_3$) δ 0.85 (t, 3, CH_2CH_3), 1.73 (s, 3, CH_3), 1.78 (s, 6, CH_3), 2.00 (m, 2, CH_2), 3.45 (br s, 2, OH, disappears with D_2O shake), 7.10–7.45 (m, 6, ArH), 7.45–7.80 (m, 2, ArH); mass spectrum (70 eV) *m/e* (rel intensity) 316 (6.7, $M^{+}\cdot$), 283 (1.0, $M^{+}\cdot - H_2O$ and CH_3), 269 (4.6, $M^{+}\cdot - H_2O$ and CH_2CH_3), 251 (2.4), 227 (6.9), 211 (4.0), 155 (6.4), 151 (12.4), 127 (10.3), 115 (30.0), 57 (100), 43 (53.6).

Anal. ($C_{19}H_{24}O_2S$) C, H, S.

The Exo and Endo Isomers of 3,3,3′-Trimethyl-3′-ethyl-1,1′-spiro[3*H*-2,1-benzoxathiole] (17a, 17b). *tert*-Butyl hypochlorite (1.36 mL, 1.30 g, 12.0 mmol) was added by syringe to a solution of diol **16** (3.79 g, 11.98 mmol) in 200 mL of dry ether at 25 °C. A yellow precipitate was filtered and washed with ether. The yellow solid was suspended in 75 mL of ether and shaken with dilute aqueous NaOH until the solid dissolved. The ether layer was separated and dried ($MgSO_4$) and solvent was evaporated leaving a light yellow oil which slowly solidified after a few days. Analysis by ^1H NMR showed a 50:50 mixture of exo and endo isomers of sulfurane **17** (2.64 g, 70.1%). All attempts to recrystallize this material failed. Analysis by TLC showed some impurities, so a sample of 2.23 g of the mixture was chromatographed on a column of 117 g of Woelm neutral alumina, activity grade 1, using 1:1 (v/v) ether–hexane. The first fraction (0.36 g) was a 83/17 mixture of exo and endo isomers. A sample of this mixture (280 mg) was recrystallized from hexane at −20 °C. A total of 211 mg of an 89/11 mixture of exo and endo isomers was isolated: mp 83–85 °C; IR (CCl_4) 3118 (w), 3065 (w), 2975 (s), 2925 (m), 1466 (m), 1441 (m), 1375 (m), 1365 (w), 1356 (m), 1286 (w), 1251 (w), 1159 (s), 1030 (m), 961 (m), 920 (m), 882 (m), 624 cm^{-1} (s); ^1H NMR (220 MHz, pyridine-d_5) **17a** (exo), δ 0.794 (t, 3, CH_2CH_3, J = 7.3 Hz), 1.606 (s, 3, exo-CH_3), 1.682 (s, 6, *endo*-CH_3), 1.72–2.05 (m, 2, CH_2CH_3), 7.11–7.57 (m, 6, ArH), 8.55–8.73 (m, 2, ArH, protons ortho to S); **17b** (endo), δ 1.138 (t, 3, CH_2CH_3, J = 7.3 Hz), 1.522 (s, 3, *exo*-CH_3 on same carbon as C_2H_5), 1.606 (s, 3, other *exo*-CH_3), 1.70 (s, 3, *endo*-CH_3), other peaks were obscured by those of the major isomer; mass spectrum (70 eV) *m/e* (rel intensity), no molecular ion, 299 (30.3 $M^{+}\cdot - CH_3$), 285 (100, $M^{+}\cdot - CH_2CH_3$), 167 (25.1), 151 (11.8), 149 (10.0), 135 (11.6), 91 (9.3).

Anal. ($C_{19}H_{22}O_2S$) C, H, S.

Further elution with 1:1 (v/v) ether–hexane failed to give any more product. Elution with methanol was necessary to obtain the remaining material (1.77 g). ^1H NMR analysis of this material in $CDCl_3$ showed it to be 50% sulfurane (79% exo, 21% endo) and 50% sulfoxide diol. Hydrolysis had occurred on the column and partial cyclodehydration of the diol in $CDCl_3$.

Interactions of Spirosulfuranes 8 and 15 with Optically Active Solvent. To a solution of 19.4 mg (0.065 mmol) of sulfurane **8** in 0.5 mL of carbon tetrachloride (0.13 M) was added 45.0 mg (0.255 mmol, 0.51 M) of L(−)-2,2,2-trifluoro-1-phenylethanol.[21] The 220-MHz ^1H NMR spectrum showed four resolved methyl singlets at δ 1.460, 1.486, 1.572, and 1.596. Also, the two protons ortho to sulfur, which are normally seen as one doublet, were resolved into two doublets (δ 8.12, 8.19) in the presence of the chiral solvent. To a solution of 25.7 mg (0.063 mmol) of sulfurane **15** in 0.5 mL of carbon tetrachloride (0.126 M) was added 45.9 mg (0.261 mmol, 0.52 M) of L(−)-2,2,2-trifluoro-1-phenylethanol.[21] The 220-MHz ^1H NMR spectrum showed four resolved methyl singlets at δ 1.568, 1.592, 1.760, and 1.774.

Hydrolysis of Sulfurane 8 to Sulfoxide Diol 18. Sulfurane **8** (1.01 g, 3.37 mmol) was boiled in 11 mL of 10:1 methanol–water solution for 2 h. The solvent was removed in vacuum leaving a clear semisolid which was dissolved in ether. Evaporation of the ether afforded 0.953 g (89%) of crystalline sulfoxide diol **18**: mp 139–144 °C; IR ($CHCl_3$) 3380 (m, OH), 3000 (s), 1472 (w), 1437 (w), 1388 (w), 1370 (m), 1245 (w), 1184 (w), 1110 (w), 1056 (w), 998 (m), 965 (m), 588 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 1.38 (s, 6, CH_3), 1.70 (s, 6, CH_3), 4.78 (br s, 2, OH), 7.01–7.75 (m, 8, ArH); mass spectrum (70 eV) *m/e* (rel intensity) 318 (6.0, $M^{+}\cdot$), 303 (10.1, $M^{+}\cdot - CH_3$), 300 (0.3, $M^{+}\cdot - H_2O$), 285 (100, $M^{+}\cdot - H_2O$ and CH_3), 167 (27.8), 151 (21.9), 149 (54.4), 135 (22.2), 91 (14.0), 43 (37.3).

Anal. ($C_{18}H_{22}O_3S$) C, H, S.

Sulfurane **18** (47 mg, 0.156 mmol) was dissolved in 0.5 mL of dry $CDCl_3$ to which was added 10 μL (0.55 mmol) of deuterium oxide. After 7.5 h at 25 °C less than 5% hydrolysis to **18** was noted. After 13 days at 25 °C, 25% hydrolysis to **18** had occurred.

Hydrolysis of Dibenzyloxysulfurane 11. To a solution of sulfurane **11** (36.3 mg, 0.149 mmol) in 0.5 mL of dry chloroform-*d* was added 10 μL (0.55 mmol) of deuterium oxide. ^1H NMR analysis showed that **11** was 94% hydrolyzed to sulfoxide diol **19** after 3.6 h at 25 °C and that hydrolysis was essentially complete after 7.1 h at 25 °C.

Bis[2-(hydroxymethyl)phenyl] Sulfoxide (19). A solution of 2.32 g of 85% *m*-chloroperbenzoic acid (MCPBA) (11.4 mmol) in 50 mL of $CHCl_3$ was added dropwise to a solution of sulfide diol **9** (2.81 g, 11.4 mmol) in 150 mL of $CHCl_3$ at 0 °C. After stirring at 25 °C for 36 h the $CHCl_3$ solution was extracted with aqueous $NaHCO_3$ and dried (Na_2SO_4), and solvent was removed to afford a light yellow oil which crystallized after 10 min leaving 2.1 g (70%) of sulfoxide **19**: mp 128–129 °C; IR (KBr) 3280 (s br, OH), 3065 (s), 2930 (s), 1470 (s), 1455 (s), 1444 (s), 1370 (s), 1217 (m), 1202 (s), 1166 (m), 1067 (m), 1050 (s), 1041 (s), 1031 (s), 994 (s), 820 (m), 766 (s), 608 (m), 542 (s), 529 (m), 454 cm^{-1} (m); ^1H NMR (CF_3COOH) δ 5.75 (s, 4, CH_2), 7.46–8.04 (m, 8, ArH); mass spectrum (70 eV) *m/e* (rel intensity), no molecular ion, 244 (3.8 $M^{+}\cdot - H_2O$), 197 (100), 165 (13.3), 138 (18.0), 137 (19.9), 109 (24.6), 91 (8.9), 77 (48.5).

Anal. ($C_{14}H_{14}O_3S$) C, H, S.

Attempted Hydrolysis of Spirosulfurane 15. Method A. A sample of spirosulfurane **15** (166 mg, 0.41 mmol) was added to 5 mL of 10% aqueous methanol and boiled for 4.75 h. Upon cooling, crystals of **15** (134 mg, 72.3%) were deposited.

Method B. Spirosulfurane **15** (149 mg, 0.36 mmol) was dissolved in 1 mL of tetrahydrofuran-d_8 containing 10 μL of water. Boiling for 0.5 h caused no change in the ^1H NMR spectrum. Concentrated HCl (10 μL) was added and the solution was boiled 1 h more. No change in the ^1H NMR spectrum was noted. Addition of 0.85 mL of 50% aqueous KOH rendered the solution basic. Boiling of this solution for 1 h caused no change in the ^1H NMR spectrum.

Reactions of Sulfurane 8 with Acids. (a) Hydrochloric Acid. Sulfurane **8** (0.702 g, 2.34 mmol), in 20 mL of CH_2Cl_2, was shaken with 10 mL of concentrated aqueous HCl. The organic layer was dried ($MgSO_4$) and solvent was removed. The product was recrystallized from CH_2Cl_2–hexane to give 0.60 g (76.5%) of chlorosulfurane **7**: mp 173.5–176 °C.

(b) Hydrobromic Acid. A comparable experiment using 16% aqueous HBr gave 72.8% of bromosulfurane **21**: mp 169.5–170.5 °C; IR ($CHCl_3$) 3400 (w), 2960 (s, br), 1472 (m), 1441 (m), 1389 (m), 1370 (m), 1239 (m), 1150 (m), 1125 (m), 835 (s), 665 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.97 (s, 6, CH_3), 2.05 (s, 6, CH_3), 7.45–8.00 (m, 6, ArH), 8.00–8.41 (m, 2, ArH, protons ortho to S).

Anal. ($C_{18}H_{21}BrO_2S$) C, H, Br, S.

(c) Fluoroboric Acid. A comparable procedure using 25% aqueous fluoroboric acid gave, after recrystallization from CH_2Cl_2–hexane, 81.6% of sulfonium salt **22a**: mp 197–199 °C; IR ($CHCl_3$) 3350 (m, OH), 3040 (m), 2990 (m), 1475 (m), 1445 (m), 1370 (m), 1150 (m), 1055 (s, B–F stretch), 835 (s), 670 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 1.87 (s, 6, CH_3), 2.01 (s, 6, CH_3), 6.67 (br s, 1, OH), 7.38–7.90 (m, 6, ArH), 7.90–8.30 (m, 2, ArH, protons ortho to S).

Anal. ($C_{18}H_{21}BF_4O_2S$) C, H, S.

(d) *d*-10-Camphorsulfonic Acid. Methylene chloride solutions of **8** (1.84 g, 6.13 mmol) and *d*-10-camphorsulfonic acid (1.42 g, 6.13 mmol) were combined and stirred for 15 min. Solvent removal left a thick clear oil which crystallized after 9 days. Recrystallization from CH_2Cl_2–ether–hexane gave 2.2 g (68%) of sulfonium salt **22c**: mp 166–168 °C; IR ($CHCl_3$) 3020 (s), 1746 (s), 1448 (w), 1375 (w), 1320–1100 (s), 1038 (s), 843 (s), 675 cm^{-1} (m).

Anal. ($C_{28}H_{36}O_6S_2$) C, H, S.

After two recrystallizations, the material was checked for any change in the optical activity compared to the unrecrystallized material. No change was detectable.

(e) Trifluoromethanesulfonic (Triflic) Acid. Triflic acid (0.50 g, 3.33 mmol, 0.294 mL), added by syringe to a solution of sulfurane **8** (1.0 g, 3.33 mmol) in 90 mL of ether at 0 °C, immediately gave a white precipitate. After overnight stirring at 25 °C, the solid was filtered, washed with ether, and air dried to give 1.486 g (99%) of sulfonium salt **22b**: mp 166–169 °C; IR ($CHCl_3$) 3130 (m), 3020 (m), 1376 (m), 1300 (s), 1253 (s), 1180 (s), 1033 (s), 839 (s), 640 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.70–2.20 (singlet and broad singlet overlapping, 12, CH_3),

7.30–7.90 (m, 8, ArH), 8.25 (br s, 1, OH); mass spectrum (70 eV) *m/e* (rel intensity) no molecular ion, 302 (3.7), 301 (1.3, M^+ · − OTf), 285 (100, M^+ · − HOTf and CH_3), 265 (39.5), 249 (27.2, 167 (24.4), 149 (64.0), 115 (25.5), 91 (20.7), 77 (12.2), 69 (82.1).

Anal. ($C_{19}H_{21}F_3O_5S_2$) C, H, S.

(f) Acetic Acid. TO SULFURANE — (121 mg, 0.403 mmol), in 0.5 mL of dry $CDCl_3$, was added 23 μL (24.2 mg, 0.403 mmol) of glacial acetic acid. No changes in the ^1H NMR spectrum of **8** were noted after 20 h at 25 °C.

Low-Temperature ^1H NMR Studies on Chlorosulfurane 7. Low-temperature 100-MHz ^1H NMR studies on chlorosulfurane **7** were carried out in CD_2Cl_2 solution from 28 to −95 °C. At 28 °C, six aromatic protons were seen as a multiplet at δ 7.34–7.75 and the two ortho protons to sulfur were seen as a broad singlet at δ 8.20. On cooling, continued broadening of the peak at δ 8.20 occurred. At −95 °C, one ortho proton was seen as a doublet at δ 8.55 and the other became a part of the aromatic multiplet (δ 7.3–8.2) which integrated for seven protons. A new singlet was observed at δ 10.33 which is assigned to the hydroxyl proton, hydrogen bonded to the chlorine atom. The methyl groups of **7** at 28 °C were seen as two singlets. On cooling, one of them broadened more rapidly than the other one. At −95 °C only a single broad peak at δ 1.92 was seen whose width at half-height was 0.5 ppm. Throughout the study, the sample remained homogeneous.

Reaction of Chlorosulfurane 7 with Diazasulfurane 24. Samples of **7** (97.5 mg, 0.29 mmol) and **24** (103.5 g, 0.29 mmol) were dissolved in ca. 1.5 mL of dry $CDCl_3$ at 25 °C. Subsequent ^1H NMR analysis showed the presence of sulfurane **8** and chloroazasulfurane **23**.

Reaction of Sulfurane 8 with Methyl Fluorosulfonate. Methyl fluorosulfonate (0.565 g, 4.95 mmol, 0.4 mL) was added by a syringe to a solution of sulfurane **8** (0.909 g, 3.03 mmol) in 80 mL of ether. After stirring at 25 °C for 11 h the precipitate was filtered, washed with ether, and air dried. A yield of 0.924 g (74%) of monocyclic sulfonium fluorosulfonate **25** was obtained: mp 153–154 °C; IR ($CHCl_3$) 3040 (s), 1469 (m), 1450 (m), 1395 (m), 1377 (m), 1293 (s), 1152 (m), 1134 (m), 1073 (s), 1057 (m), 942 (m), 840 (s), 588 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.78 (s, 3, CH_3), 1.87 (s, 3, CH_3), 1.98 (s, 3, CH_3), 2.17 (s, 3, CH_3), 3.73 (s, 3, OCH_3), 7.30–8.05 (m, 8, ArH); mass spectrum (70 eV) *m/e* (rel intensity) no molecular ion, 315 (1.2, M^+ · − O_3SF), 314 (6.1, M^+ · − HO_3SF), 265 (89.2), 211 (22.7), 165 (14.0), 149 (100), 134 (45.6), 115 (47.9), 91 (43.3), 77 (19.6).

Anal. ($C_{19}H_{23}FO_5S_2$) C, H, S.

Reactions of Spirosulfurane 8 and 15 with Acetyl Chloride. To a sample of sulfurane **8** (346.5 mg, 1.15 mmol) dissolved in 1 mL of dry $CDCl_3$ was added 82 μL (1.15 mmol) of acetyl chloride. The reaction was complete within 3.5 h at 25 °C (^1H NMR). The chlorosulfurane **26** was crystallized from a $CDCl_3$–CH_2Cl_2–ether–hexane solvent mixture: 344.7 mg (79%); mp 129–132 °C; IR ($CHCl_3$) 3380 (w, OH, slight hydrolysis), 2960 (s), 1742 (s, C=O), 1470 (m), 1443 (m), 1288 (m), 1370 (s), 1243 (s), 1150 (s), 1120 (s), 1018 (m), 935 (m), 836 (s), 666 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.23 (s, 3, CH_3), 1.73 (s, 3, CH_3), 2.06 (s, 3, CH_3), 2.20 (s, 3, acetyl CH_3), 2.26 (s, 3, CH_3), 6.73 (d, 1, ArH, J = 8 Hz), 7.13 (m, 1, ArH), 7.45–8.00 (m, 5, ArH), 9.54 (d, 1, proton ortho to S on the fused ring, J = 8 Hz).

Anal. ($C_{20}H_{23}ClO_3S$) C, H, Cl, S.

To a sample of sulfurane **18** (78.5 mg, 0.192 mmol) dissolved in 1 mL of dry $CDCl_3$ was added 14 μL (0.197 mmol) of acetyl chloride. After 21.5 h at 25 °C, ^1H NMR analysis showed that no reaction had taken place.

Attempted Reaction of Spirosulfurane 8 and Benzoyl Fluoride. Sulfurane **8** (190.7 mg, 0.634 mmol) and benzoyl fluoride (78.9 mg, 0.635 mmol) were combined in 1.1 mL of dry $CDCl_3$ at 25 °C. After 80 h no change in the ^1H NMR spectrum was evident. After 19 days at 25 °C a few small peaks in the aliphatic region were seen (7% of total aliphatic integral). A catalytic amount of BF_3 was added, but even after 24 h at 25 °C no further change in the ^1H NMR spectrum was noted.

Reduction of Sulfurane 8 to Sulfide Diol 6. (a) With Lithium Aluminum Hydride. Sulfurane **8** (1.065 g, 3.54 mmol), in 25 mL of dry THF, was added dropwise to a solution of excess $LiAlH_4$ in 25 mL of THF under N_2. The solution was boiled for 2 h and added to an ice–water mixture. The THF was removed in vacuum and the aqueous layer was extracted with ether three times. The ether layer was dried ($MgSO_4$) and solvent was removed to give sulfide diol **6**, an oil which crystallized after 24 h: 0.98 g (91.5%).

(b) With Hydriodic Acid. Sulfurane **8** (1.13 g, 3.76 mmol), in 20 mL of methylene chloride, was shaken with 30 mL of 19% aqueous HI. Almost immediately the mixture became very dark red (I_2). The CH_2Cl_2 layer was extracted with aqueous sodium thiosulfate and dried ($MgSO_4$), and solvent was removed, which left a solid mixture of sulfide diol **6** (68%) and sulfurane **8** (32%) (^1H NMR analysis).

Interaction of Spirosulfuranes with Eu(fod)$_3$.[22] (a) Sulfurane 8 (22.2 mg, 0.074 mmol) in 1.0 mL of CCl_4 (0.074 M) was examined by ^1H NMR before and after successive additions of Eu(fod)$_3$ until the concentration of Eu(fod)$_3$ reached 0.073 M. Relative concentrations were determined through comparison of the integrals of the *tert*-butyl groups of Eu(fod)$_3$ and the methyl resonances of sulfurane **8**. The *exo*-methyls (δ 1.51) shift rapidly downfield (82.4 ppm/M), with a linear dependence of Eu(fod)$_3$ concentration, with much peak broadening. The *endo*-methyls shift downfield more slowly (32.4 ppm/M) with less peak broadening. At a Eu(fod)$_3$ concentration of 0.026 M, the aromatic protons were resolved into two triplets at δ 7.24 and 7.58 and two doublets at δ 7.87 and 9.06. The doublet at δ 9.06 represents the two protons ortho to sulfur.

In a parallel experiment at a higher initial concentration of **8** (0.26 M), at concentrations of Eu(fod)$_3$ up to 0.22 M significantly smaller concentration dependence of chemical shifts were seen for the *exo*-methyls (23.0 ppm/M) and the *endo*-methyls (9.3 ppm/M), evidence for a large formation constant for the Eu(fod)$_3$ complex. In this experiment, the protons ortho to sulfur shifted downfield at a rate of 7.1 ppm/M.

(b) Sulfurane 15 (30.1 mg, 0.074 mmol) in 1.0 mL of CCl_4 (0.074 M) was examined in the same way with increments of Eu(fod)$_3$ up to a concentration of 0.069 M. The interaction of **15** with Eu(fod)$_3$ is much weaker than with sulfurane **8**, as evidenced by smaller downfield shifts for the methyl singlets at δ 1.60 (3.92 ppm/M) and 1.76 (.378 ppm/M) as Eu(fod)$_3$ concentration was increased.

(c) Diastereomeric Sulfuranes 17 (40.8 mg, 0.13 mmol, 86/14 mixture of **17a** and **17b**) in 0.5 mL of CCl_4 (0.26 M total) was examined as above at Eu(fod)$_3$ concentrations up to 0.193 M. Downfield shifts for the *exo*-methyl at δ 1.51 (36.1 ppm/M) and the two *endo*-methyls at δ 1.60 (14.5 and 5.5 ppm/M) were assigned to the major isomer (**17a**), along with the peak for the two ortho protons of **17a**, at δ 8.31 (10.7 and 2.7 ppm/M).

The ortho protons of **17b** were located between the ortho protons of **17a**. The peaks were too indistinct after broadening by Eu(fod)$_3$ to allow a similar study to be performed for the minor isomer **17b**.

Interaction of Sulfurane 8 Simultaneously with Chiral Alcohol and Eu(fod)$_3$. Sulfurane **8** (30 mg, 0.10 mmol) and (*S*)-(+)-2,2,2-trifluoro-9-(anthryl)ethanol[23] (82.5 mg, 0.30 mmol) in 0.5 mL of CCl_4 (0.2 M in **8**, 0.6 M in carbinol) was examined as above with incremental addition of Eu(fod)$_3$ to a final concentration of 0.16 M. Initially, only one of the methyl peaks split into two peaks (δ 1.18, 1.34) and during addition of Eu(fod)$_3$ the peak (δ 1.23) that was unsplit broadened and moved rapidly downfield. Hence, this peak was assigned to the *exo*-methyls by comparing the results of the interaction of **8** with Eu(fod)$_3$ only. The other singlet that was split into two singlets moved downfield more slowly. The separation of the two singlets stayed nearly the same. Only when the molar ratio reached about 0.53 did a small change occur.

Pyrolyses of Spirosulfuranes 8, 11, and 15. Sulfurane **8** (0.695 g, 2.31 mm) was heated to 205 °C for 20 min leaving an amber oil. This oil was dissolved in CH_2Cl_2, the solution was dried ($MgSO_4$), and solvent was removed to give 0.464 g (71.3%) of sulfoxide–diolefin **27**: IR (neat) 3040–2900 (s), 1825 (w), 1640 (s), 1585 (s), 1465 (s), 1425 (s), 1370 (s), 1300 (m), 1245 (m), 1160 (w), 1110 (s), 1065 (s), 1030 (s), 907 (s), 765 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.90 (m, 6, CH_3), 5.01 (m, 2, vinyl CH), 5.16 (m, 2, vinyl CH), 7.00–7.90 (m, 8, ArH); mass spectrum (70 eV) *m/e* (rel intensity) 282 (0.9, M^+ ·), 266 (25.5), 265 (64.4), 264 (11.5), 251 (16.4), 249 (20.4), 234 (15.2), 210 (15.5), 151 (23.0), 149 (100), 147 (30.4), 134 (39.2), 115 (34.9), 91 (28.2), 77 (12.7).

Anal. ($C_{18}H_{18}OS$) C, H, S.

Spirosulfurane **11** (138.7 mg, 0.57 mmol) was heated to 180 °C for 10 min. Analysis by ^1H NMR showed that fragmentation to *o*-arylthiobenzaldehyde **28** was 90% complete. Chromatography on a short column of silica gel (5 g) with chloroform gave 83 mg (60%) of sulfide **28** as a light yellow oil: IR ($CHCl_3$) 3620 (w, OH), 2860 (w, aldehyde CH), 2755 (w, aldehyde CH), 1697 (s, C=O); ^1H NMR ($CDCl_3$) δ 2.36 (br s, 1, OH), 4.72 (s, 2, CH_2), 6.70–6.95 (m, 1, ArH), 7.10–7.65 (m, 6, ArH), 7.70–7.90 (m, 1, ArH), 10.24 (s, 1, aldehyde CH); mass spectrum (70 eV) *m/e* (rel intensity) 244 (4.9, M^+ ·), 226 (5.7, M^+ · − H_2O), 197 (31.3, M^+ · − CH_3O_2), 85 (66.4), 83 (100), 47 (20.4). After 3 days, ^1H NMR analysis showed that a new compound was forming, possibly the dibenzyl ether. Also, infrared analysis showed another carbonyl absorption at 1681 cm^{-1}.

Two samples (76 mg and 36.3 mg) of spirosulfurane **15** were heated to 205 °C for 20 min and to 295 °C for 10 min, respectively. ^1H NMR analysis showed that no reaction had occurred in either procedure. Another sample (23 mg), heated to 355 °C for 15 min, gave a nearly

black product whose ^1H NMR in $CDCl_3$ showed that the sulfurane was completely gone. There were characteristic peaks for the 2-propenyl group and other unidentified peaks were seen. The ^{19}F NMR showed no quartets but showed a series of singlets or doublets near ϕ 74.7. No products were isolated from this reaction.

Reaction of Sulfide Diols with 2 Equiv of *m*-Chloroperbenzoic Acid. (a) Sulfide Diol 6. A solution of MCPBA (1.40 g of 85% peracid, 6.90 mmol of peracid) in 15 mL of chloroform was added dropwise to a cooled solution of sulfide diol **6** (1.04 g, 3.45 mmol) in 25 mL of $CHCl_3$. After stirring for 3 days at 25 °C, the solution was twice extracted with aqueous Na_2HCO_3 and dried (Na_2SO_4), and solvent was removed leaving 1.09 g (95%) of sulfone **29** which was recrystallized from CH_2Cl_2–hexane: mp 165.5–167 °C; IR ($CHCl_3$) 3480 (s, OH), 3000 (s), 1435 (w), 1367 (m), 1290 (s), 1151 (s), 1134 (s), 1115 (s), 966 (m), 599 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.70 (s, 12, CH_3), 4.40 (br s, 2, OH), 7.10–7.93 (m, 8, ArH); mass spectrum (70 eV) *m/e* (rel intensity) no molecular ion, 302 (12.1), 301 (54.8, $M^+ - H_2O$ and CH_3), 283 (1.2, $M^+ - 2H_2O$ and CH_3), 259 (12.1), 237 (17.7), 183 (100), 134 (21.1), 115 (27.8), 91 (82.3), 77 (31.7).

Anal. ($C_{18}H_{22}O_4S$) C, H, S.

(b) Sulfide Diol 9. A solution of 1.97 g of 85% MCPBA (9.76 mmol peracid) in 50 mL of $CHCl_3$ was added dropwise to a solution of sulfide diol **9** (1.28 g, 4.88 mmol) in 150 mL of $CHCl_3$ at 0 °C. After stirring at 25 °C for 12 h the solution was extracted with aqueous $NaHCO_3$ and dried ($MgSO_4$), and solvent was removed to give a clear oil which crystallized upon addition of ether. Filtration yielded 0.81 g of sulfone **30** and removal of the ether in the filtrate yielded 0.27 g of sulfone. Total yield of **30** was 1.08 g (80%): mp 109–115 °C; IR (KBr) 3541 (s), 1476 (w), 1453 (w), 1398 (m), 1304 (s), 1227 (w), 1193 (m), 1159 (s), 1133 (m), 1082 (m), 1038 (s), 977 (w), 955 (w), 775 (s), 731 (s), 614 (s), 593 (m), 568 cm^{-1} (s); mass spectrum (70 eV) *m/e* (rel intensity) no molecular ion, 260 (5.5, $M^+ - H_2O$), 231 (13.8), 213 (82.7), 195 (100), 165 (41.8), 137 (23.0), 91 (36.8), 77 (69.0).

Anal. ($C_{14}H_{14}O_4S$) C, H, S.

(c) Sulfide Diol 14. *m*-Chloroperbenzoic acid (319 mg of 85% peracid, 1.57 mmol) in 10 mL of CH_2Cl_2 was added within 15 s to a cooled (0 °C) solution of diol **14** (320 mg, 0.78 mmol) in 15 mL of CH_2Cl_2. The solution was stirred for 14 h at 25 °C followed by extraction with aqueous $NaHCO_3$. After separating the organic layer and drying ($MgSO_4$), the solvent was removed, leaving 311 mg (86%) of white solid, sulfoxide-ene-ol **31**. Two unidentified minor peaks (14% of total methyl group of **31**) were also seen, perhaps attributable to sulfone diol **35** or sulfurane **15**.

Rate of Isomerization of 17. An 89/11 mixture of sulfurane **17a** and **17b** (29.1 mg, 0.093 mmol) in 0.5 mL of pyridine-d_5 was sealed in an NMR sample tube. The rate of isomerization to the equilibrium mixture (exo/endo::78/22) was followed by 220-MHz ^1H NMR by integration of the ethyl triplets of each isomer. The isomerization was followed for about three half-lives. The data were fit to a first-order least-squares plot (R = 0.987) to give a first-order rate constant $k_1 = 3 \times 10^{-6}$ s^{-1}. This corresponds to a free energy of activation of 30 kcal/mol.

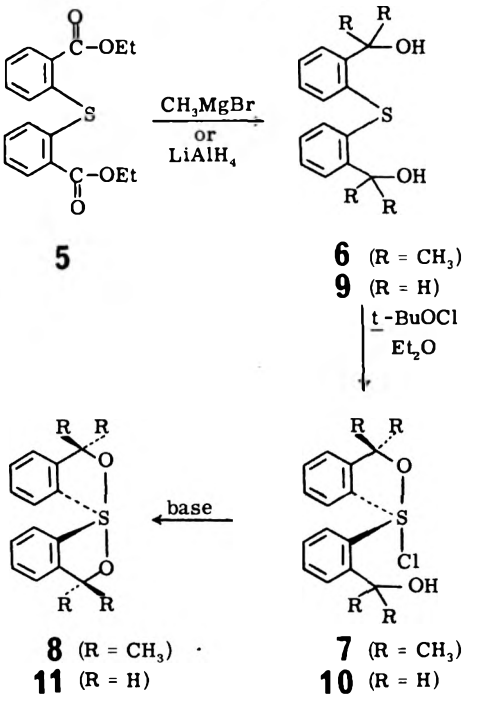
A 50/50 mixture of **17a** and **17b** in pyridine-d_5 was heated to 84 °C for a few days. Subsequent ^1H NMR analysis confirmed the earlier quoted equilibrium composition (78/22) with approach from the opposite direction.

Results

Synthesis. Spirosulfurane **8**, prepared by the method shown in Scheme I, is a white, crystalline material whose ^1H NMR spectrum (CD_2Cl_2) shows diastereotopic methyl singlets at δ 1.53 and 1.63. The 220-MHz spectrum of a carbon tetrachloride solution of **8** containing L(−)-2,2,2-trifluoro-1-phenylethanol[21] shows four resolved methyl singlets, consistent with the expected trigonal bipyramidal geometry about chiral sulfur. The two aromatic protons ortho to sulfur show a low-field chemical shift (δ 8.24–8.42 in CD_2Cl_2) characteristic of sulfuranes and selenuranes of this type.[9b,17]

Spirodibenzyloxysulfurane **11** was synthesized by a related method (Scheme I). Final ring closure of **10** to form **11** required use of triethylamine in dry ether or potassium hydride in dry tetrahydrofuran because of the reactivity of **11** toward water. Crystalline **11** can, however, be handled in air without hydrolysis from atmospheric moisture. The 220-MHz ^1H NMR spectrum of **11** shows an AB pattern at δ 5.100 and 5.195 (J = 14 Hz) for the diastereotopic benzyl hydrogens. Also seen

Scheme I



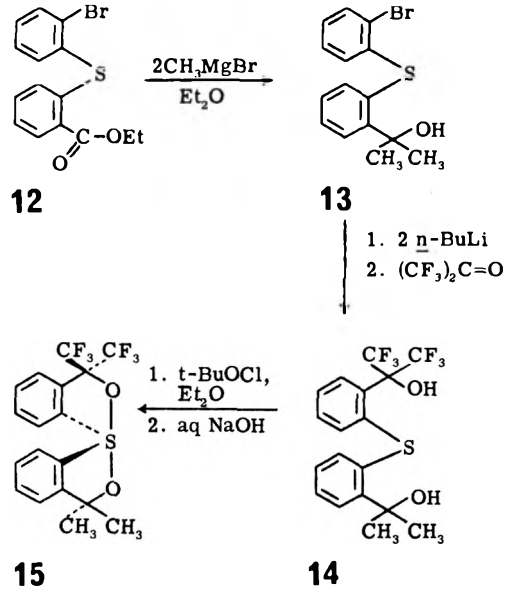
5 **6** (R = CH_3) **9** (R = H) **8** (R = CH_3) **11** (R = H) **7** (R = CH_3) **10** (R = H)

is the characteristic downfield shift of the two aromatic protons ortho to sulfur at δ 7.95–8.14.

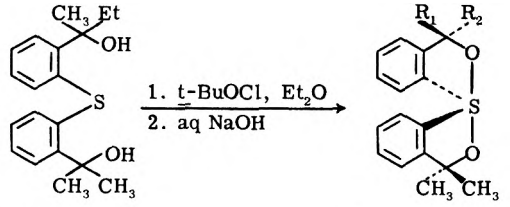
Unsymmetrical spirosulfurane **15** was prepared by oxidation of sulfide diol **14** by the same procedure used for sulfurane **8** (Scheme II). The ^1H NMR spectrum of **15** in $CDCl_3$ shows two diastereotopic methyl singlets at δ 1.65 and 1.83. The two protons ortho to sulfur are seen at δ 8.27–8.67. The ^{19}F NMR shows two quartets at ϕ 74.15 and 77.06 (J_{FF} = 9.2 Hz) which correspond to the diastereotopic trifluoromethyl groups. The chiral nature of **15** is demonstrated by the observation of four methyl singlets for the enantiomers of **15** in a 220-MHz spectrum of **15** in a chiral medium.[21] It should be pointed out that the hydrochloride of **15**, presumed to be an intermediate in its synthesis, loses HCl too rapidly to permit isolation.

Diastereomeric spirosulfuranes **17a** and **17b** were formed in almost equal amounts upon applying the standard procedure to **16**. Column chromatography on neutral alumina followed by one recrystallization gave an 89/11 mixture of isomers **17a** and **17b**. The 220-MHz ^1H NMR of the mixture in

Scheme II



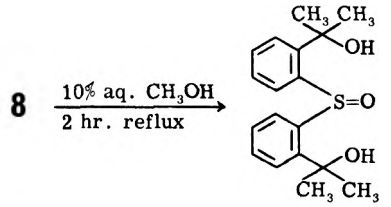
12 **13** **15** **14**



16 17a $R_1 = CH_3$; R_2 = Et
17b R_1 = Et; $R_2 = CH_3$

pyridine-d_5 shows *exo*- (**17a**) and *endo*- (**17b**) ethyl triplets at δ 0.794 and 1.606. These assignments are based in part on an examination of molecular models which places the *endo*-ethyl group in the deshielded region of the cis aromatic rings and in part on the expectation that the thermodynamically favored isomer would be that with the more bulky ethyl group in the less hindered exo position (**17a**). More substantial evidence for the assignments by the interaction of $Eu(fod)_3$ with **17** will be discussed later.

Hydrolysis. Sulfurane **8** can be handled in air and is not easily hydrolyzed. It is hydrolyzed to sulfoxide diol **18** upon boiling for 2 h in 10% aqeuous methanol. The ^1H NMR spectrum of **18** in $CDCl_3$ shows diastereotopic methyl singlets at



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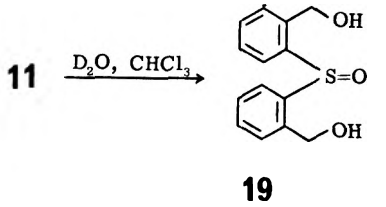
δ 1.38 and 1.70. Similar spectroscopic evidence shows that **18** slowly loses water to re-form spirosulfurane **8** in $CDCl_3$. After 5 days at 25 °C, reversion to **8** had occurred to the extent of 63%, starting with pure **18**.

Sulfurane **11** is more easily hydrolyzed than is **8**. The addition of D_2O to a chloroform solution of **11** resulted in 94% hydrolysis to sulfoxide diol **19** after 3.6 h at 25 °C. An alternative route to **19** is by oxidation of **9** with *m*-chloroperbenzoic acid (MCPBA). A parallel hydrolysis experiment using sulfurane **8** showed only 25% hydrolysis after 13 days at 25 °C. Unsymmetrical sulfurane **15** failed to hydrolyze to sulfoxide diol **20** even under stringent conditions such as boiling it in



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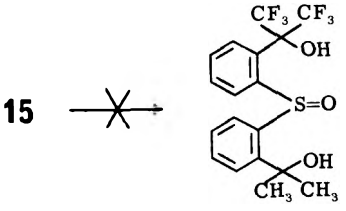

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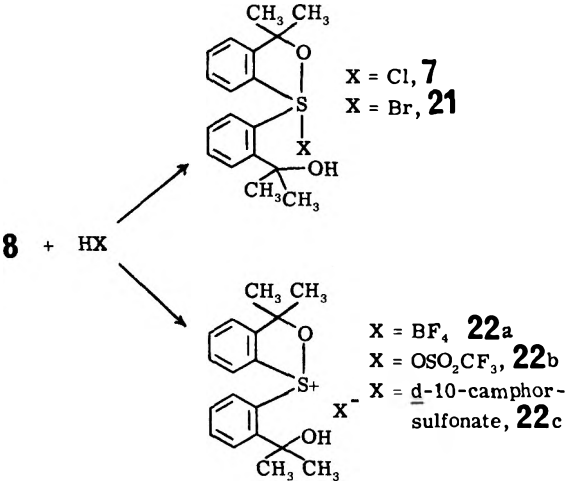
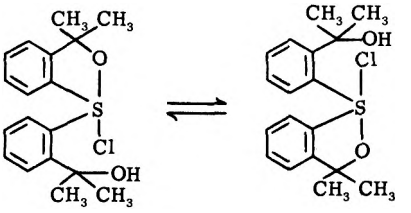
10% aqueous methanol for 4.75 h or using acidic or basic solutions.

Reactions and Interactions. Sulfurane **8** reacts with strong acids (HCl, HBr, HBF_4, CF_3SO_3H, *d*-10-camphorsulfonic acid) to form halosulfuranes or sulfonium salts. All of



these monocyclic compounds are isolable and can be handled in air without hydrolysis. They are insoluble in ether but are quite soluble in methylene chloride or chloroform. Repeated recrystallizations of *d*-10-camphorsulfonate **22c** failed to resolve the two diastereomers.

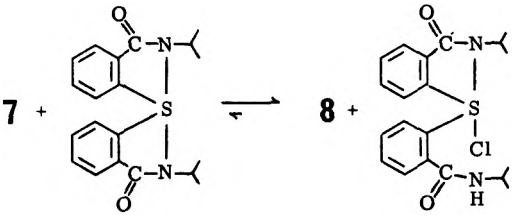
A rapid degenerate intramolecular ligand exchange, interconverting **7a** and **7b**, was first suspected upon examining its



7a **7b**

^1H NMR spectrum. Because of the chirality about sulfur, a total of four methyl singlets would be expected. However, the 100-MHz ^1H NMR spectrum of **7** at 28 °C in CD_2Cl_2 showed only two methyl singlets at δ 1.86 and 1.94. It was also observed that peaks for the two protons ortho to sulfur at δ 8.20 were broadened, unlike the usual sharp peaks seen for ortho protons in sulfuranes and selenuranes.[9b,17] On stepwise cooling, the peak at δ 8.20 was further broadened and then sharpened at −95 °C to show peaks for one ortho proton as a doublet at δ 8.55 and the other as a part of the unresolved aromatic multiplet. Also, a new peak appeared at δ 10.33, as a singlet, which is assigned to the hydroxyl proton, strongly hydrogen-bonded to the chlorine atom. The −95 °C temperature was not sufficiently low to resolve the four methyl singlets expected for **7**. At this temperature, which was the lowest permitted by solubility characteristics of **7**, the methyl region showed a single broad peak.

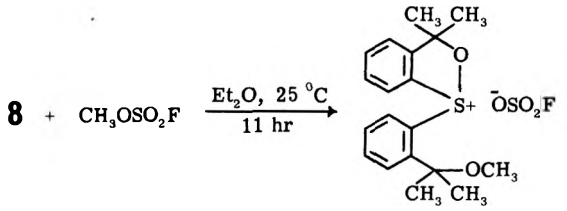
A similar downfield shift is seen for the amide NH proton (δ 11.60) in chloroazasulfurane **23**.[18] Failure to see evidence for the intramolecular ligand exchange in **23** may result from the greater basicity of diazasulfurane **24** compared to **8**. This order of basicities was demonstrated by combining **24** and chlorosulfurane **7** in dry $CDCl_3$ to give sulfurane **8** and chloroazasulfurane **23**. The ^1H NMR spectra for bromosulfurane **21** and sulfonium salts **22a–c** also show evidence for an in-



24 **23**

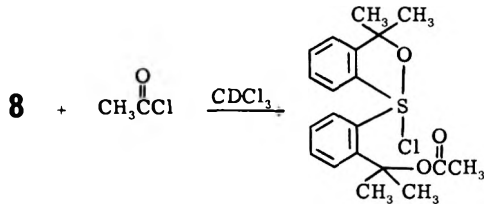
tramolecular exchange process similar to the one seen for **7**. No evidence was seen for reaction of **8** with the weaker acetic acid.

Spirosulfurane **8** reacts with methyl fluorosulfonate at 25 °C to methylate one of the apical oxygens to give **25**. This



25

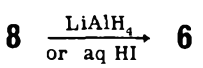
compound provides a model for the low-temperature ^{1}H NMR spectrum for protonated analogues **21** and **22**, since it cannot show the degenerate intramolecular ligand exchange postulated for the protonated species. It shows four resolved methyl singlets as anticipated. A similar model compound which cannot undergo the degenerate exchange is provided by acetylation of **8**, using acetyl chloride to give **26**, which also



26

shows four methyl singlets. The less nucleophilic fluorinated analogue, sulfurane **15**, does not react with acetyl chloride under these conditions. Treatment of sulfurane **8** with benzoyl fluoride gave no reaction after 80 h at 25 °C.

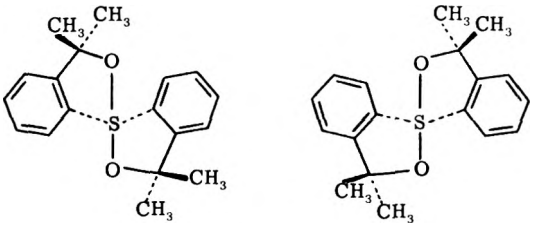
Sulfurane **8** is reduced to sulfide diol **6** with lithium aluminum hydride or by treatment of a methylene chloride solution with aqueous hydriodic acid.



Successive additions of Eu(fod)$_3$[22] to a carbon tetrachloride solution of **8** caused the two methyl singlets at δ 1.51 and 1.59 to move downfield, the peak at δ 1.51 more rapidly than the peak at δ 1.59. Plots of the chemical shift of each singlet vs. the concentration of Eu(fod)$_3$ are nearly linear with slopes of 82.4 and 32.4 ppm/M for the peaks initially at δ 1.51 and 1.59. The complexation of Eu(fod)$_3$ with the less basic sulfurane **15** is much weaker. Similar plots of chemical shift vs. Eu(fod)$_3$ concentrations are nearly linear with slopes of 3.92 and 3.78 ppm/M for the peaks initially at δ 1.60 and 1.76. The aromatic protons in **8** also shift downfield and are eventually completely resolved into two doublets and two triplets. In **15**, the aromatic protons shift less and never become completely resolved.

Pirkle and Sikkenga[24] have used Eu(fod)$_3$ to indicate relative stabilities of diastereomeric solvates. In the presence of chiral arylperfluoroalkylcarbinols, the ^{1}H NMR spectra of sulfoxide enantiomers are nonequivalent. The addition of Eu(fod)$_3$ alters the magnitude of the nonequivalence. The detailed dependence of the nonequivalence on concentration of Eu(fod)$_3$ was related to energies of solvation of the sulfoxide enantiomers by the chiral alcohol.

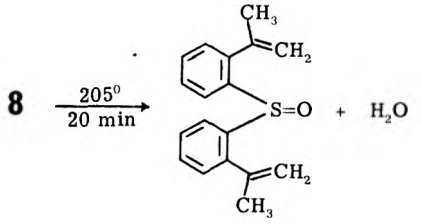
Since sulfurane enantiomers **8a** and **8b** interact with chiral carbinols to give nonequivalent ^{1}H NMR spectra and since sulfurane **8** also interacts strongly with Eu(fod)$_3$, Pirkle's method was applied to determine the relative solvation energies of **8a** and **8b** with a chiral alcohol. In the absence of Eu(fod)$_3$, sulfurane **8** (0.2 M) and (*S*)-2,2,2-trifluoro(9-anthryl)ethanol (0.6 M) interact in CCl_4 such that one of the



8a **8b**

diastereotopic methyl singlets seen for the racemic mixture in achiral media is resolved into two singlets at δ 1.18 and 1.34. The other methyl singlet at δ 1.23 is not resolved. Successive additions of Eu(fod)$_3$ cause the peaks to move progressively downfield. The change in the magnitude of the chemical shift of the two resolved singlets was monitored with each addition of Eu(fod)$_3$. Except for the change from no Eu(fod)$_3$ to the first increment of Eu(fod)$_3$, there was very little change in the magnitude of nonequivalence of the resolved methyl singlets as more Eu(fod)$_3$ was added. This suggests that the energies of the interaction of sulfurane enantiomers with chiral alcohol are nearly the same.

Sulfurane **8**, when heated to 205 °C for 20 min, loses 1 equiv of water and forms sulfoxide diene **27**. In comparison, Reich[17]



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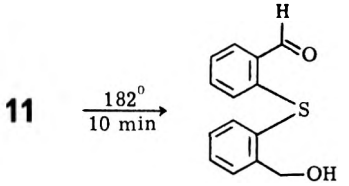
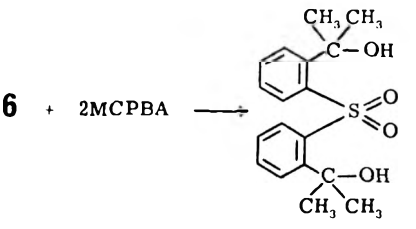
has reported that the selenium analogue of **8** decomposes at its melting point (123 °C), but is stable in solution to at least 200 °C. Pyrolysis of sulfurane **11**, which cannot give such a dehydration, at 182 °C gives sulfide **28**, with disproportiona-



28

tion of the apical alkoxy ligands. Sulfurane **15** fails to pyrolyze when heated to 205 °C for 20 min or at 295 °C for 10 min. When **15** was heated to 355 °C for 15 min, the ^{1}H NMR spectrum of the nearly black sample showed that **15** was completely gone. There were characteristic peaks for the 2-propenyl group as a minor product and other unidentified peaks were seen. The ^{19}F NMR spectrum showed no quartets but showed a series of singlets or doublets at about ϕ 75. No products were isolated from this reaction.

The oxidation of sulfide diol **6** with 2 equiv of MCPBA gives sulfone diol **29**. In a parallel reaction, sulfide diol **9** is oxidized



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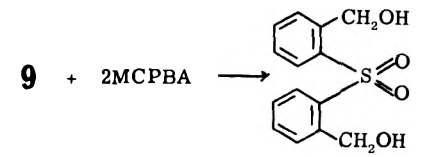

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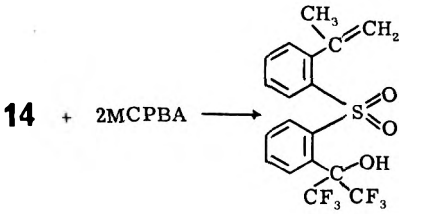


31

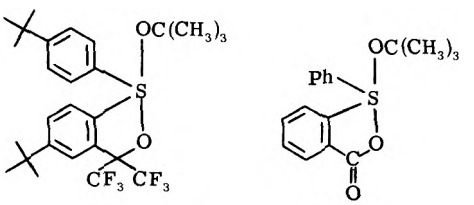
to give sulfone diol **30**. In contrast, oxidation of sulfide diol **14** gives sulfone-ene-ol **31** in greater than 86% yield. Some minor peaks in the ^{1}H NMR spectrum of the product may be due to the corresponding sulfone diol or sulfurane.

Interconversion of 17a and 17b. The barrier for interconversion of diastereomers **17a** and **17b** was determined in pyridine-d_5 solution at 84 °C. An equilibrium ratio **17a/17b** of 78/22 was determined by heating a 89/11 mixture of diastereomers at 84 °C for a few days. The same ratio was reached from the opposite direction, starting with a 50/50 sample of diastereomers. The rate of approach to equilibrium of a mixture of **17** initially 89/11 (exo/endo) was followed by 220-MHz ^{1}H NMR integral comparisons of the resolved ethyl triplets of **17a** and **17b**. The resulting rate constant ($k_1 = 3 \times 10^{-6}$ s^{-1}) corresponds to a free energy of activation (at 84 °C) of 30 kcal mol^{-1}. No decomposition of **17** was observed during this experiment.

Discussion

Sulfurane Reactivity. The remarkable unreactivity of spirosulfurane **1** toward water has been mainly attributed to the "five-membered ring effect".[6] Westheimer has shown that five-membered-ring phosphate esters hydrolyze a million times faster than their acyclic analogues.[25] Much of this acceleration results from the relief of strain which accompanies a change from a tetrahedral ground state to a trigonal bipyramidal (TBP) transition state. A similar but smaller accelerating effect seen in the hydrolysis of cyclic sulfites[26] has been attributed primarily to "entropy strain" factors favoring approach to a TBP transition state. For cyclic sulfuranes the inverse transformation of a "trigonal bipyrimidal" ground state to a "tetrahedral" transition state results in an increase in ring strain, which is reflected in the failure of **1** to hydrolyze. Other factors cited[6] as possible contributors to the low reactivity of **1** relative to its acyclic analogue include (a) retardation of the ionization of apical ligands by the electron-withdrawing effect of the fluoroalkyl substituents ortho to sulfur and (b) the minimization of possible repulsive interactions between the π-donor equatorial ligands and the apical three-center four-electron bond which is a consequence of the geometry of the spiro system.

Acyclic sulfurane **2** rapidly converts *tert*-butyl alcohol to isobutylene, even at −60 °C, by a route believed to involve a very unstable intermediate *tert*-butoxy sulfurane formed by a ligand-exchange reaction.[27] The fact that two monocyclic *tert*-butoxy sulfuranes **32** and **33** have been isolated[6,28] illustrates the great stabilizing effect of a single five-membered ring. The addition of a second five-membered ring as in sulfurane **8** adds sufficient stability that the tertiary alkoxy ligands do not give elimination reactions except at elevated temperatures.

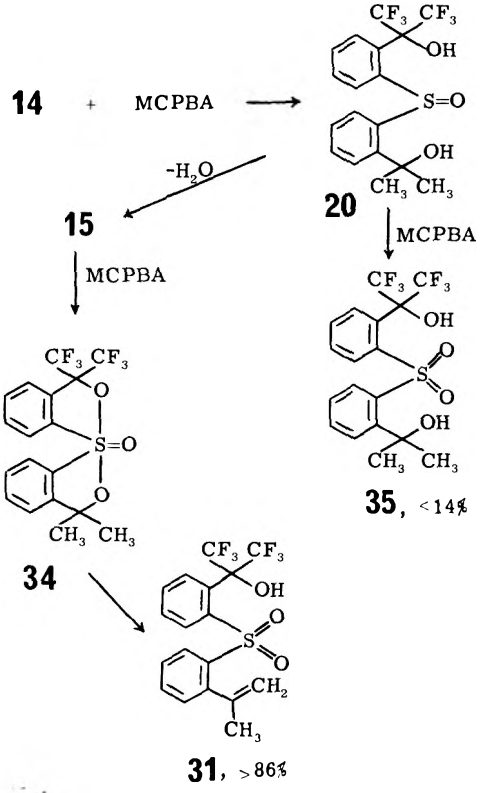


32 33

Not only does sulfurane **1** fail to hydrolyze, but attempts to observe or isolate the corresponding sulfoxide diol also give only **1**. This suggests that the reasons for this failure to hydrolyze **1** are to be found in both kinetic and thermodynamic properties of the molecule. The equilibrium clearly favors the spirosulfurane and cyclodehydration of the sulfoxide diol is a rapid process. Sulfurane **8** is hydrolyzed to sulfoxide diol **18** in protic media, reflecting a lesser thermodynamic stability, relative to the hydrolysis product, than is the case for **1**. Strenuous attempts to hydrolyze unsymmetrical sulfurane **15** fail, suggesting that it is also favored at equilibrium relative to the hydrolysis product. The stabilization of **1** and **15** by the five-membered ring effect is clearly enhanced by the electron-withdrawing inductive effect of the CF_3 substituents. Dehydrative ring closures to form sulfuranes **1**, **8**, and **15** are all favored by the presence in the five-membered rings of *gem*-dialkyl groups. Many examples of facilitated ring closures in systems possessing this structural feature, manifestations of the Thorpe–Ingold effect, have been noted.[29] It is therefore not surprising that the analogous sulfurane lacking this *gem*-dialkyl group, **11**, is less stable toward hydrolysis than is **8**. it is also more rapidly hydrolyzed than **8**.

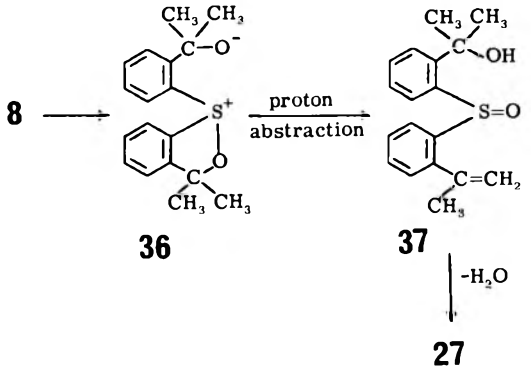
Parallel experiments in which sulfides **6**, **9**, and **14** were each treated with 2 equiv of MCPBA led to further insight into their relative rates of cyclodehydration. For **6** and **9** the corresponding sulfone diols are obtained, but for unsymmetrical sulfide **14** more than 86% of sulfone-ene-ol **31** is obtained. In all three of these oxidations, the first step is expected to be oxidation to give the corresponding sulfoxide diols. In the first two cases, further oxidation simply gives sulfone diols **29** and **30**. However, in the third case (Scheme III), the dehydration

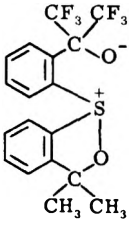
Scheme III



of sulfoxide diol **20** to give sulfurane oxide **34** is faster than further oxidation with MCPBA to form sulfone diol **35**. Fragmentations of sulfurane oxides analogous to that converting **34** to **31** have been reported.[30] These results further suggest a high stability of sulfurane **15** compared to **8**.

The relative thermal stabilities of spirosulfuranes **8**, **11**, and **15** parallel their relative hydrolysis rates. Zwitterion **36**, a possible intermediate in the pyrolysis of **8**, could perhaps abstract a proton to give sulfoxide-ene-ol **37**, and then undergo dehydration to **27**. Similar intermediates have been postulated in the pyrolysis of **4** and in the reaction of **2** with perfluoropinacol.[9a,31] The pyrolysis of **11** may follow a route involving an intermediate similar to **36**. In this case, α-proton abstraction would lead directly to **26**. The two trifluoromethyl groups on **15** render the alkoxide function of the possible intermediate zwitterion **38** much less basic than the analogous





38

alkoxide function in **8** or **11**. This may account in part for the remarkable thermal stability of **15**.

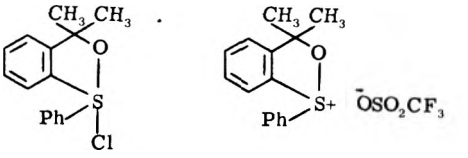
The "five-membered-ring effect" is well established as a major factor that increases the stability of sulfuranes. Hydrolytic equilibria, the rates of hydrolyses and pyrolyses of **8**, **11**, and **15**, and the reactions of the corresponding sulfide diols with *m*-chloroperbenzoic acid suggest another major factor that enhances sulfurane stability, i.e., an increase in the electronegativity of the apical ligand or ligands. The results also show that the "*gem*-dialkyl effect"[29] can also play a role in stabilizing spirosulfuranes.

Basicities of Sulfuranes. Pirkle[21,24] has developed a set of chiral alcohols which are useful in making enantiomers separately observable by NMR. In addition to confirming the chiral nature of our spirosulfuranes, these alcohols have been used to provide information about their relative basicities. Since (−)-2,2,2-trifluoro-1-phenylethanol is moderately acidic, the major type of interaction converting enantiomers into diastereomeric solvates involves hydrogen bonds to basic sites on solute molecules. Racemic spirosulfuranes **8** and **15** both interact with this chiral solvent to allow resolution of the two methyl singlets into two peaks each, with sulfurane **8** interacting with the chiral solvent more strongly than **15**, as evidenced by the magnitude of nonequivalence of enantiomeric methyl peaks. For **8** the differences in chemical shift for each set of peaks was 0.026 and 0.024 ppm, but for **15** these same differences were less (0.024 and 0.017 ppm), even though the concentration of chiral solvent for **15** (0.52 M) was slightly higher than for **8** (0.51 M). Sulfurane **1** shows no nonequivalence in ^{19}F NMR for CF_3 peaks of enantiomers in this chiral medium;[6] thus, the relative order of basicity is **8** > **15** > **1**.

More dramatic evidence for this ordering is found in interactions of these spirosulfuranes with the lanthanide-shift reagent Eu(fod)$_3$,[22] a Lewis acid. Sulfurane **1** is reported[6] to show no chemical-shift changes in the presence of Eu(fod)$_3$, in keeping with the low basicity of **1**. Sulfurane **15** shows a moderately strong interaction with Eu(fod)$_3$, while a very large interaction is seen for **8**. Complexation of Eu(fod)$_3$ with spirosulfuranes might occur at the oxygen or sulfur atoms or both.

Spirosulfurane **8** reacts with strong acids to give halosulfuranes or sulfonium salts; no such reaction occurs for the less basic **1**. The chlorosulfurane of **15**, from the reaction of **14** and *tert*-butyl hypochlorite, was not isolable, losing HCl to generate **15**, reflecting the reduced basicity of **15** relative to **8**. Treatment of **8** with other electrophiles showed it unreactive toward the weaker acid, acetic acid, but reactive toward methyl fluorosulfonate and acetyl chloride. The less nucleophilic sulfurane **15**, however, does not react with acetyl chloride and methylation is very slow.[32] The order of decreasing basicity and nucleophilicity (**8** > **15** > **1**) parallels the increase in number of CF_3 groups on the oxygen apical ligands.

Ligand Exchange. Chlorosulfurane **7** is closely related to previously described[16,33] chlorosulfurane **39**. Strong evidence

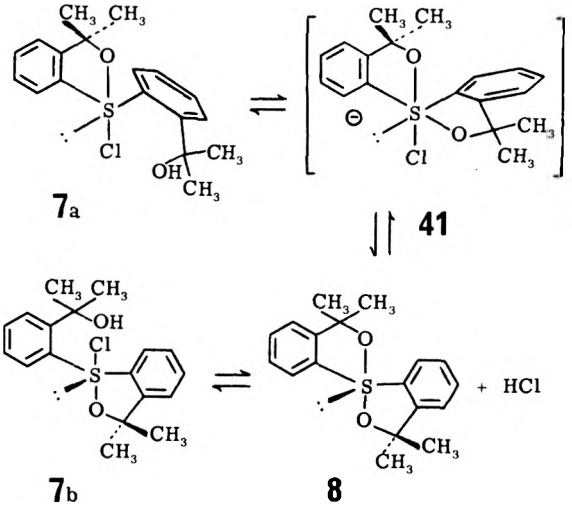


39 **40**

is reported[16] for the covalent nature of the S–Cl bond in **39**, partly through ^1H NMR spectroscopic comparison with the ionic sulfonium triflate **40**. The addition of the alcohol function in **7**, **21**, and **22a–c** provides the opportunity for a facile intramolecular ligand exchange which is fast on the NMR time scale at room temperature. When the exchange is slowed at low temperature, the proton ortho to sulfur on the fused ring in **7** is seen at very low field characteristic[9b] of such protons in, for example, model compound **39**.

An associative mechanism (Scheme IV) similar to the one postulated[16,33] for the hydrolysis of chlorosulfurane **39** may be operating for the exchange reaction of **7**. The failure to detect intramolecular exchange in the more weakly acidic chloroazasulfurane **23** is consistent with this mechanism, since loss of HCl to form the more basic diazasulfurane might be expected to be slower than for the more acidic **7**.

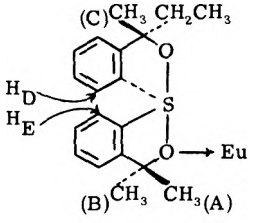
Scheme IV



The Structures of 17a and 17b. The two *endo*-methyl groups of 8 (δ 1.59) are held in the deshielded region of space relative to the cis aromatic ring, causing them to be shifted downfield relative to the *exo*-methyl groups (δ 1.51). This assignment is consistent with the results of the Eu(fod)$_3$ study on 8 in which the singlet at δ 1.51 broadens more and moves downfield faster than the singlet at δ 1.59 as the concentration of Eu(fod)$_3$ increases. If we make the reasonable assumption that Eu(fod)$_3$ interacts with the oxygens and/or sulfur lone pair of 8 from the less hindered direction away from the aryl rings, the *exo*-methyls, being closer to the Eu(fod)$_3$ than the *endo*-methyls, would be expected to move downfield more rapidly.

Tentative ^{1}H NMR assignments for 17 were made on the basis of the expected greater stability of *exo*-ethyl sulfurane **17a** because of the greater steric crowding of the *endo*-ethyl group in **17b**. The ^{1}H NMR spectrum of **17a** shows two methyl singlets at δ 1.51 and 1.60. Successive additions of Eu(fod)$_3$ causes the singlet initially at δ 1.51 (A) to broaden and move rapidly downfield. One of the other two methyl peaks initially at δ 1.60 (B) broadens less and moves downfield more slowly. The other methyl peak initially at δ 1.60 (C) broadens only slightly and moves downfield even more slowly. Plots of chemical shift vs. concentration of Eu(fod)$_3$ were nearly linear with slopes for the three methyl peaks of **17a** of 36.1 (A), 14.5 (B), and 5.5 (C) ppm M^{-1}.

This is consistent with our tentative assignment of structure **17a** (exo) to the major isomer. The *exo*-ethyl group of **17a** might be expected to provide greater steric hindrance to complex formation by Eu(fod)$_3$ at the nearer oxygen, favoring complexation at the oxygen α to the *gem*-dimethyl group as in **42**.

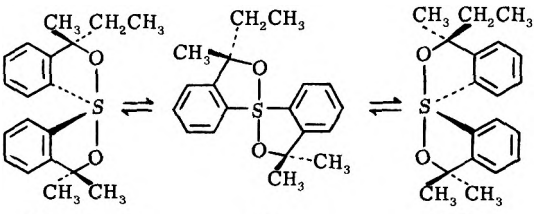


42

The greater proximity of the europium to methyl group A in **42** causes it to move downfield most rapidly, with B, second nearest, second most rapidly. The more distant *endo*-methyl (C) moves downfield most slowly. The chemical shift for A in the absence of Eu(fod)$_3$ (δ 1 51) is identical to the *exo*-methyl peaks in 8 (which also move downfield with addition of Eu(fod)$_3$ more rapidly than do the *endo*-methyl peaks, as expected). These observations are consistent with the idea that the oxygen atoms, rather than the sulfur, provide the primary sites for Eu(fod)$_3$ complex formation in these sulfuranes.

Added evidence for complexation of Eu(fod)$_3$ at oxygen rather than at sulfur comes from the shifts seen for the downfield protons ortho to sulfur. Both ortho protons of 8 shift downfield with a slope of 7.1 ppm M^{-1}. The two ortho protons of **17a**, initially at δ 8.31, move downfield at different rates (slopes = 10.65 and 2.73 ppm M^{-1}). The ortho proton with a slope of 10.65 is postulated to be H_D, which is nearer the preferred site of complex formation in **42** than is H_E. In the presence of Eu(fod)$_3$, the ortho protons of the minor isomer **17b** are seen as two resolved doublets *between* the two ortho protons of the major isomer **17a**. This is expected for an interaction of Eu(fod)$_3$ with **17b**, whose less obtrusive *endo*-ethyl group provides less basis for steric differentiation between the two basic sites than is the case for the exo isomer **17a**.

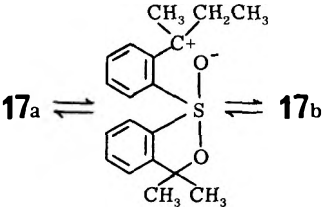
Possible Interconversion Mechanisms. Our kinetic study of the equilibration of mixtures of **17a** and **17b** provides a free energy of activation for whatever process converts **17a** to **17b** of 30 kcal mol^{-1} at 84 °C. One mechanism for this process interconverting wedge-shaped conformers could be called cuneal inversion (by analogy to the pyramidal inversions common for many species with tricoordinated central atoms), inversion through planar transition state **43**. From high-



17a **43** **17b**

temperature ^{19}F NMR of spirosulfurane **1**, Martin, Perozzi, and Paul[15] set a lower limit of 25.3 kcal mol^{-1} for ΔG^* at 200 °C for the comparable cuneal inversion for **1**. The racemization of the optically active (*S*)-**39** may also involve such an inversion, for which a lower limit for ΔG^* of 25 kcal mol^{-1} at 23 °C was determined.[33]

Another possible mechanism for the equilibration of **17a** and **17b** would begin by ionization of one of the apical S–O bonds, followed by pyramidal inversion of the resulting sulfonium ions and then recombination. Inversion barriers for some sulfonium ions have been determined[10-14] to be in the range 25–29 kcal mol^{-1}, very similar to the lower limit obtained for **17**. It should be noted, however, that the sulfonium species in this case has an electronegative alkoxy substituent, a structural feature expected[34] to increase the barrier to pyramidal inversion. The use of pyridine as a medium for this study minimizes the importance of acid-catalyzed ionization to a alkoxysulfonium ion as a mechanism for the isomerization of **17**. It is conceivable that interconversion may be occuring at chiral carbon via inversion through a carbonium ion **44**,

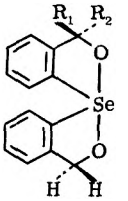


17a ⇌ ⇌ **17b**

44

although the failure to see any olefin makes this mode extremely unlikely.

Related work by Reich[17] on the configurational stability of selenuranes has established the equilibrium mixture of diastereotopic selenurane **45a** and **45b** to be 74/26 (vs. 78/22 for **17a** and **17b**). In both cases, the more stable isomer has the greater steric bulk located exo to the aryl function.[35] The rate of exo–endo isomerization for **45** showed ΔG^* = 30.9 kcal mol^{-1} at 120 °C, very similar to that for **17**. Reich[17] also reported evidence that trace amounts of water in benzene might catalyze the isomerization. Since this may also be occurring in our system (trace amounts of water in pyridine-d_5), higher



45a R_1 = H; R_2 = CH_3

45b R_1 = CH_3; R_2 = H

barriers for cuneal inversion at sulfur(IV) may be obtainable in systems which are inert toward hydrolysis or with more rigorous exclusion of water.

Conclusion

Additional factors that influence sulfurane stability have been found. An increase in the electronegativity of the apical ligands is reflected in an increase in the stability of sulfuranes. Hydrolyses of spirosulfuranes are slowed by the presence of *gem*-dialkyl groups on the carbon α to the apical atoms, and sulfurane stability is enhanced by this structural feature.

A lower limit of 30 kcal mol^{-1} has been set for $\Delta G^*_{84°C}$ for the cuneal inversion at sulfur(IV), a process that interconverts a pair of diastereomeric spirosulfuranes. This value is the highest yet found for sulfuranyl sulfur but still represents only a lower limit to the value because inversion by another mechanism or catalysis by water, acids, or bases cannot rigorously be ruled out.

Acknowledgment. This research was supported in part by a grant from the National Science Foundation, CHE 75-17742.

Registry No.—**5**, 62220-51-3; **6**, 62750-57-6; **7**, 63743-90-8; **8**, 62750-58-7; **9**, 38059-09-5; **10**, 63743-91-9; **11**, 34400-24-3; **12**, 63743-92-0; **13**, 63743-93-1; **14**, 63743-94-2; **15**, 63731-54-4; **16**, 63743-95-3; **17a**, 63743-96-4; **17b**, 63813-46-7; **18**, 62750-61-2; **19**, 63743-97-5; **21**, 63743-98-6; **22a**, 63744-00-3; **22b**, 63744-01-4; **22c**, 63813-47-8; **24**, 63744-02-5; **25**, 63731-59-9; **26**, 63744-03-6; **27**, 63744-04-7; **28**, 63744-05-8; **29**, 63744-06-9; **30**, 24536-81-0; 2,2′-dicarboxydiphenyl sulfide, 22219-02-9; 2-bromo-2′-carboxydiphenyl sulfide, 20076-94-2; 2-bromothiophenol, 6320-02-1; 2-iodobenzoic acid, 88-67-5; methyl ethyl ketone, 78-93-3; L(−)-2,2,2-trifluoro-1-phenylethanol, 10531-50-7; fluoroboric acid, 14874-70-5; *d*-10-camphorsulfonic acid, 3144-16-9; triflic acid, 1493-13-6; acetyl chloride, 75-36-5; (*S*)-(+)-2,2,2-trifluoro-9-(anthryl)ethanol, 60646-30-2; hexafluoroacetone, 684-16-2.

References and Notes

(1) Paper 34 in a series on sulfuranes. For paper 33 in this series, see: L. J. Adzima, E. N. Duesler, and J. C. Martin, *J. Org. Chem.*, preceding paper in this issue.
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(35) It should be noted that the chemical-shift assignments for *exo*- and *endo*-methyl groups of **45** are inverted from those for the sulfuranes of this study, with the *endo*-methyl being found at higher field than the *exo*-methyl of **45**. Differences in geometry between the two systems may provide an explanation.

Synthesis of Methyl-Substituted *trans*- and *cis*-1-Thiadecalins

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Received May 4, 1977

Synthetic procedures for *trans*-1-thiadecalin (**1**), *cis*-1-thiadecalin (**11**), and 15 *trans*- (**2–10**) and *cis*-1-thiadecalins (**12–17**) with methyl substituents in various positions of the heterocyclic or the carbocyclic ring are described.

Interest in the conformational and configurational properties,[1] and in the rearrangement reactions[2] of thiane-1-*N*-arylimides motivated us to synthesize a number of methyl-substituted 1-thiadecalins. Configuration and conformational equilibria of the compounds were established by ^{13}C and ^{1}H NMR spectroscopy;[3] here the synthetic procedures are discussed in some detail. The formulas of the compounds prepared are collected in Schemes I and II; in Table I the compositions of the product mixtures are summarized.

The following procedures were used. **Method A.** Addition of a (methyl)allylmagnesium halide to a (methyl)cyclohexene sulfide[4] and ring closure of the resulting (methyl-substituted) 1-allyl-2-mercaptocyclohexane (Schemes III and IV).

Methods B and C. Cyclization of (methyl substituted) 1-(3′-mercaptopropyl)cyclohexene-1 and (methyl substituted) 3-(3′-mercaptopropyl)cyclohexene-1 (Schemes V and VI).

Method D. Reaction of (methyl substituted) 1-(3′-methylsulfonyloxypropyl)-2-methylsulfonyloxycyclohexane (cis and trans mixtures) with sodium sulfide, in 50% ethanol or in dimethylformamide (Scheme VII).

Table I. Composition of Products from the Syntheses of 1-Thiadecalins

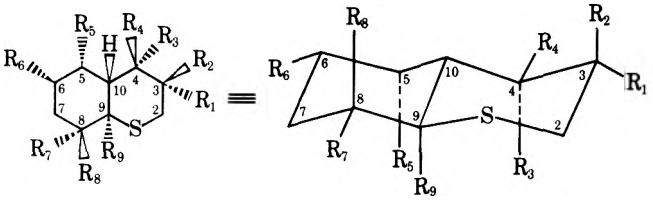
Starting material	Registry no.	Method[b]	Product[c]	%[a]
22a, 23a	286-28-2, 115-07-1	A	1	>97
22a, 23b[g]	115-11-7	A	3	97
			2	3
22a, 23c[g]	106-98-9	A	4	51
			5	49
cis-**22c, 23a**		A	9	90
cis-**22c**[g] (38%) +	40072-08-0,	A	9	63
trans-**22c**[g] (62%),	40072-07-9		8	13
23a			6	11
22b, 23a	7272-23-3	A	10	90
34a		B	11	68
			1	16
			18	16
34d		B	12	58.5
			13	17.5
			2	10
			19	14
34c[d]		B	15	70
			7	10
			20	14
34b[d]		B	16	70
			8	15
			17	7
			20	8
34b[d]		C	16	60
			8	15
			17	10
			20	14.5
30e	63714-74-9	C	14	>95
37a[d,e]		D	11	51
			1	8.5
			18	40.5
37a[d,f]		D	11	62
			1	7
			18	31
37d[d,e]	63714-75-0	D	12	45
			13	16.5
			2	<4
			3	<4
			19	34.5
37c[d,e]	63714-76-1	D	15	61
			20	24.5
			21	14.5
37b[d,e]	63714-77-2	D	16	46
			8	11
			20	27
			21	16
37b[d,f]		D	16	69
			8	11
			20	13
			21	8
16	63730-19-8	E	8	95
15	63730-18-7	E	15	<10
			7	>90

[a] Crude product mixtures were distilled from high-boiling material by distillation in a Kugelrohr apparatus and compositions of the resulting mixtures were determined by gas chromatography; differences to 100% result from small amounts of unidentified compounds. [b] See Text. [c] 1-Thiadecalin unless otherwise indicated. "α" means the substituent is on the opposite ring side as the substituent on C-10; "β" means the substituent is on the same ring side as the substituent on C-10. [d] Mixture of cis and trans isomers. [e] Solvent DMF. [f] Solvent 50% ethanol. [g] Registry numbers; *cis*-**22c**, 40072-08-0; *trans*-**22c**, 40072-07-9.

Method E. Equilibration of lithio derivatives of methyl *cis*-1-thiadecalin 1-oxides to methyl-*trans*-1-thiadecalin 1-oxides and reduction to the methyl-*trans*-1-thiadecalins (Scheme VIII).

Method A. Synthesis of compounds 1,[4a] 4 and 5,[4b] and 9[4c] by this method has already been described, the trans fusion

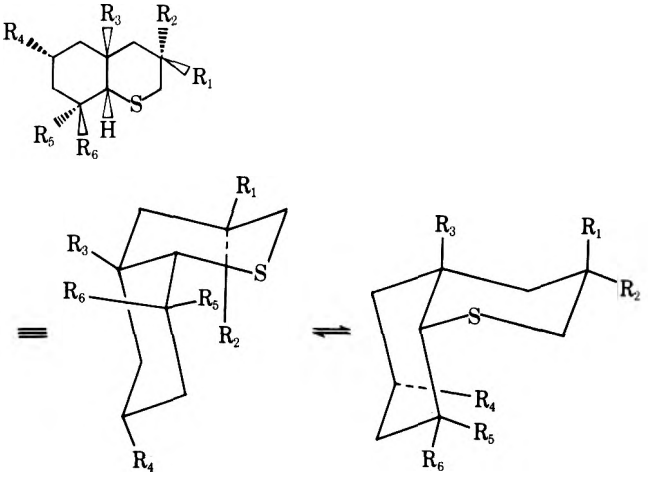
Scheme I



R = H unless indicated

1, all R's = H
2, R_1 = CH_3 (3α-CH_3)
3, R_2 = CH_3 (3β-CH_3)
4, R_3 = CH_3 (4α-CH_3)
5, R_4 = CH_3 (4β-CH_3)
6, R_5 = CH_3 (5α-CH_3)
7, R_6 = CH_3 (6α-CH_3)
8, R_7 = CH_3 (8α-CH_3)
9, R_8 = CH_3 (8β-CH_3)
10, R_9 = CH_3 (9-CH_3)

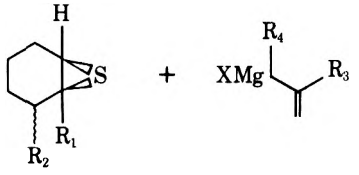
Scheme II



R = H unless indicated

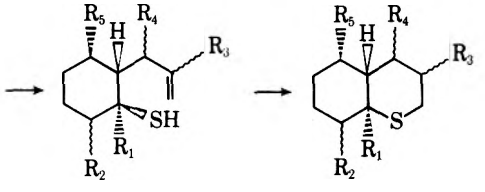
11, all R's = H
12, R_1 = CH_3 (3β-CH_3)
13, R_2 = CH_3 (3α-CH_3)
14, R_3 = CH_3 (10-CH_3)
15, R_4 = CH_3 (6α-CH_3)
16, R_5 = CH_3 (8α-CH_3)
17, R_6 = CH_3 (8β-CH_3)

Scheme III



22a, all R's = H
22b, R_1 = CH_3
22c, R_2 = CH_3
23a, all R's = H
23b, R_3 = CH_3
23c, R_4 = CH_3

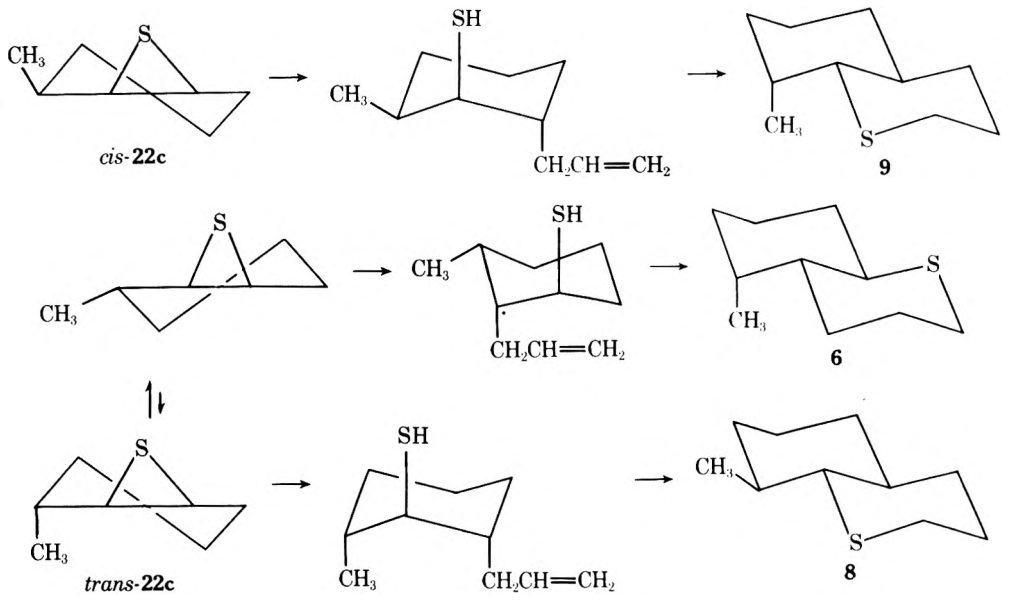
All R's = H unless indicated



24a, all R's = H
24b, R_1 = CH_3
24c, R_2 = CH_3
24d, R_3 = CH_3
24e, R_4 = CH_3
24f, R_5 = CH_3

1, all R's = H
2,3, R_3 = CH_3
4,5, R_4 = CH_3
6, R_5 = CH_3
8,9, R_2 = CH_3
10, R_1 = CH_3

Scheme IV



of the carbocyclic and heterocyclic rings being assumed.[4c] This assumption has now been verified by ^{13}C NMR[3], and the configuration of the methyl groups in **4** and **5**, previously not determined,[4b] has been established. When cyclohexene sulfide was allowed to react with methallylmagnesium chloride, a mixture of **2** and **3** was obtained; reaction of 3-methylcyclohexene sulfides (**22c**) with allylmagnesium bromide gave **9**, **6**, and **8**. Both the synthesis of the 3-methylcyclohexene sulfides and their reaction with the Grignard reagent require some discussion. It has been reported[5] that reaction of α-cyclohexene oxides with thiourea[6] leads to cyclohexene sulfides with retention of configuration. We found, however, that the reaction of pure *trans*-3-methylcyclohexene oxide with thiourea gave pure *cis*-3-methylcyclohexene sulfide, and reaction of a 1:1 mixture of *trans*- and *cis*-3-methylcyclohexene oxides with thiourea gave a mixture of *cis*- and *trans*-3-methylcyclohexene sulfides of the same composition. It is clear from these results that this reaction proceeds with clean inversion of configuration, not retention as claimed.[5] It also has been reported[5] that treatment of α-cyclohexene oxides with KSCN leads to mixtures of α- and β-cyclohexene sulfides (i.e., the reaction is nonstereospecific); thus, a 2:1 mixture of *cis*- and *trans*-3-methylcyclohexene oxides was reported to give a 1:2.5 mixture of *cis*- and *trans*-3-methylcyclohexene sulfides when treated with KSCN.[5] In our hands, reaction of a 1:1 mixture of *cis*- and *trans*-3-methylcyclohexene oxides with KSCN gave a mixture of *trans*- and *cis*-3-methylcyclohexene sulfides definitely richer in the trans product. However, this would seem to result not from the reaction being nonstereospecific but from the fact that the *trans*-3-methylcyclohexene oxide is much less reactive than the cis;[8] if the reaction was followed gas chromatographically the remaining starting material was seen to become gradually richer in the less reactive *trans*-3-methylcyclohexene oxide which could, in fact, be isolated in nearly pure form from the reaction mixture. ^1H NMR data of both epoxides and episulfides were found to differ from the previously reported values[5] and are listed together with the ^{13}C NMR data in Table III. The ^{13}C data confirm the configurational assignments (see ref 8 for the 3-methylcyclohexene oxides); the C-5s of the *trans*-3-CH_3 isomers are shifted upfield compared to the parent compounds due to the γ_a effect of the axial methyl group in one of the possible half-chair conformers (see Scheme IV), whereas the corresponding conformation for the cis isomers is depopulated because of sterical crowding between CH_3 and the heteroatom, as can be seen on a Dreiding model.

Reaction of *cis*-3-methylcyclohexene sulfide with allylmagnesium bromide, followed by cyclization of the intermediate **24**, gave only thiadecalin **9**. This agrees with the expected trans diaxial transition state, following an attack on the equatorially sulfur-substituted carbon atom 1 in the inverted conformation.

When mixtures of *trans*- and *cis*-3-methylcyclohexene sulfides were added to allylmagnesium bromide solutions, the major product after cyclization was **9**, even when *trans*-**22c** predominated in the starting material (see Table I), since, because of its greater stability, *trans*-**22c** reacts only partly and because two products (**6** and **8**) are formed from it in comparable amounts; attack on the preferred conformation of *trans*-**22c** (leading to **6**) is probably somewhat hindered for steric reasons.

Cyclization of the intermediate *trans*-1-allyl-2-mercaptocyclohexanes **24** was performed with 0.1 mol equiv of azobis(isobutyronitrile)[9] rather than by irradiation with UV light;[4] the reaction took place without changes in configuration, and only small amounts of thiahydrindanes (by addition to the less hydrogen-substituted carbon atom of the double bond) were formed as by-products.

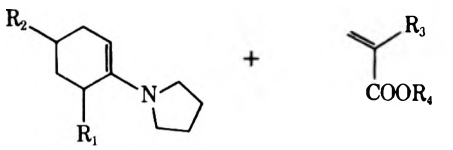
Products **2** and **3** (from **24d**) were found in very unequal amounts (~1:30). Model considerations show that formation of **3** must be preferred if the free-radical addition of the thiol to the double bond occurs trans, as it normally does.[10]

Method B. The condensation of pyrrolidino(methyl)cyclohexenes **25** with (meth-)acrylates to give (methyl substituted) 3-(2-oxocyclohexyl)propionates **27** has been described.[11] Reaction of **25b** with **26b** in anhydrous ethanol gave **27b** as the only product; no reaction at the methyl-substituted carbon atom occurred, while with dioxane as a solvent the formation of approximately equal amounts of the two products has been reported.[12a]

Reduction of the ketones with sodium borohydride gave mixtures of the cis and trans isomers of the cyclohexanols **28**. Temperatures during reaction were kept low to avoid the formation of the diols **36**.[12b] No attempts were made to separate the isomers, but the mixtures were converted into the methanesulfonates **29** and heated (without isolation of **29**) to induce elimination. Yields in this step were rather poor (<45%), since only methylsulfonyloxy groups cis to at least one of the other substituents of the cyclohexane ring could be expected to be suitably (i.e., axially) orientated for elimination.

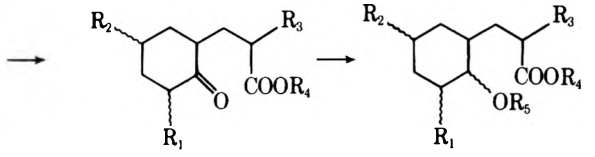
The resulting 3-cyclohexenylpropionates (**30**) were mixtures

Scheme V



25a, $R_1 = R_2 = H$
25b, $R_1 = CH_3$
25c, $R_2 = CH_3$

26a, $R_4 = CH_3$
26b, $R_4 = C_2H_5$
26c, $R_3 = R_4 = CH_3$

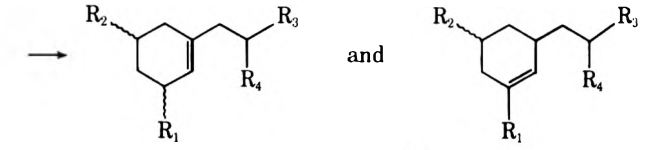


28, 29

27a, $R_4 = CH_3$
27b, $R_1 = CH_3$; $R_4 = C_2H_5$
27c, $R_2 = R_4 = CH_3$
27d, $R_3 = R_4 = CH_3$

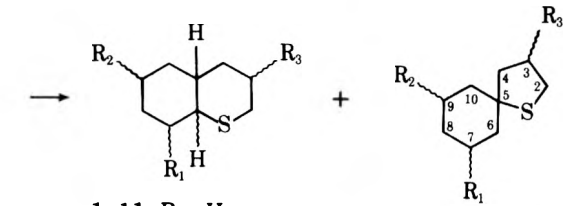
28a, $R_4 = CH_3$
28b, $R_1 = CH_3$; $R_4 = C_2H_5$
28c, $R_2 = R_4 = CH_3$
28d, $R_3 = R_4 = CH_3$

29a, $R_4 = CH_3$; $R_5 = SO_2CH_3$
29b, $R_1 = CH_3$; $R_4 = C_2H_5$; $R_5 = SO_2CH_3$
29c, $R_2 = R_4 = CH_3$; $R_5 = SO_2CH_3$
29d, $R_3 = R_4 = CH_3$; $R_5 = SO_2CH_3$



30, 31, 32, 33, 34

30a, $R_4 = COOCH_3$
30b, $R_1 = CH_3$; $R_4 = COOC_2H_5$
30c, $R_2 = CH_3$; $R_4 = COOCH_3$
30d, $R_3 = CH_3$; $R_4 = COOCH_3$
31a, $R_4 = CH_2OH$
31b, $R_1 = CH_3$; $R_4 = CH_2OH$
31c, $R_2 = CH_3$; $R_4 = CH_2OH$
31d, $R_3 = CH_3$; $R_4 = CH_2OH$
32a, $R_4 = CH_2OSO_2CH_3$
32b, $R_1 = CH_3$; $R_4 = CH_2OSO_2CH_3$
32c, $R_2 = CH_3$; $R_4 = CH_2OSO_2CH_3$
32d, $R_3 = CH_3$; $R_4 = CH_2OSO_2CH_3$
33a, $R_4 = CH_2SCN$
33b, $R_1 = CH_3$; $R_4 = CH_2SCN$
33c, $R_2 = CH_3$; $R_4 = CH_2SCN$
33d, $R_3 = CH_3$; $R_4 = CH_2SCN$
34a, $R_4 = CH_2SH$
34b, $R_1 = CH_3$; $R_4 = CH_2SH$
34c, $R_2 = CH_3$; $R_4 = CH_2SH$
34d, $R_3 = CH_3$; $R_4 = CH_2SH$



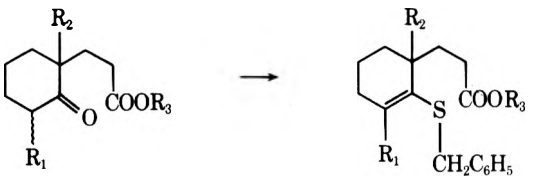
1, 11, R = H
8, 16, 17, $R_1 = CH_3$
7, 15, $R_2 = CH_3$
2, 12, 13, $R_3 = CH_3$

18, R = H
20, R_1 or $R_2 = CH_3$ (trans to S)
21, R_1 or $R_2 = CH_3$ (cis to S)
19, $R_3 = CH_3$

All R's = H unless indicated

of isomers as indicated in Scheme V. The ester groups were converted by a sequence of steps[13] into mercaptomethyl groups (see Scheme V), and the 3′-mercaptopropylcyclohexenes **34** were cyclized by heating with azobis(isobutyronitrile) in benzene as described for method A.

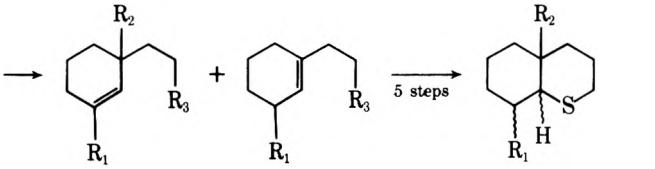
Scheme VI



27b, $R_1 = CH_3$, $R_3 = C_2H_5$
27e, $R_2 = R_3 = CH_3$

35b, $R_1 = CH_3$, $R_3 = C_2H_5$
35e, $R_2 = R_3 = CH_3$

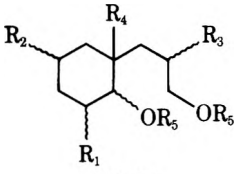
All R's = H unless indicated



30b, $R_1 = CH_3$, $R_3 = COOC_2H_5$
30e, $R_2 = CH_3$, $R_3 = COOCH_3$

8, 16, 17, $R_1 = CH_3$
14, $R_2 = CH_3$

Scheme VII

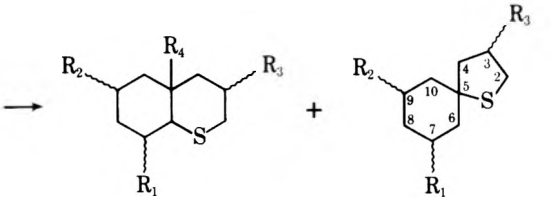


36, 37

36a, all R's = H
36b, $R_1 = CH_3$
36c, $R_2 = CH_3$
36d, $R_3 = CH_3$
36e, $R_4 = CH_3$

37a, $R_5 = SO_2CH_3$
37b, $R_1 = CH_3$, $R_5 = SO_2CH_3$
37c, $R_2 = CH_3$, $R_5 = SO_2CH_3$
37d, $R_3 = CH_3$, $R_5 = SO_2CH_3$
37e, $R_4 = CH_3$, $R_5 = SO_2CH_3$

All R's = H unless indicated

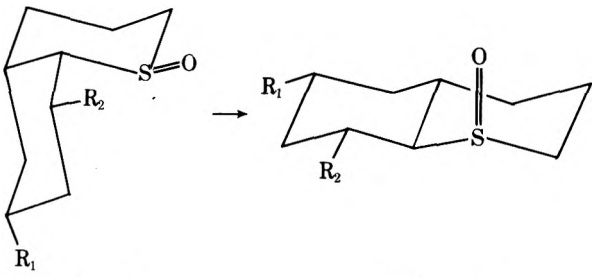


1,11, all R's = H
8,16, $R_1 = CH_3$
15, $R_2 = CH_3$
2,3,12,13, $R_3 = CH_3$
14, $R_4 = CH_3$

18, all R's = H
20, R_1 or $R_2 = CH_3$ (trans to S)
21, R_1 or $R_2 = CH_3$ (cis to S)
19, $R_3 = CH_3$

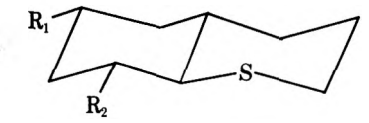
In addition to ring closure to give thiane derivatives, cyclization to give either thiepanes [from 3-(3′-mercaptopropyl)cyclohexene-1's] or thiolanes [from 1-(3′-mercaptopropyl)cyclohexene-1's] might be expected. No seven-membered ring products were isolated, the steric demand for such a reaction apparently being too high, but five-membered ring products (1-thiaspiro[4.5]decanes, **18–21**) were found in appreciable amounts. The mixtures of products were separated by precipitation and recrystallization of the $HgCl_2$ complexes, decomposition of the complexes with acid and steam distillation, and finally by preparative gas chromatography of the prepurified compounds or of the mother liquors. Configuration [cis or trans fusion of the rings, α or β position (see footnote *c*, Table 1) of the methyl groups] and conformation of the products were determined by ^{13}C and ^1H NMR spectroscopy.[3] From the data in Table I it is evident that formation of the cis-fused products is strongly preferred, in agreement with the

Scheme VIII



38a, $R_1 = CH_3$ **39a**, $R_1 = CH_3$
38b, $R_2 = CH_3$ **39b**, $R_2 = CH_3$

All R's = H unless indicated



7, $R_1 = CH_3$
8, $R_2 = CH_3$

known preference in addition of thio radicals to cyclohexenes to give axially substituted cyclohexanes.[13,14]

Method C. Since elimination of a methylsulfonyloxy group from 3-(1-methyl-2-methylsulfonyloxycyclohexyl)propionate was expected to be accompanied by skeletal rearrangements,[13] an alternative route, which had been successfully applied for the synthesis of 4-thia-5β-cholestanes,[13] was used to prepare 10-methyl-1-thiadecalin: 3-(1-methyl-2-oxocyclohexyl)propionate **27e** was converted into the benzyl thioenol ether **35e**, which was then desulfurized by treatment with Raney nickel previously partially deactivated by heating in acetone. Careful judgement of the time of deactivation is a somewhat crucial point of this method, or else the reaction does not go to completion; however, if the Raney nickel is properly prepared, yields in this step are excellent.

The reaction sequence from **30e** to **14** follows the procedure described above for method B (see also ref 13). An analogous synthesis starting with **27b** gave **8**, **16**, **17**, and **20** in the proportion listed in Table I, slightly different than in method B, presumably because different amounts of the two isomeric cyclohexenes **30b** are formed by the two paths. In general, method C is necessary for compounds with quaternary centers next to the carbonyl group on the cyclohexane ring, and the yields of compounds **30** are better than in method B; for large-scale synthesis, the large amount of Raney nickel required (see Experimental Section) poses a problem.

Method D. Reduction of the 3-(2-oxocyclohexyl)propionates **27** with lithium aluminum hydride afforded mixtures of cis and trans isomers of the diols **36**. The products were esterified with methanesulfonyl chloride without separation, and the bis(methanesulfonates) **37** were allowed to react with sodium sulfide in either dimethylformamide[4a] or 50% ethanol.[15,16]

The resulting (methyl-) 1-thiadecalins were admixed with very considerable amounts of 1-thiaspiro[4.5]decanes. Since the same products (**20** and **21**) are formed from **37b** and **37c**, the way of their formation may be inferred: instead of being replaced by S^-, the methylsulfonyloxy group on the cyclohexane ring reacts via elimination, and the sulfur on the propyl side chain subsequently adds to the resulting double bond. For the same reason, formation of the cis-fused thiadecalins is again strongly preferred, since the bis(methanesulfonate) with axial orientation of the CH_3SO_3 group on the cyclohexane ring (leading to trans products in case of nucleophilic displacement) is also oriented favorably for elimination.

An attempt to prepare 10-methyl-1-thiadecalins by this method gave a fraction of sulfides in only 9% theoretical yield, containing **14** and (by ^1H NMR spectrum) 10-methyl-*trans*-1-thiadecalin, but too little for positive identification. The low yield in this instance is explained by side reactions due to the quaternary carbon next to the methylsulfonyloxy group (see above).

Separation of the various product mixtures was accomplished in the manner described for methods A–C.

Method E. A number of *trans*-1-thiadecalins [especially the interesting 8α-methyl-*trans*-1-thiadecalin[1c] (**8**)] were obtained only in small amounts by the methods described above (see Table I). Moreover, the retention times of **8** and of *cis*-7-methyl-1-*r*-thiaspiro[4.5]decane (**21**) were practically identical on all available GC columns, which made purification of **8** nearly impossible.

Both **16** and **15**, on the other hand, were readily available in pure form: the mercuric chloride complex of **16** is not very soluble, allowing recrystallization, and **15** is a solid at room temperature and could itself be recrystallized. Since **16** and **15** are effectively locked in one conformation,[3] oxidation to the sulfoxides gave only one product in each case, the β-sulfoxides **38a** and **38b**, respectively, the α-sulfoxides being excluded because of severe syn–axial interactions in both possible conformations.

The sulfoxide oxygen in thiane 1-oxides is known[15,17] to prefer the axial position, and the *trans*-1-thiadecalin system has been calculated[18] to be more stable than the corresponding *cis*-1-thiadecalin by 1.7 kcal/mol. In addition, an interaction corresponding to a syn–axial interaction between oxygen and the methyl group in **38b** is absent in **39b**. Consequently, equilibration between **38** and **39** should lead to a high preference of the trans-fused system.

Equilibration was achieved by adding butyllithium to the benzene solutions of **38a** and **38b** and quenching with water after 2 h. Isolation of the sulfoxides **39** and reduction with phosphorus trichloride[19] indeed gave nearly pure **8**, and **7** containing less than 10% **15**.

The dideuterated analogue of **10** (9-methyl-*trans*-1-thiadecalin-2,2-d_2), which was needed to aid the identification of the signals of **10** in the ^{13}C NMR spectrum,[3] was also prepared via the sulfoxide: a mixture of the α- and β-1-oxides of **10** was reacted two times with butyllithium and with D_2O, and a mixture of mainly **10**-d_2, **10**-d_1, and **10** was obtained upon reduction of the sulfoxides.

Experimental Section

Melting points of compounds **1–21** and of their $HgCl_2$ complexes are summarized in Table II (for methods see footnotes *a* and *b*). Microanalyses were carried out by Dr. Zak, Physikalisch-Chemisches Institut der Universität Wien. Compounds **1**, **3–5**, and **8–16** were further characterized by preparing their 1-*N*-*p*-chlorophenyl imides; melting points and elemental analyses of these compounds are reported elsewhere.[1c]

Analytical gas chromatography was carried out on a Varian Aerograph Series 1400 equipped with FID, on 0.125-in. columns. Columns used were 12-ft, 20% Carbowax 20M + 10% KOH, and a 12-ft, 20% SE 30, on Chromosorb W, 80–100 mesh. A Varian Aerograph Model 920 equipped with a thermal-conductivity detector, with 0.375-in. aluminum columns with matching phases, was used for preparative gas chromatography.

The ^1H and ^{13}C NMR spectra of compounds **1–17** are reported in the following paper of this issue.[3] The proton and variable temperature ^{13}C spectra of compounds **18–21** will be presented elsewhere.[20] 60-MHz ^1H spectra were recorded on a Varian EM-360 with internal lock facility; ^{13}C spectra were recorded in the pulsed mode at 25.16 MHz on a Varian XL-100 spectrometer. Solvent was $CDCl_3$, and the reference was Me_4Si.

Starting materials were purchased from various sources unless methods of preparation are indicated.

In the sequel, only one representative preparation of methods A–D

Table II. Characteristics of Thiadecalins 1–17 and Thiaspirodecanes 18–21

Compd	Registry no.	Mp (lit.)[a]	Mp of $HgCl_2$ complex (lit.)[b]	Registry no.
1	54340-73-7	17–18 (17.7[4a])	170–171 (172–173.5[4a])	63743-83-9
2	63702-90-9	c	172–176	63782-93-4
3	63730-12-1	8–10	152–153	63782-94-5
4	63730-13-2	9–11	176–177 (161–162[4b])	63782-95-6
5	63730-14-3	0–1	148–149 (141–142[4b])	63782-96-7
6	63702-91-0	2–3	e	
7	63702-92-1	8–10	161	63782-97-8
8	63702-93-2	d	132–133	63782-98-9
9	63730-15-4	6–8	145–146	63782-99-0
10	63702-94-3	d	153–154 (117.5–118.5[4c])	63714-81-8
11	57259-80-0	−1–1	176–177	63714-82-9
12	63730-16-5	12–14	187–188	63783-00-6
13	63730-17-6	31–32	158–159	63783-01-7
14	63702-95-4	−8 to −7	137–139	63714-83-0
15		46–47	154–155	63783-02-8
16		7–9	153–154	63783-03-9
17	63730-20-1	c	160–162	63783-04-0
18	53703-51-8	d	97–100	63714-84-1
19	63714-78-3	d	93–94	63714-85-2
20	63714-79-4	d	125–127	63714-86-3
21	63714-80-7	d	e	

[a] In °C. Melting points of sulfides melting below room temperature were determined by placing the crystalline compound in a sealed ampule into a stirred 2-propanol bath which was gradually warmed from −30 °C to room temperature. [b] In °C. Since some of the complexes showed a tendency to sublime the melting points were determined in sealed capillaries in an electrically heated Hoover type silicon bath. Differences to values previously reported (note for **10**[4c]) are probably due to this sublimation. [c] Sample contained small amounts of other isomers and did not crystallize. [d] Did not crystallize at −30 °C, although pure by GC. [e] Not determined because of very small amounts of material isolated. All compounds gave satisfactory elemental analysis, with exception of **6** and **21** where no analysis was attempted for the same reason.

Table III. ^{13}C[a] and Pertinent ^{1}H[b] Chemical Shifts of Cyclohexene Oxides[c] and Cyclohexene Sulfides[d]

	40[c]	*trans*-3-CH_3-**40**[g]	*cis*-3-CH_3-**40**[h]	**22a**	*trans*-**22c**	*cis*-**22c**
			^{13}C			
C-1	51.9^{e}	52.6_8	52.8_6	36.7_2	37.7_6	36.4_3
C-2	51.9^{e}	57.1_7	56.7_8	36.7_2	41.4_0	45.8_6
C-3	24.7^{e}	29.1_1	30.2_1	25.8_9	31.7_4	30.9_0
C-4	19.7^{e}	29.2_6	27.1_7	19.4_9	30.8_5	24.5_9
C-5	19.7^{e}	17.1_4	20.3_3	19.4_9	16.8_9	21.2_2
C-6	24.7^{e}	24.7_9	23.8_0	25.8_9	26.4_8	25.6_8
CH_3		19.1_6	18.5_3		22.8_0	22.5_6
			^{1}H			
H-1		3.08 ($w_{1/2}$ = 9)	3.08 ($w_{1/2}$ = 9)		3.18[f]	
H-2	3.08 ($w_{1/2}$ = 5)	2.78 (d, 4)	2.91 (d, 4 of d, 2)	3.18 ($w_{1/2}$ = 6)	2.77 (d, 6.5 of d, 1.5)	3.20 ($w_{1/2}$ = 5)
CH_3		1.06 (d, 7)	1.08 (d, 7)		1.15 (d, 7)	1.10 (d, 6.5)

[a] In ppm from Me_4Si; solvent $CDCl_3$. [b] H-1 and H-2 refer to the protons at C-1 and C-2, respectively. Ppm from Me_4Si, solvent $CDCl_3$. In parentheses: coupling constants, and half-width of not resolved signals, in Hz. Data are apparent values measured in spectra. [c] **40**: Cyclohexene oxide; registry no.: 286-20-4. [d] See Schemes III and IV. [e] Taken from the literature: S. G. Daves and G. H. Whitham, *J. Chem. Soc., Perkin Trans. 2*, 861 (1975). [f] Taken from a mixture of **22c**'s. [g] Registry no.: 7443-54-1. [h] Registry no.: 7443-69-8.

is reported. More detailed procedures for the compounds prepared are given in the Supplemental Material.

Method A. 8α-Methyl-*trans*-1-thiadecalin (9), 8α-Methyl-*trans*-1-thiadecalin (8), 5α-Methyl-*trans*-1-thiadecalin (6). *trans*-3-Methylcyclohexene Sulfide (*trans*-22c) and *cis*-3-Methylcyclohexene Sulfide (*cis*-22c). (a) Thiourea Method.[6] 3-Methylcyclohexene oxide[8] (50% trans, 50% cis isomer, by NMR and GC; bp 42–47 °C/11 mm; bp lit.[8] 75 °C/6 mm) (11.2 g) was added to a suspension of 12 g of thiourea in 28 mL of water and 7.4 g of H_2SO_4 without external cooling; when addition was complete, the mixture was stirred for 2 h. A solution of 16 g of Na_2CO_3 in 100 mL of water was added dropwise, and the resulting (basic) solution was extracted repeatedly with petroleum ether. The organic solution was dried, and the solvent was distilled off. The product mixture was distilled (Kugelrohr, air bath ~85 °C/20 mm) and found free of starting epoxides by GC. Yield of **22c**: 10.6 g (83% of theory). Isomer ratio (by NMR): 50% *cis*-**22c**, 50% *trans*-**22c**.

(b) Thiocyanate Method[7]. 3-Methylcyclohexene oxide (mixture as for a) (11.2 g) was added to a solution of 20 g of KSCN in 13 mL of ethanol plus 15 mL of H_2O, and the mixture was stirred magnetically

at room temperature for 48 h. The mixture was extracted with petroleum ether, the extract was dried, and the solvent was distilled off. The residue was found by GC to consist of 42% epoxide (isomer ratio trans/cis = 65:35) and of 52% episulfide. The mixture was once more reacted with KSCN as above for 72 h. The product mixture consisted of 20% epoxide (trans/cis = 94:6) and of 80% episulfide. The epoxides were distilled from the mixture; pure *trans*-3-methylcyclohexene oxide was obtained from this fraction by preparative GC (Carbowax–KOH, 90 °C). The episulfides were distilled (Kugelrohr); composition (NMR): 62% *trans*-**22c**, 38% *cis*-**22c**. Yield 43%.

8β-Methyl-*trans*-1-thiadecalin (9). A solution of allylmagnesium bromide (from 5.7 g of magnesium turnings and 7.2 g of allyl bromide in anhydrous ether) was prepared and separated from excess magnesium by rapid decantation through a glass Büchner funnel. A solution of 1.1 g of pure *cis*-**22c** (prepared by the thiourea method from recovered *trans*-3-methylcyclohexene oxide, see above) in anhydrous ether was added slowly to the stirred Grignard solution. When the addition was complete, the mixture was heated to reflux for 12 h, and was then hydrolyzed with saturated NH_4Cl solution. The ether was decanted, the aqueous phase was repeatedly extracted with ether, and the ether solutions were united and dried. The solvent was distilled off at reduced pressure, and the residue (**24c**) was used without purification.

The crude **24c** was dissolved in 50 mL of anhydrous benzene and 100 mg of azobis(isobutyronitrile) was added. The solution was heated to reflux overnight. The solvent was distilled off at reduced pressure, and the residue was distilled in a Kugelrohr apparatus (~120 °C air bath temperature/10 mm). Gas chromatography of the product mixture showed one major product **9** and an unknown compound (presumably 2,7-dimethyl-1-thiahydrindane). No signals of **8** and **6** could be detected. Yield 410 mg (48% from *cis*-**22c**).

8β-Methyl- (9), 8α-Methyl- (8), and 5α-Methyl-*trans*-1-thiadecalin (6). A mixture of *trans*-**22c** (62%) and *cis*-**22c** (38%) (11.5 g) was added to a solution of allylmagnesium bromide (from 19 g of allyl bromide and 15 g of magnesium). The intermediates **24c** and **24f** were cyclized [500 mg of azobis(isobutyronitrile)] as described above. Yield of product mixture after distillation (Kugelrohr) 5.3 g; for composition, see Table I.

The mixture of products was dissolved in ethanol and added to a solution of 17 g of $HgCl_2$ in ethanol. The mixture was heated on a hot plate for 10 min and then brought to room temperature. The precipitate was collected and recrystallized three times from boiling ethanol. Decomposition of the recrystallized complex with 50% HCl and steam distillation and extraction of the distillate with petroleum ether gave pure **9**. Preparative gas chromatography (Carbowax–KOH, 145 °C) of the similarly treated mother liquor gave **6** and **8**.

Method B. *cis*-1-Thiadecalin (11). Methyl 3-(2-Hydroxycyclohexyl)propionate (28a). To a stirred solution of 14.7 g of **27a**[11] in 160 mL of anhydrous methanol, 3 g of $NaBH_4$ was slowly added, at 0 °C.[12b] When the addition was complete, the mixture was stirred for an additional 3 h at 0 °C and then was neutralized with CH_3COOH. After concentration to near dryness at reduced pressure, the residue was dissolved in CH_2Cl_2, the solution was washed with water and sodium bicarbonate solution, the organic solution was dried, and the solvent was distilled off. The residue was distilled in a Kugelrohr unit. Yield of **28a** 8.7 g; bp 120–130 °C/0.1 mm.

Methyl 3-Cyclohexen(1- or 2-)ylpropionate (30a). A solution of 8.7 g of **28a** in 150 mL of anhydrous pyridine was cooled to 0 °C, and 20 g of methanesulfonyl chloride was added gradually. The mixture was kept at +5 °C for 100 h and was then heated to reflux for 5 h. Most of the solvent was distilled off at reduced pressure, and the residue was poured on a mixture of ice, water, and HCl. The organic material was extracted with CH_2Cl_2, the extracts were washed with dilute HCl and sodium bicarbonate solution, and the solvent was distilled off. The residue was distilled in a Kugelrohr apparatus. Yield of **30a** 3.6 g; bp 120 °C/8 mm.

1-(3′-Hydroxypropyl)cyclohexene and 3-(3′-Hydroxypropyl)cyclohexene (31a). A solution of **30a** (8 g) in anhydrous ether was slowly added to 1.75 g of $LiAlH_4$ in anhydrous ether. The mixture was heated to reflux overnight and was then hydrolyzed with water. The ether was decanted, the precipitate was repeatedly washed with ether, the combined ether extracts were dried, and the solvent was distilled off. The residue was distilled in a Kugelrohr apparatus. Yield of **31a** 6 g; bp ~130 °C/8 mm.

1-(3′-Methylsulfonyloxypropyl)cyclohexene and 3-(3′-Methylsulfonyloxypropyl)cyclohexene (32a). To a solution of 6.5 g of **31a** in 200 mL of anhydrous pyridine at 0 °C, 30 g of methanesulfonyl chloride was added gradually. The resulting mixture was kept at +5 °C for 12 h and then poured on a mixture of ice, water, and HCl. The product was extracted with CH_2Cl_2, the extracts were washed with dilute HCl and sodium bicarbonate solution, the solvent was distilled off at reduced pressure, and the residue was used without further purification.

1-(3′-Thiocyanopropyl)cyclohexene and 3-(3′-Thiocyanopropyl)cyclohexene (33a). A solution of 8.7 g of **32a** and 50 g of KSCN in 200 mL of anhydrous acetone was heated to reflux overnight. The solvent was distilled off, the residue was extracted repeatedly with petroleum ether, the petroleum ether extracts were united and dried, and the solvent was distilled off. The residue was distilled in a Kugelrohr apparatus. Yield of **33a** 6.7 g; bp ~150 °C/8 mm.

1-(3′-Mercaptopropyl)cyclohexene and 3-(3′-Mercaptopropyl)cyclohexene (34a). A solution of 6.7 g of **33a** in anhydrous ether was added to 2 g of $LiAlH_4$ in anhydrous ether, and the mixture was stirred overnight at room temperature. After isolation of the product as described for **31a**, 5.22 g of **34a** (bp ~140 °C/8 mm) was obtained.

***cis*-1-Thiadecalin (11).** A solution of 5.1 g of **34a** and 0.5 g of azobis(isobutyronitrile) in dry benzene was reacted as described for method A. Distillation of the product in a Kugelrohr gave 4.8 g of a mixture; for composition, see Table I. Purification of **11** by repeated recrystallization of the $HgCl_2$ complex, or by preparative GC (Carbowax–KOH; 140 °C).

Method C. 8α-Methyl-*cis*-1-thiadecalin (16), 8β-Methyl-*cis*-1-thiadecalin, 8α-Methyl-*trans*-1-thiadecalin (8). Ethyl 3-(2-Oxo-3-methylcyclohexyl)propionate (27b). A solution of 66 g of **25b**[11] and 70 g of freshly distilled **26b** in 150 mL of anhydrous ethanol was heated to reflux for 48 h. Water (100 mL) was added, and the mixture was heated for 1 h. Most of the solvent was distilled off at reduced pressure, and the residue was worked up as described[11] for **27a**. Yield of **27b** 42.4 g; bp 147–149 °C/10 mm.

Ethyl 3-(2-Benzylthio-3-methylcyclohexen(1- or 2-)yl)propionate (35b). A solution of 39.6 g of **27b**, 40.9 g of benzyl mercaptan, and 2 g of toluenesulfonic acid in 500 mL of benzene was heated to reflux for 48 h, and the water formed was separated with a Dean–Stark trap. After the theoretical amount of water had been collected, the solvent was distilled off and the residue was distilled in a Kugelrohr distillation unit (air bath temperature 140–150 °C/10^{-3} mm). Yield of **35b** 53.6 g.

Ethyl 3-(3-Methylcyclohexen(1- or 2-)yl)propionate (30b). Raney nickel[21] from 300 g of alloy was washed with ethanol and acetone, and was heated in 1 L of acetone (Merck grade) to reflux for 45 min; 23.5 g of **35b** in 100 mL of acetone was rapidly added, and the mixture was heated to reflux, with stirring, for 18 h. The mixture was brought to room temperature, and the acetone was decanted. The solid was washed three times with acetone, and the combined acetone solutions were filtered through a bed of Celite. The solvent was distilled off, the residue was dissolved in petroleum ether, the solution was dried over Na_2SO_4, and the solvent was distilled off. The residue was distilled; yield of **30b** 13.4 g. Isomer ratio by GC 52:48. As was the case in method B, no attempt was made to determine which of the two isomers was the predominant one. The CH_3– signals in the ^1H NMR spectrum (–cyclohexen-1-yl: 1.63 ppm, s, half-width 6 Hz; –cyclohexen-2-yl: 0.93 ppm, d, J = 6.5 Hz) were superimposed with the rest of the molecule and could not be accurately integrated. The product composition of the thiadecalins indicates that more ethyl 3-(3-methylcyclohexen-2-yl)propionate is formed with method B, ultimately leading to the formation of less spiro-compound **20** (see Table I).

From the mixture of **30b**, **16**, **17**, and **8** were prepared analogously as described for **11**, method B. For composition of products, see Table I.

10-Methyl-*cis*-1-thiadecalin (14). Methyl 3-(1-Methyl-2-benzylthiocyclohexen-2-yl)propionate (35e). A solution of **27e**[12a] (39.6 g), 40.9 g of benzyl mercaptan, and 2 g of toluenesulfonic acid in 500 mL of benzene was reacted as described for **35b**. Kugelrohr distillation (bp ~150 °C/10^{-3} mm) gave 48.7 g of **35e**. Decomposition during distillation occurred if the bath temperature was raised above 160 °C.

Methyl 3-(1-Methylcyclohexen-2-yl)propionate (30e). From **35e** with Raney nickel as described for **30b**. Yield (from 23.5 g of **35e**) 10 g.

10-Methyl-*cis*-1-thiadecalin (14). From 9 g of **30e**, in an analogous procedure to **11** (see method B), 5.1 g of **14** was obtained after distillation. Purification was by recrystallization of the $HgCl_2$ complex.

Method D. *cis*-1-Thiadecalin (11). 2-(3′-Hydroxypropyl)cyclohexanol (cis and trans) (36a). A solution of 18.4 g of **27a**[11] in anhydrous ether was added to a stirred suspension of 5 g of $LiAlH_4$ in anhydrous ether. The mixture was heated to reflux overnight and

was hydrolyzed with water. The ether was decanted, the solid was washed repeatedly with ether, and the ether solutions were united and dried. The solvent was distilled off, and the residue was distilled in a Kugelrohr apparatus (bp lit.[12b] 119–120 °C/0.3 mm); yield 15.4 g.

1-(3'-Methylsulfonyloxypropyl)-2-methylsulfonyloxycyclohexane (cis and trans) (37a). To a solution of 15.4 g of **36a** in 160 mL of dry pyridine cooled to 0 °C, methanesulfonyl chloride (36 g) was slowly added. The mixture was kept at +5 °C for 100 h and was then poured on ice, water, and HCl. The products were extracted with CH_2Cl_2, and the organic extracts were washed with dilute HCl and sodium bicarbonate solution and dried. The solvent was distilled off at low temperature, and the crude product was used for the next step without purification.

***cis*-1-Thiadecalin (11). (a) Solvent Dimethylformamide.**[4a] A solution of 58 g of $Na_2S{\cdot}9H_2O$ in 250 mL of DMF was gradually heated to ~130 °C, and the water was distilled off. A solution of the crude **37a** in dry DMF was gradually added, and the mixture was kept at ~130 °C for 12 h. The mixture was brought to room temperature and poured on a fourfold volume of water. The aqueous mixture was extracted with petroleum ether, the extract was dried, the solvent was distilled off, and the residue was distilled in a Kugelrohr apparatus. Yield of product mixture 6.6 g; for composition, see Table I. Purification of **11** by recrystallization of the $HgCl_2$ complex and/or preparative GC (Carbowax-KOH, 140 °C).

(b) Solvent 50% Aqueous Ethanol. A solution of crude **37a** from 29.3 g of **36a** in the minimum amount of tetrahydrofuran was slowly added to a boiling solution of 61 g of $Na_2S{\cdot}9H_2O$ in 800 mL of 50% ethanol, and the mixture was heated to reflux for 72 h. After that period, the mixture was steam distilled, and the distillate was diluted with water to a total volume of 3 L and was extracted with petroleum ether. The extracts were dried, the solvent was distilled off, and the residue was distilled in a Kugelrohr apparatus. Yield of product mixture 11.9 g; for composition, see Table I. Separation of products as reported above.

Method E. 8α-Methyl-*trans*-1-thiadecalin (8). 8α-Methyl-*cis*-1-thiadecalin 1β-Oxide (38b). To a solution of 10.3 g of **16** in CH_2Cl_2, 100 mL of an 0.59 M solution of *m*-chloroperbenzoic acid in CH_2Cl_2 was added at 0 °C, and the sulfoxide was isolated analogous to ref 15. Gas chromatography of the product mixture after separation from unreacted starting material showed one major (**38b**, >90%) and three minor products (SE 30, 230 °C). The product was used for the next step without purification: ^1H NMR 1.27 (d, CH_3, J = 6 Hz), 2.73 (s, H_9, half-width = 7 Hz), 3.42 ppm (d of m, H_{2e}, J = 11.5 Hz).

8α-Methyl-*trans*-1-thiadecalin 1β-Oxide (39b). A solution of 7.6 g of crude **38b** in dry benzene was cooled to <10 °C; a slow stream of dry nitrogen was passed through the reaction flask. A solution of butyllithium (17 mL of a 2.6 M solution in hexane, diluted with 20 mL of dry benzene) was added dropwise. When the addition was complete, the mixture was stirred at room temperature for 1.5 h and was then hydrolyzed with external cooling. The benzene layer was separated, and the aqueous layer was acidified and extracted with CH_2Cl_2. The organic solutions were united and dried, and the solvent was distilled off. The residue was distributed between an aqueous NaCl solution and petroleum ether; the aqueous solution was extracted with CH_2Cl_2, the extract was dried, and the solvent was distilled off. The residue consisted of one major (**39b**; >90%) and three minor unidentified products: yield 7 g; ^1H NMR 1.14 (d, CH_3, J = 5 Hz), 3.10 ppm (d of m, H_{2e}, J = 10 Hz).

8α-Methyl-*trans*-1-thiadecalin (8). A solution of 7 g of crude **39b** and of 18 mL of PCl_3 in 100 mL of CH_2Cl_2 was heated to reflux for 1 h. The mixture was poured on ice with stirring. After 2 h, the dichloromethane layer was separated, the aqueous layer was extracted with CH_2Cl_2, the dichloromethane solutions were united and dried, the solvent was distilled off, and the residue was distilled in a Kugelrohr apparatus. Yield of 8 5.5 g.

6α-Methyl-*trans*-1-thiadecalin (7). 6α-Methyl-*cis*-1-thiadecalin 1β-Oxide (38a). From 1.9 g of **15**, analogous to **38b**: Yield 2.0 g of crude **38a**; ^1H NMR 0.95 (d, CH_3, J = 5 Hz), 2.68 (s, H_9, half-width = 9 Hz), 3.40 ppm (d of m, H_{2e}, J = 10 Hz).

6α-Methyl-*trans*-1-thiadecalin 1β-Oxide (39a). From 2.0 g of crude **38a**, analogous to **39b**: ^1H NMR 0.88 (d, CH_3, J = 5.5 Hz), 3.05 ppm (d of m, H_{2e}, J = 10 Hz).

6α-Methyl-*trans*-1-thiadecalin (7). From **39a**, as described for **8**. Composition >90% **7**, <10% **15**. Purification of **7** by recrystallization of $HgCl_2$ complex.

9-Methyl-*trans*-1-thiadecalin-2,2-d_2 (10-d_2). Crude **10** (see method A) (2 g) was oxidized as described for **38b**. The sulfoxides were distilled in a Kugelrohr apparatus; yield of approximately equal amounts of 1α- and 1β-oxide 1.4 g (by GC and ^1H NMR): ^1H NMR 1.25 (s, CH_3 1-α-oxide), 1.13 ppm (s, CH_3 1-β-oxide). The mixture was dissolved in benzene and treated with butyllithium as described for **39a** and **39b**. After 1.5 h, the mixture was hydrolyzed with a solution of 3 mL of D_2O and 1.6 g of acetyl chloride. The sulfoxides were recovered and the butyllithium–D_2O treatment was repeated. The recovered sulfoxides were reduced with PCl_3 as described above; yield of sulfides 0.5 g (mixture of **10**-d_2, **10**-d_1, and a little **10**).

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Registry No.—**24a**, 63714-87-4; **24b**, 63714-88-5; **24c**, 63714-89-6; **24d**, 63714-90-9; **24e**, 63714-91-0; **24f**, 63714-92-1; **25b**, 5049-1-4; **25c**, 39716-23-9; **26a**, 96-33-3; **26b**, 140-88-5; **27a**, 10407-33-7; **27b**, 63714-93-2; **27c**, 40265-48-3; **27d**, 63714-94-3; **27e**, 53068-89-6; **28a**, 63714-95-4; **28b**, 63714-96-5; **28c**, 63714-97-6; **28d**, 63714-98-7; **29c**, 63714-9908; **30a** 1-ene, 544445-57-7; **30a** 2-ene, 60211-02-1; **30b** 1-ene, 63715-00-4; **30b** 2-ene, 63715-01-5; **30c** 1-ene, 63715-02-6; **30c** 2-ene, 63715-03-7; **30d** 1-ene, 63715-04-8; **30d** 2-ene, 63715-05-9; **31a** 1-ene, 22516-18-3; **31a** 2-ene, 15745-87-6; **31b** 1-ene, 63715-06-0; **31b** 2-ene, 63715-07-1; **31c** 1-ene, 63715-08-2; **31c** 2-ene, 63715-09-3; **31d** 1-ene, 63715-10-6; **31d** 2-ene, 63715-11-7; **32a** 1-ene, 63715-12-8; **32a** 2-ene, 63715-13-9; **32b** 1-ene, 63715-14-0; **32b** 2-ene, 63715-15-1; **32c** 1-ene, 63715-16-2; **32c** 2-ene, 63715-17-3; **32d** 1-ene, 63715-18-4; **32d** 2-ene, 63715-19-5; **33a** 1-ene, 63715-20-8; **33a** 2-ene, 63715-21-9; **33b** 1-ene, 63715-22-0; **33b** 2-ene, 63715-23-1; **33c** 1-ene, 63715-24-2; **33c** 2-ene, 63715-25-3; **33d** 1-ene, 63715-26-4; **33d** 2-ene, 63715-27-5; **34a** 1-ene, 63715-28-6; **34a** 2-ene, 63715-29-7; **34b** 1-ene, 63715-30-0; **34b** 2-ene, 63715-31-1; **34c** 1-ene, 63715-32-2; **34c** 2-ene, 63715-33-3; **34d** 1-ene, 63715-34-4; **34d** 2-ene, 63715-35-5; **35b**, 63743-84-0; **35e**, 63715-36-6; *cis*-**36a**, 60211-12-3; *trans*-**36a**, 60211-13-4; **36b**, 63715-37-7; **36c**, 63715-38-8; **36d**, 63715-39-9; *cis*-**37a**, 63715-40-2; *trans*-**37a**, 63715-41-3; **38a**, 63715-42-4; **38b**, 63715-43-5; **39a**, 63783-05-1; **39b**, 63783-06-2; KSCN, 333-20-0; thiourea, 62-56-6; allyl bromide, 106-95-6; methanesulfonyl chloride, 124-63-0; benzyl mercaptan, 100-53-8; methallyl chloride, 563-47-3; 3-chloro-1-butene, 563-52-0.

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Configuration and Conformational Equilibria of Methyl-Substituted *trans*- and *cis*-1-Thiadecalins

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^{13}C and ^{1}H NMR spectra of a number of methyl-substituted *trans*- and *cis*-1-thiadecalins have been recorded. Assignment of signals was made by off-resonance decoupling, parametrization of substituent effects, and comparison with carbon and nitrogen analogues; at the same time, the configuration of the compounds was established. The conformational equilibria of the conformationally heterogeneous parent, 3β-methyl-, 8β-methyl-, and 10-methyl-*cis*-1-thiadecalins were determined by low-temperature ^{13}C NMR.

In the last few years the chemistry of saturated sulfur-containing heterocycles and their S-substituted derivatives have been the subject of a fair amount of interest.[1] In order to further our investigations of the conformational and configurational preferences and the rearrangement reactions of thiane- and 1,3-dithiane-1-imides[2] a conformationally rigid system offering the possibility of biasing the conformational preferences of substituents on sulfur and on the adjacent carbon atoms was needed. *trans*-1-Thiadecalin (**1**) provides such a system: ring inversion is prohibited for reasons of strain, and substitution at certain positions will bias the site of a new substituent on S-1 or C-2 through syn–axial interactions. Suitable substitution of *cis*-1-thiadecalin (**11**) also leads to conformationally homogeneous compounds with similar properties. Finally, the conformational preferences of mobile *cis*-1-thiadecalins of the sulfimides derived from them promised to be interesting.

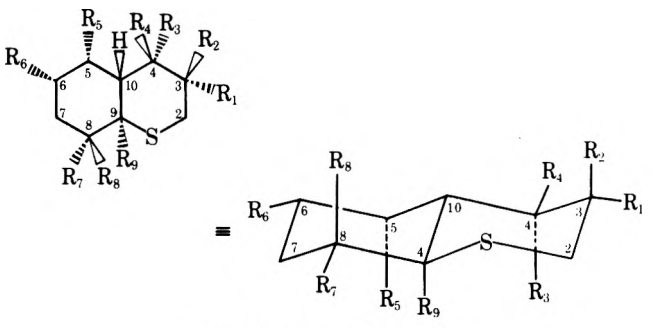
A number of methyl-substituted *trans*- and *cis*-1-thiadecalins (Schemes I and II) were accordingly prepared,[3] and their ^{13}C and ^{1}H NMR spectra were recorded at room temperature (Tables I and IV). When compounds proved to be conformationally heterogeneous at room temperature (**11, 12, 14,** and **17**), the low temperature ^{13}C NMR spectra were recorded and the proportion of conformers determined by integration of appropriate signals. In the sequel, the spectral assignments and, at the same time, the configuration and conformation of the 17 compounds investigated are discussed, and the conformational equilibria of the four mobile compounds are rationalized.

^{13}C NMR Spectra. The noise-decoupled room temperature ^{13}C spectrum of *trans*-1-thiadecalin (**1**) shows the expected nine sharp lines. The most downfield signals appear as doublets in the off resonance decoupled spectrum and are thus identified as C-9 and C-10. Comparison of the spectra of thiane[5a,6] and cyclohexane[4,7] shows that carbon atoms α and β to sulfur experience downfield shifts of 2.9 and 0.6 ppm, respectively. The most downfield doublet is accordingly assigned to C-9, the more upfield one to C-10.

The three signals at next higher field belong to carbon atoms 4, 5, and 8, which have two α and three β substituents.[4] Replacement of CH_2 by sulfur has nearly no influence at the exocyclic γ position (compare the CH_3 shifts of *cis*-3,5-dimethylthiane[5a] with the CH_3 shifts in *cis*-1,3-dimethylcyclohexane[7]) and the most downfield signal of the three is therefore assigned to C-5 (the corresponding shift in *trans*-decalin is 34.48[5c]). C-4 is "doubly γ" to the sulfur atom, which in thiane leads to an upfield shift of 0.7 ppm compared to cyclohexane; the signal at 34.40 consequently must be C-4. C-8 is in a position analogous to that of the CH_3(2) group in *cis*-2,4-dimethylthiane[5a] which is shifted upfield by 1.2 ppm compared to *cis*-3,5-dimethylcyclohexane; the signal at 32.58 ppm comes closest to the value computed from the shift in *trans*-decalin (34.48 − 1.2 = 33.28).

The four most upfield signals belong to C-2, C-3, C-6 and C-7, which have only two α and two β substituents.[4] C-2 is shifted downfield (similar to C-9) from the corresponding

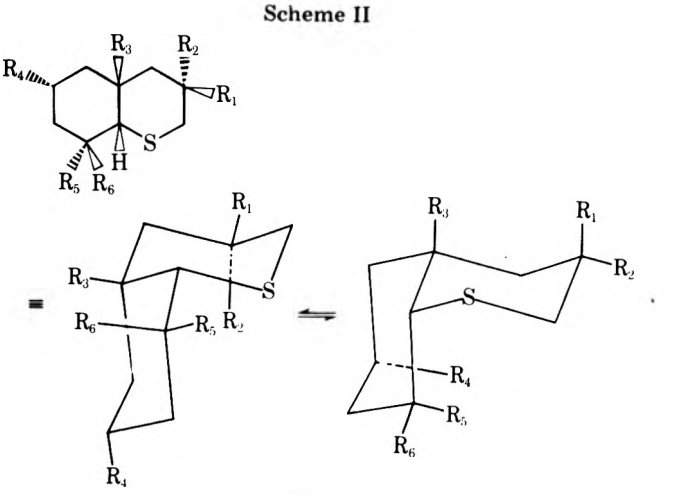
Scheme I



R = H unless indicated

1, all R's = H
2, R_1 = CH_3 (3α-CH_3)
3, R_2 = CH_3 (3β-CH_3)
4, R_3 = CH_3 (4α-CH_3)
5, R_4 = CH_3 (4β-CH_3)
6, R_5 = CH_3 (5α-CH_3)
7, R_6 = CH_3 (6α-CH_3)
8, R_7 = CH_3 (8α-CH_3)
9, R_8 = CH_3 (8β-CH_3)
10, R_9 = CH_3 (9-CH_3)

Scheme II



R = H unless indicated

11, all R's = H
12, R_1 = CH_3 (3β-CH_3)
13, R_2 = CH_3 (3α-CH_3)
14, R_3 = CH_3 (10-CH_3)
15, R_4 = CH_3 (6α-CH_3)
16, R_5 = CH_3 (8α-CH_3)
17, R_6 = CH_3 (8β-CH_3)

Table I. ^{13}C Chemical Shifts[a] of *trans*- and *cis*-1-Thiadecalins

Compd[b]	Registry no.	Temp[c]	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	CH_3
						trans-1-Thiadecalin						
Parent, 1	54340-73-7	+30	30.0$_4$	28.2$_3$	34.4$_0$	34.5$_6$	26.3$_4$	26.7$_6$	32.5$_8$	47.0$_1$	44.2$_7$	—
3α-CH_3, 2	63702-90-9	+30	36.7$_6$	34.2$_2$	43.2$_6$	34.5$_1$	26.2$_3$	26.7$_8$	32.0$_6$	46.3$_8$	44.5$_4$	22.7$_8$
3β-CH_3, 3	63730-12-1	+30	36.2$_1$	28.1$_0$	40.2$_7$	34.7$_6$	26.4$_5$	26.8$_3$	32.3$_4$	47.6$_5$	37.7$_2$	17.3$_7$
4α-CH_3, 4	63730-13-2	+30	23.1$_0$	35.3$_0$	32.4$_4$	31.9$_9$	26.7$_3$	26.7$_3$	33.2$_3$	38.5$_0$	47.2$_0$	12.3$_2$
4β-CH_3, 5	63730-14-3	+30	29.2$_8$	37.3$_8$	37.7$_2$	30.2$_1$	26.5$_7$	26.5$_7$	32.7$_5$	46.4$_4$	50.3$_9$	20.1$_0$
5α-CH_3, 6	63730-91-0	+30	29.8$_3$	28.6$_9$	31.7$_3$	34.1$_4$	33.7$_7$	20.5$_4$	33.1$_2$	40.5$_7$	46.8$_1$	13.0$_7$
6α-CH_3, 7	63702-92-1	+30	30.0$_3$	28.1$_4$	34.3$_4$	43.2$_9$	(32.5$_8$)	35.2$_2$	(32.5$_0$)	46.6$_5$	43.9$_3$	22.5$_1$
8α-CH_3, 8	63702-93-2	+30	29.9$_6$	28.1$_0$	34.6$_6$	34.8$_7$	25.7$_0$	36.1$_9$	37.2$_3$	54.6$_4$	44.0$_3$	20.3$_6$
8β-CH_3, 9	63730-15-4	+30	30.0$_9$	28.1$_9$	35.2$_5$	35.1$_6$	20.1$_4$	33.7$_7$	32.4$_3$	51.4$_1$	36.7$_1$	13.8$_1$
9-CH_3, 10	63702-94-3	+30	26.4$_6$	28.8$_5$	29.1$_3$	30.6$_7$	26.8$_8$	22.1$_5$	40.4$_6$	43.9$_6$	47.3$_7$	18.1$_9$
						cis-1-Thiadecalin						
Parent, 11	57259-80-0	+30	27.4$_5$	*d*	*d*	*d*	*d*	*d*	30.6$_9$	42.1$_5$	36.7$_5$	
		+60	27.6$_2$	24.5$_9$	30.0$_4$	29.0$_0$	23.8$_7$	24.2$_3$	30.9$_4$	42.4$_6$	37.1$_0$	
Parent, 11A[e]		−70	29.9$_2$	21.1$_0$	32.5$_0$	24.4$_0$	26.6$_9$	20.8$_8$	31.8$_6$	43.1$_1$	36.0$_1$	
Parent, 11B[e]		−70	23.5$_9$	28.2$_8$	24.9$_2$	34.2$_2$	19.6$_1$	28.2$_8$	27.3$_4$	40.4$_1$	36.7$_5$	
3β-CH_3, 12	63730-16-5	+30	36.6$_3$	27.0$_7$	41.4$_5$	26.0$_1$	26.7$_4$	21.4$_0$	31.4$_5$	42.7$_8$	37.4$_2$	22.5$_0$
3β-CH_3, 12		+55	36.7$_1$	27.2$_4$	41.5$_2$	26.3$_3$	26.7$_7$	21.6$_2$	31.5$_7$	42.9$_3$	37.5$_9$	22.3$_8$
3β-CH_3, 12A[f]		−68	36.6$_0$	26.7$_2$	41.4$_0$	25.1$_4$	26.7$_2$	20.8$_3$	31.2$_4$	42.6$_7$	37.1$_5$	22.8$_5$
3α-CH_3, 13(B)	63730-17-6	+30	30.7$_0$	34.8$_5$	(34.2$_8$)	(34.4$_6$)	19.9$_3$	28.5$_6$	27.5$_0$	40.0$_1$	37.8$_1$	23.1$_0$
10-CH_3, 14	63702-95-4	+30	*d*	23.5$_9$	*d*	*d*	21.7$_9$	*d*	29.1$_4$	47.0$_9$	32.8$_5$	28.2$_0$
10-CH_3, 14		+55	26.1$_5$	23.7$_4$	34.5$_9$	37.8$_3$	21.9$_5$	25.1$_9$	29.2$_6$	47.3$_3$	32.9$_8$	28.2$_5$
10-CH_3, 14A[g]		−68	30.0$_3$	23.3$_4$	41.3$_5$	28.2$_8$	21.8$_7$	20.5$_5$	27.0$_1$	47.0$_5$	32.7$_0$	27.3$_2$
10-CH_3, 14B[g]		−68	23.3$_8$	23.3$_4$	29.8$_2$	42.5$_5$	21.3$_3$	27.5$_3$	29.3$_0$	46.5$_3$	32.7$_0$	28.3$_9$
6α-CH_3, 15 (A)	63730-18-7	+30	30.0$_7$	21.4$_2$	32.7$_6$	(33.6$_1$)	(33.5$_6$)	29.6$_8$	32.0$_9$	42.6$_1$	36.5$_3$	22.6$_8$
8α-CH_3, 16 (A)	63730-19-8	+30	29.5$_3$	22.2$_8$	33.0$_3$	24.3$_2$	26.7$_9$	29.0$_9$	38.1$_4$	50.7$_5$	37.5$_0$	20.0$_3$
8β-CH_3, 17	63730-20-1	+30	24.9$_5$	27.8$_6$	27.3$_1$	32.9$_0$	21.1$_9$	*d*	30.6$_7$	49.0$_5$	36.7$_7$	21.0$_2$
8β-CH_3, 17		+55	25.1$_7$	28.1$_5$	27.2$_9$	32.8$_4$	21.3$_1$	34.4$_3$	30.9$_1$	49.2$_2$	36.8$_4$	20.9$_5$
8β-CH_3, 17A[h]		−68	29.7$_9$	*i*	32.1$_2$	24.6$_3$	*i*	26.3$_8$	33.3$_6$	47.8$_2$	30.2$_1$	18.3$_9$
8β-CH_3, 17B[h]		−68	23.2$_3$	28.2$_7$	25.8$_9$	34.5$_1$	20.7$_7$	35.8$_8$	29.3$_1$	48.6$_4$	37.7$_6$	21.7$_4$

[a] In $CDCl_3$, from internal Me_4Si. Parentheses indicate that assignments are not unambiguous. [b] *trans*- or *cis*-1-Thiadecalin. C-9 and C-10 are used instead of C-8a and C-4a to allow unambiguous use of "a" for axial. "α" means the substituent is on the opposite ring side as the hydrogen at C-10; "β" means on the same side of the ring as this hydrogen. For conformations A and B, see formula schemes in text. [c] °C. Only when compounds were found to be conformationally inhomogeneous at room temperature, low and high temperature ^{13}C NMR spectra were recorded. [d] Signals were broad to very broad due to slow ring inversion at this temperature and could not be measured accurately. [e] 58% A, 42% B. We are grateful to Professor W. v. Philipsborn, Universität Zürich, for measuring spectra of this compound at a number of temperatures. [f] >95% A; no signals of B could be detected. [g] 33% A, 67% B. [h] 17% A, 83% B. [i] Not observed because either overlaid by a signal of the major component or too small to be discerned.

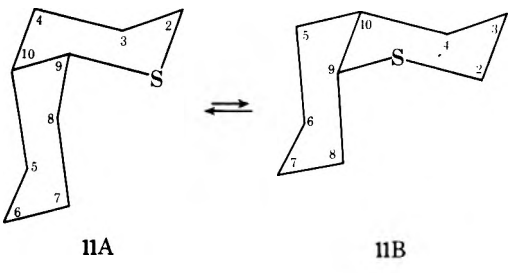
signal (26.99 ppm) in *trans*-decalin,[5c] and is found at 30.04. C-3, like C-10, is also shifted slightly downfield, and the remaining, most upfield two signals are carbon atoms 6 and 7. Comparison of the spectra of ethylcyclohexane[5c] and methyl cyclohexyl sulfide[5b] shows that the C-atom "doubly δ" to the sulfur (C-4) is shifted slightly more upfield than the one γ to it (C-3,5). The most upfield signal in *trans*-1-thiadecalin is consequently assigned to C-6.

The positions of methyl substitution in compounds **2–10** follow from the synthetic procedures;[3] the ^{13}C spectra (and to a lesser extent, the proton spectra) indicate the configuration (α or β; see footnote *b*, Table I) of the methyl groups and the trans character of the ring fusion. The signals of axial methyl groups (in **3, 4,** and **9**) are invariably at higher field than the corresponding equatorial signals (**2, 5,** and **8**); when only one isomer was isolated, the position of the methyl group was still evident by comparison with signals of analogously orientated methyl groups (**6** with **4**; **7** with **2**). Shift changes in carbon atoms near the methyl substituent (α, β, and γ) were in agreement with values calculated using the parameters developed for methylcyclohexanes[4,7] and methyldecahydroquinolines.[8,9] Chemical shifts of carbon atoms remote (>γ) from the site of methyl substitution were generally close to corresponding shifts in the parent compound **1**, which allowed unambiguous assignment of trans ring fusion in **2–10**. To facilitate assignments in **10**, where most of the signals were substantially shifted compared to **1**, 9-methyl-*trans*-1-thiadecalin-2,2-d_2 (**10**-d_2) was prepared,[3] in which the signal due to C-2 disappears through loss of NOE and by coupling with the deuterium C-3 is shifted palpably upfield (−0.18 ppm), and C-4 is noticeably broadened.

The noise-decoupled room temperature ^{13}C spectrum of *cis*-1-thiadecalin (**11**) shows only four sharp signals; the remaining five signals are broad to very broad depending on the chemical shifts of the corresponding carbon atoms in conformation A and B. Ring inversion therefore is already slow at +30 °C. Elevation of the probe temperature to +60 °C results in sharpening of all nine signals due to fast inversion between A and B. Lowering the temperature stepwise to −70 °C leads through coalescence (ca. −20 °C) to two sets of sharp signals which can be assigned to conformers A and B because of their unequal proportion (ratio 58% A, 42% B).

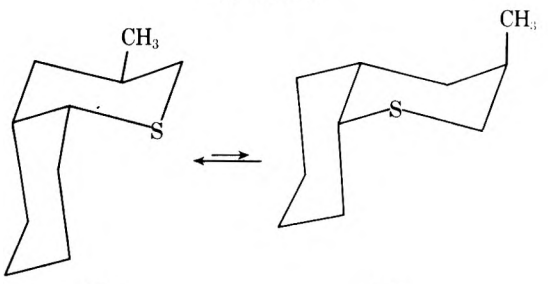
Assignment of the signals of each conformer to the various ring atoms is based on a combination of off resonance decoupling, comparison with chemical shifts in the low-temperature spectrum of *cis*-decalin[4c] corrected for the replacement of C-1

Scheme III



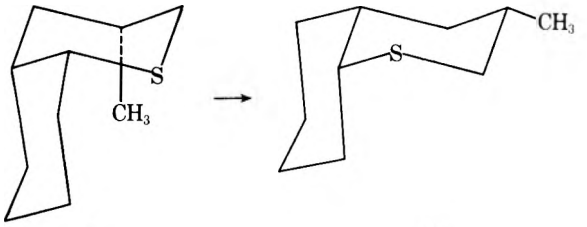
11A 11B

Scheme IV



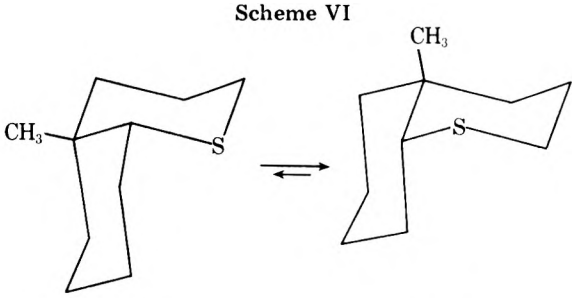
12A 12B

Scheme V



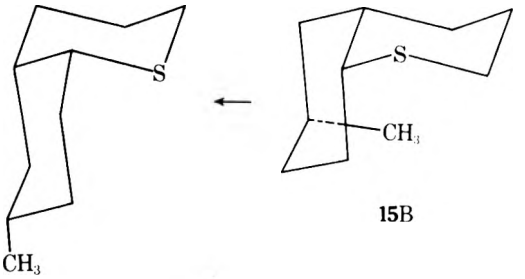
13A 13B

Scheme VI



14A 14B

Scheme VII



15B

15A

by S, effects of methyl substitution (in compounds **12–17**), and shift changes of corresponding signals in A and B upon raising the temperature. The two most downfield signals in **11A** and **11B** are clearly C-9 and C-10; the remaining signals can be split into four groups for each conformer depending on the number of α, β, and γ effects[4] they encounter. Thus, **11A** has C-4 and C-8 (two α, three β, no γ_a) next to C-9 and C-10; C-8, in an analogous position relative to S-1 as in **1**, must resonate at higher field. Next come C-2 and C-6 (two α, two β, no γ_a), with C-2, adjacent to the sulfur atom, shifted more downfield. C-5 (two α, three β, one γ_a) is at next higher field. The two most upfield signals belong to C-3 and C-7 (two α, two β, one γ_a) with C-3, β to the sulfur atom, the more downfield signal. The signals of **11B** can be assigned in an entirely analogous way. C-5 (two α, three β, no γ_a) and C-3 and C-7 (two α, two β, no γ_a) are the three most downfield signals next to C-9 and C-10. C-8 and C-4 are analogously substituted (two α, three β, one γ_a), but here C-8 is more *downfield* shifted by the sulfur β to it. The two most upfield signals are C-2 and C-6. Assignment of the spectrum of **11** at +60 °C follows from the spectra of the two frozen conformers, taking into account a downfield shifting of the signals of ~0.8 ppm upon raising the temperature by ~100 °C.

A number of signals in the room-temperature ^{13}C spectrum of 3β-methyl-*cis*-1-thiadecalin (**12**) are slightly broadened, the biasing influence of the methyl group being insufficient to make **12A** the exclusive conformation. At +55 °C the signals are sharp, as at −68 °C; only the signals due to **12A** can be detected at low temperature, indicating that this conformer predominates to >95%. Chemical shifts of C atoms close to the site of the methyl substituent show the expected α_e, β_e and γ_e effects compared with **11A**, whereas C-6, C-7, and C-8 show only very minor changes. The configuration and conformation of **12**(A) are thus established.

All signals in the room-temperature spectrum of 3α-methyl-*cis*-1-thiadecalin (**13**), on the other hand, are sharp, and no changes except the usual temperature dependence of ^{13}C shifts are observed upon variation of the probe temperature. **13** must be conformationally homogeneous (**13B**), since a severe syn-axial interaction exists between CH_3 and C-5 in conformation A. As in the case of **12**(A), the signals next to the methyl substituent show the expected shift changes (α_e, β_e), while C-6, C-7, and C-8 are in good agreement with their values in **11B**.

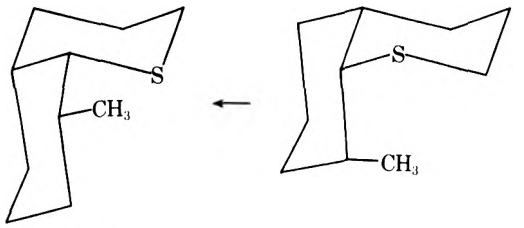
Compound **14**, 10-methyl-*cis*-1-thiadecalin (see footnote *b*, Table I), like the parent compound **11**, is conformationally heterogeneous, as indicated by the broad signals for C-2, C-4, C-5, and C-7 in the rt ^{13}C spectrum. Once more the signals become sharp at +55 °C, and two sets of signals (ratio 33% A, 67% B) are observed at −68 °C.

Replacement of H by CH_3 on C-10 is known in *cis*-decalin[4c] and *cis*-decahydroquinoline[9] to bring about considerable shift changes in most of the carbon atoms compared to the parent compound. Only C-2 and C-7 in both **14A** and **14B** are expected to be shifted by less than 1 ppm, relative to **11A** and **11B**. However, assignment was complicated since 8 signals (four of each conformer) appear between 30 and 27 ppm. To aid the decision which of the two conformers was the minor and which the major one, the room- and low-temperature spectra of **14**-2,2-d_2 were therefore recorded. Here the signals due to C-2 disappear through loss of the NOE and through being split into quintets. This makes possible the assignment of C-2 at 30.03 (minor) and 23.38 ppm (major) in the undeuterated analogues at low temperature. Since C-2 in conformation B (one γ_a) resonates at much higher field than in A (no γ_a), the major set of signals can be assigned unambiguously to **14B** and the minor one to **14A**. The rest of the signals are matched to the carbon atoms by the same criteria as listed for **11**.

The signals of **15** (6α-methyl-*cis*-1-thiadecalin) are sharp at room temperature, since conformation **15B** is prohibited because of the syn-axial CH_3/C-4 interaction. The signals in the thiane ring (C-2, C-3, C-4) are in excellent agreement with **11A**, which confirms the configurational and conformational assignment. Signals of C-6, C-5, and C-7 show the expected downfield shifts due to α_e and β_e effects.

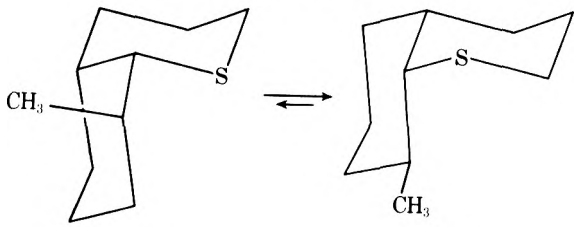
In **16**, conformation B is excluded because of the two syn-axial interactions of the methyl group with C-2 and C-4, opposed by only one additional gauche interaction between CH_3 and S in **16A**. This consideration is verified by the sharpness of the signals of **16A** at room temperature, which does not change upon lowering the temperature. The strain imposed upon the molecule by the CH_3/S interaction manifests itself in less good agreement of signals remote from the site of substitution (C-3, C-4) compared to **11A** or **15A**. The carbon

Scheme VIII



16A 16B

Scheme IX



17A 17B

atoms close to the methyl group show shift effects similar to the ones observed in the corresponding 8α-methyl-*cis*-decahydroquinoline.[9]

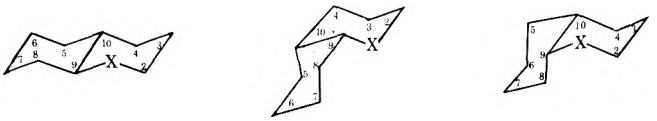
In compound **17**, finally, the effect of two syn-axial CH_3/H interactions in **17A** is set against one gauche CH_3/S in **17B**. The compound is conformationally heterogeneous, as indicated by the broadened signals of the rt spectrum. At −69 °C the two conformers appear in a ratio of 17:83, with conformation **17B** predominating. Assignment of the signals is straightforward for the major conformer, using the criteria listed for **11**; it is less easy for **17A**, since two of the signals (C-3 and C-6) are not observed and off-resonance decoupling could not be performed on the rest. Comparison with the shift effects reported for the corresponding conformers of 8β-methyl-*cis*-decahydroquinoline,[9] however, leaves no doubt as to the correctness of the conformational assignments.

Comparison with Carbocyclic Analogues and Shift Effects Produced by Methyl Substitution. Comparison with carbocyclic analogues for which ^{13}C data have been reported allows calculation of a set of increments for replacement of CH_2 by S. These data have been compiled in Table II for *trans*-1-thiadecalin and for the two conformers of *cis*-1-thiadecalin, A and B.

As in the case of the corresponding parameters for replacement of CH_2 with NH,[8] the standard deviations of the values are relatively large, indicating differences in geometry between individual pairs of methyl-substituted decalins and 1-thiadecalins. This reduces the worth of such averaged parameters and makes the calculation of chemical shifts with two parameters (one multiplicative and one additive), which has been suggested in other heterocyclic systems[14] fruitless, since deviations between values calculated and found are far larger than between values calculated with or without the multiplicative parameter which is always close to unity. For this reason, **10** and its matching decalin have not been used for the calculation of the values in Table II, since geometrical differences to the other compounds in the corresponding series seem very pronounced. Generally the effects of replacing CH_2 by S are small with the exception of the α carbons, but they are still noticeable on positions four bonds removed (C-6; "double δ").

Comparison of the chemical shifts of the three parent compounds **1**, **11A**, and **11B** with the methyl-substituted thiadecalins allows the calculation of effects of methyl substitution. The results are similar to the values found for methyldecalins[4] and methyldecahydroquinolines,[8,9] and for methylthianes.[5,6] Individual α, β, etc. values, however, once more differ quite strongly, especially for carbon atoms close to sulfur. The worth of averaged methyl-substitution parameters with (large) standard deviations, therefore, is rather low; as in similar cases it seems more opportune to calculate individual parameters from the shift data as needed.

Table II. Shift Differences $\Delta\delta^a$ between 1-Thiadecalins (X = S) and Decalins[b] (X = CH_2)



C atom	Effect	Shift differences: Trans[c]	Cis A[d]	Cis B[e]
C-2	α	+2.4 ± 0.8	+2.2 ± 0.2	+1.3 ± 0.8
C-3	β	+0.9 ± 0.4	+0.1 ± 0.5	+0.5 ± 0.1
C-4	dγ	−0.3 ± 0.4	−0.7 ± 0.2	−1.2 ± 0.6
C-5	γ	+0.2 ± 0.5	−1.9 ± 0.3	+0.8 ± 0.5
C-6	dδ	−0.8 ± 0.2	−0.8 ± 0.3	−1.7 ± 0.4
C-7	γ	−0.5 ± 0.3	−0.8 ± 0.3	+0.3 ± 0.6
C-8	β	−1.9 ± 0.5	−1.1 ± 0.4	+1.1 ± 0.3
C-9	α	+3.2 ± 0.6	+6.4 ± 1.0	+3.9 ± 0.3
C-10	β	+0.3 ± 0.5	−0.3 ± 0.5	+0.1 ± 0.6

[a] In parts per million. A plus sign indicates that the signal in the S compound is downfield from the signal in the CH_2 analogue. The differences reported are averages for the pairs of compounds considered (see footnotes *c*, *d*, and *e*) with their standard deviations. [b] ^{13}C chemical shifts of *trans*-decalin in $CDCl_3$ are reported in this paper; the other decalin values are from ref 4c, but values of C-1 and C-10 of *cis-syn*-1-methyldecalin and of C-3 and C-7 of *trans-anti*-1-methyldecalin have been reversed. [c] Compounds 1, 2, 5, 7, and 8 and the corresponding decalins were used for the calculation. [d] Compounds 11A (−68 °C), 14A (−68 °C), 15A, and 16A and the corresponding decalins were used for the calculation. [e] Compounds 11B (−68 °C), 14B (−68 °C), and 13B and the corresponding decalins were used for the calculation.

Table III. Conformational Equilibria in Mobile *cis*-1-Thiadecalins[a]

Compd	A, %	B, %	K	ΔG° (kcal/mol)
Parent, 11	58	42	1.4	+0.14
3β-CH_3, 12	>95	<5	>19	>+1.2
10-CH_3, 14	33	67	0.49	−0.29
8β-CH_3, 17	17	83	0.20	−0.65

[a] In $CDCl_3$ at −68 °C (205 K). For enumeration of signals used in integration, see Experimental Section.

Conformation of *cis*-1-Thiadecalins. The room-temperature ^{13}C NMR spectra of **11**, **12**, **14**, and **17** showed the presence of the two conformers in these compounds. Inversion was frozen out at −70 °C and the signal areas of corresponding carbon atoms (see Experimental Section) could then be integrated. Nuclear Overhauser enhancement and T-1's of such carbon atoms have been reported to be nearly equal in other heterocyclic systems.[10] The resulting equilibrium constants and conformational free-energy differences are summarized in Table III.

Conformation A in *cis*-1-thiadecalin (**11**) is preferred by 0.14 kcal/mol. This is in reasonable, if not complete, agreement with the value calculated by a force-field method[11] (0.32 kcal/mol); a comparison of the experimental with the calculated ΔG° values in the methylthiane series,[5a] however, leads

Table IV. Pertinent ^{1}H Chemical Shifts[a] of *trans*- and *cis*-1-Thiadecalins[b]

Compd	H_{2e}	H_{2a}	H_9	CH_3
		Trans		
Parent, 1	2.48–2.89, not resolved		~2.40 (br m)	
3α-CH_3, 2	2.15–2.55, not resolved		~2.43 (br m)	0.92 (d, 6)
3β-CH_3, 3	2.21 (d, 13, of d, 3)	3.03 (d, 13, of d, 3)	overlap H_{2e}, H_{2a}	1.19 (d, 7.5)
4α-CH_3, 4	2.21 (d, 13, of t, 4)	2.97 (d, 13, of d, 10.5 of d, 2.5)	~2.97 (br)	0.86 (d, 7)
4β-CH_3, 5	2.47 (d, 13, of t, 4)	2.97 (d, 13, of d, 11, of d, 3)	~2.45 (br)	0.92 (d, 5)
5α-CH_3, 6		2.30–2.93, not resolved		0.89 (d, 7)
6α-CH_3, 7	2.48–2.89, not resolved		2.34 (br m)	0.87 (d, 6.5)
8α-CH_3, 8	~2.64, not resolved		2.16 (t, 10)	0.99 (d, 6)
8β-CH_3, 9		2.43–2.87, not resolved		1.01 (d, 7)
9-CH_3, 10	2.39 (d, 14, of t, 3.5)	2.89 (d, 14, of d, 12, of d, 3.5)		1.36 (s)
		Cis		
Parent, 11 (A ⇌ B)	~2.55, not resolved		2.97 (half-width 13)	
3α-CH_3, 12B	2.18–2.44, not resolved		2.57 (d, 12, of t, 4)	0.95 (d, 6)
3β-CH_3, 13A	2.08–2.62, overlap w H_{3a}		3.15 (half-width 9)	0.84 (d, 6)
10-CH_3, 14 (A ⇌ B)	2.24–2.82, overlap w H_9		2.46[c] (d, 6 of d, 3)	1.16 (s)
6α-CH_3, 15A	~2.63, not resolved		3.25 (half-width 8)	0.94 (d, 5.5)
8α-CH_3, 16A	~2.57, not resolved		3.20 (half-width 7)	0.97 (d, 7)
8β-CH_3, 17 (A ⇌ B)	2.26 – 2.78, not resolved			1.11 (d, 6)

[a] In ppm, from Me_4Si; the reported shift values are centers of groups of signals in the spectra. The parenthesized data are multiplicity and coupling constants in Hz. [b] For preferred conformations of *cis*-1-thiadecalins, see Schemes III–IX. [c] From 14-2,2-d_2.

to the conclusion that this agreement may be coincidental. Assuming additivity of conformational free energies and using the values from the methylthianes,[5a] one would predict conformation A to be the more favored, as indeed it is. In *cis*-2,3-dimethylthiane, the 2-CH_3-*e*-3-CH_3-*a* conformer is favored by 0.16 kcal/mol compared to 0.02 kcal/mol calculated with the values from the monomethylthianes.[5a] If the experimental value of *cis*-2,3-dimethylthiane is used as a basis for calculation, conformation 11B differs from the 2-CH_3-*a*-3-CH_3-*e* form of this molecule by a gauche interaction between C-4 and C-6, and conformation 11A from 2-CH_3-*e*-3-CH_3-*a* by a gauche interaction between S-1 and C-7. With a C–C–C–C gauche interaction from methylcyclohexane[12] (0.87 kcal/mol) and a C–C–C–S interaction similar to the one between CH_3 and S in 17B (see below; 0.95 kcal/mol) one obtains a calculated preference of 0.08 kcal/mol for conformation A, reasonably close to the experimental value.

Introduction of a methyl group instead of a proton at C-10 in 11 (compound 14) leads to a marked preference of conformer B (67%). In addition to the situation in 11, one has to offset the $\Delta G°$ in methylcyclohexane (−1.74 kcal/mol[12b]) against 3-methylthiane (−1.40 kcal/mol[5a]), giving a preference of 11B of 0.14 − 1.74 − (−1.40) = −0.20 kcal/mol, in good agreement with the experimental result of *−0.29 kcal/mol*. Closer agreement can hardly be expected, since the second ring obviously changes the opportunities of the axial methyl group in both conformations for reducing sterical strain by bending outward, and the change is not likely to be identical for the two conformers.

The sizeable changes in chemical shift upon cooling of 12 indicate a nonnegligible proportion of conformation B at room temperature. However, at −68 °C there is less than 5% of this conformation, since no signals of the minor conformer are detected. The slight preference for A in 11 is enhanced in 12 by 1.40 kcal/mol (the preference of the methyl group in 3-methylthiane for the equatorial position) to 0.14 + 1.40 = 1.54 kcal/mol. This corresponds to 2% of B at −68 °C, which is too little to be detected by ^{13}C NMR.

Compound 17, finally, exists predominantly ($\Delta G°_{205}$ = 0.65 kcal/mol) in conformation B. Here the preference of a methyl group in methylcyclohexane for the equatorial position is opposed by the CH_3/S gauche interaction, which can thus be estimated as −0.65 = 0.14 − 1.74 + *x*; *x* = −0.65 + −0.14 + 1.74 = 0.95 kcal/mol. This value is slightly larger than the gauche-butane interaction found in methylcyclohexane, and rather larger than the value deduced for a CH_3–C–C–S interaction from the experimental data of 3-methylthiane, 5-methyl-1,3-dithiane, and cyclohexyl methyl sulfide[5a] (~0.6 kcal/mol). Obviously, the deviation of the bond angles from tetrahedral geometry due to the sulfur atoms are such that CH_3 in 17 (and C-7 in the A conformation of *cis*-1-thiadecalins, generally; see above) are closer to the sulfur than axial CH_3 in 3-methylthiane, *and a different C/S gauche interaction* must be used. Similar reasoning may apply in the case of *cis*-decahydroquinolines, where a similar difference between C/N gauche interactions was observed.[9]

The remaining compounds are conformationally homogeneous either because trans ring fusion forbids inversion, or because of severe C/C syn-axial interections in the alternative conformations.

^{1}H NMR Spectra. Since only the protons on the C atoms adjacent to sulfur are resolved, and since the shift difference is less pronounced than in other heterocyclic systems (e.g., the decahydroquinolines[9]), even 100-MHz ^{1}H NMR spectra offer only limited information regarding the configurational and *conformational properties of the trans- and cis*-1-thiadecalins. The apparent chemical shifts and coupling constants of the protons at C-2 (H_{2e}, H_{2a}) and C-9 (H_9) and of the methyl groups, if any, of the compounds 1–17 are collected in Table IV.

The most telling ^{1}H signal is the one due to H_9: in *cis*-1-thiadecalins preferentially in conformation A this proton is coupled to three protons which are all gauche positioned, and the signal appears as a broad singlet with a half-width of ~8 Hz (13, 15). If conformation B is preferred, a large anti coupling with H_{8a} occurs and the signal appears as a doublet (*J* ≈ 12 Hz) of triplets. If the conformational equilibrium allows for comparable amounts of conformations A and B, the half-width of the signal is intermediate (11, 14). Another aid in structural assignment is the apparent coupling constant of the methyl groups in the *trans*-1-thiadecalin series which is larger (~7 Hz) for axial CH_3 (3, 4, 6, 9) than for equatorial (~6 Hz; 5, 7, 8). Thus, the limited information that could be extracted from the ^{1}H spectra of 1–17 confirms the conclusions from the

^{13}C spectra which proved considerably more valuable in the structural analysis of 1-thiadecalins.

Experimental Section

Synthesis and analytical data of the compounds investigated are described in detail elsewhere.[3]

NMR spectra were recorded on a Varian XL-100 pulsed Fourier transform nuclear magnetic resonance spectrometer. ^1H NMR spectra were recorded in the CW mode, in 5-mm o.d. tubes. ^{13}C spectra were measured at 25.16 MHz, in the pulsed mode, in 10-mm o.d. tubes. Solvent in both cases was $CDCl_3$, with 2–5% Me_4Si admixed as internal reference; the deuterium of the solvent provided the internal lock signal. Integration of corresponding signals in the low-temperature spectra was effected by counting squares of the signal areas, and by multiplication of signal height with half-width, after expanding electronically as much as resolution and noise level permitted. The following signals (numbers refer to position of carbon atoms) were integrated and gave the following (parenthesized) percentages (only one conformer of each pair is reported): 11A 2 (60), 4 (58), 5 (58), 6 (59), 9 (58), 10 (58); 14A 4 (32), 6 (34), 9 (33); 17A 5 (14), 9 (17), CH_3 (19). Error limits are estimated to be of the same size as reported in ref 13, that is, ±2% (in favorable cases of $K \approx 1$) to ±10% (in unfavorable cases of $K \approx 20$). The resulting errors for the $\Delta G°$ values in Table II are ±0.06 kcal/mol or better.

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Stereochemistry of α Halogenation of Sulfoxides. 1. A Proton Nuclear Magnetic Resonance Study of the Bromination of *trans*-2-Thiahydrindan 2-Oxide

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The stereochemistry of bromination of the title compound with bromine in the presence of pyridine to give the α-bromo sulfoxide has been studied by ^1H NMR and stereospecific deuterium labeling methods. The reaction appears to be completely regio- and stereospecific and involves inversion of configuration at both sulfur and α carbon. This result is discussed on the basis of various possible halogenation mechanisms. However, no clear-cut mechanistic choice appears to be possible.

The stereochemistry of α halogenation of sulfoxides by halogens or halogen sources (X_2) in the presence of base (B:)[1] has been extensively investigated in recent years.

$$RS(O)CHR_1R_2 \xrightarrow[B:]{X_2} RS(O)CXR_1R_2$$

The reaction is normally found to be stereospecific, and occasionally highly so, at both sulfur and α carbon.[7] The results, however, are puzzling, as the actual steric course appears to depend rather unpredictably both on sulfoxide structure (open chain[7] or cyclic,[8-11] type and nature of the substituent at C_α[7,12]) and reaction conditions (halogenating agent, presence or absence of an electrophile such as $AgNO_3$).[7] Thus, if it is reasonable to suppose that a single fundamental mechanism is operating in every case, it has been nevertheless impossible to fit all the results in a coherent framework. Apparently, the factors which ultimately control the stereochemistry are incompletely understood.

It has been suggested that the conformational flexibility of the substrate and/or reactive intermediates formed along the reaction path may play a key role in determining the steric course,[11,12] yet no comprehensive study has been reported on the halogenation of conformationally rigid sulfoxides.[13] In this paper we report on the stereochemistry of bromination of *trans*-2-thiahydrindan 2-oxide (**1a**), a system which, by virtue of the trans ring fusion, cannot undergo appreciable skeletal deformation at the reaction centers.[14] This system is particularly advantageous, since the four α protons are all stereochemically different, either because of their relation to the S–O bond or the ring fusion, and can be readily identified in

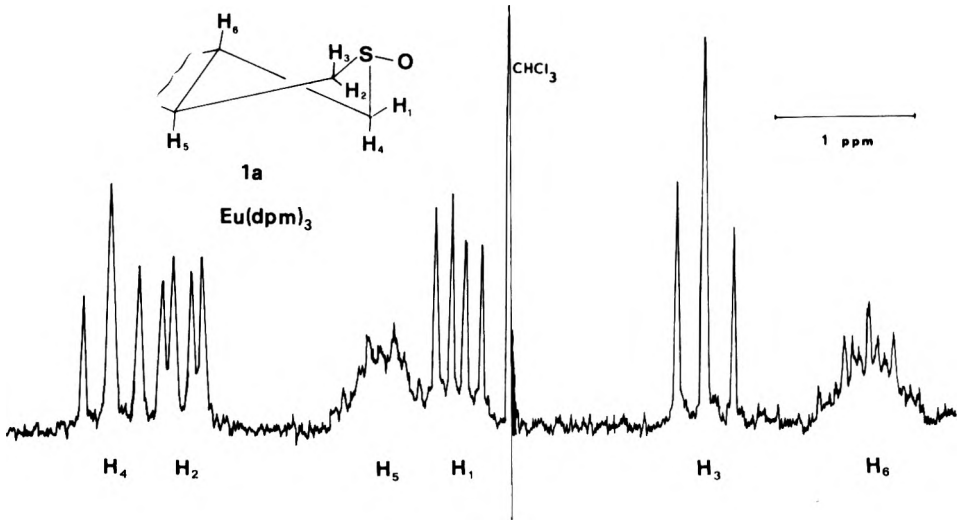


Figure 1. Proton NMR spectrum of *trans*-2-thiahydrindan 2-oxide (**1a**) in $CDCl_3$ in the presence of $Eu(dpm)_3$ 4:3 molar ratio.

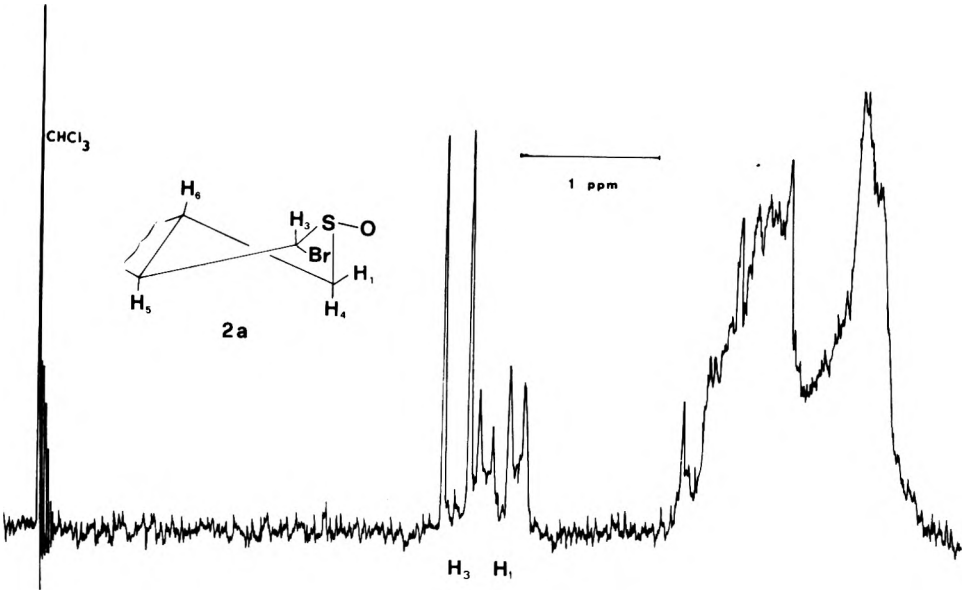
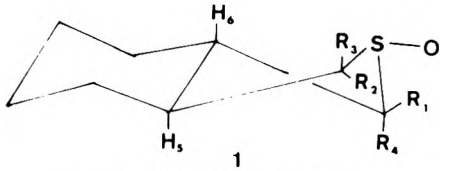


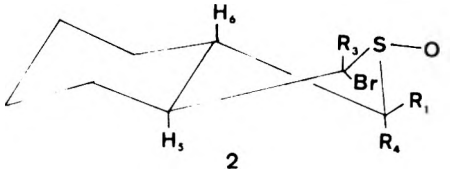
Figure 2. Proton NMR spectrum of *trans*-2-thia-1-bromohydrindan 2-oxide (**2a**) in $CDCl_3$

the NMR. This is true also for the bromosulfoxide product and, consequently, the steric course of halogenation can be conveniently followed by NMR methods.



1

a, $R_1 = R_2 = R_3 = R_4 = H$
b, $R_1 = R_2 = R_4 = H$; $R_3 = D$
c, $R_1 = R_3 = R_4 = H$; $R_2 = D$



2

a, $R_1 = R_3 = R_4 = H$
b, $R_1 = R_3 = H$; $R_4 = D$
c, $R_3 = R_4 = H$; $R_1 = D$

Results

The 100-MHz NMR spectrum of **1a** has been previously discussed.[16] At 60 MHz the two quasi-equatorial protons H_1 and H_2 still appear as separate resonances, δ 3.65 and 2.83, respectively. (In $CDCl_3$ the shifts are concentration dependent; these values refer to a 0.44 M solution.) All other protons appear as two very broad signals centered at δ 1.95 and 1.2, respectively. The addition of shift reagent [$Eu(dpm)_3$] gradually resolves the heterocyclic part of the spectrum, all the protons eventually becoming neatly separated. This is shown in Figure 1, which corresponds to a 4:3 sulfoxide/shift reagent molar ratio.

Bromination of **1a** in acetonitrile in the presence of pyridine (48 h, room temperature) gave, together with unreacted sulfoxide and some sulfone (<10%), a 30% yield of a α-bromosulfoxide. Its presence was clearly evinced in the NMR spectrum of the crude reaction product by the appearance of a low-field doublet[17] [1 H, J = 11 Hz, δ 4.18 (concentration dependent)] whose splitting unequivocally establishes the axial orientation of the methyne proton geminal to bromine (henceforth the equatorial orientation of bromine itself). No other doublet was visible in the NMR of the crude product,

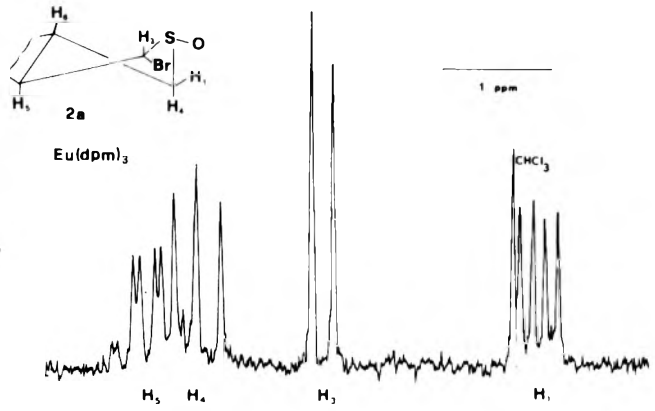


Figure 3. Proton NMR spectrum of *trans*-2-thia-1-bromohydrindan 2-oxide (**2a**) in $CDCl_3$ in the presence of Eu(dpm)$_3$ 1:1 molar ratio.

as well as in the isolated bromosulfoxide fraction. In TLC this appears to be a single product. Therefore, within the limits of the sensitivity of the NMR method, only one α-bromosulfoxide was formed, and the reaction appears to be extremely regio- and stereoselective. The spectra of the isolated bromosulfoxide fraction in the absence and in the presence of shift reagent [Eu(dpm)$_3$, 1:1 molar ratio] are reported in Figures 2 and 3, respectively. It is immediately apparent that the methyne doublet has been shifted downfield much less than the signal of the other axial α proton (H_4), strong evidence[18] that the proton geminal to bromine is trans with respect to oxygen; hence the bromosulfoxide has the structure **2a.** Additional definitive stereochemical proof was provided by the finding (see below) that in the reductive debromination (Zn/MeOD/D$^+$) of the bromosulfoxide product, the deuterium label turned up exclusively at positions R_2 and R_3, bound, that is, to C_1. Henceforth the Br atom must also be bound to C_1, a result that, given the axial setting of the geminal methyne, is compatible only with structure **2a.**

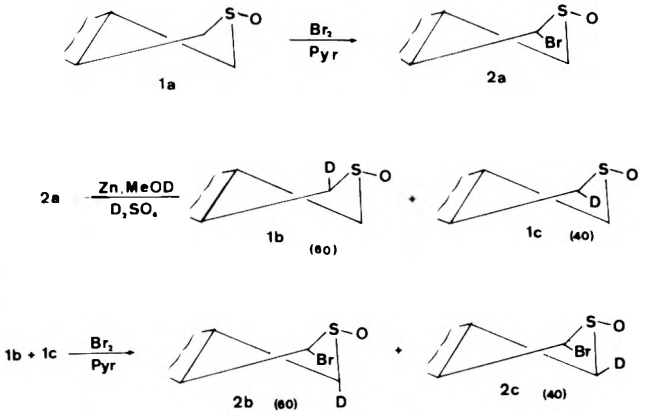
Since the steric course of halogenation is known to often change drastically in the presence of silver nitrate,[7] the bromination of **1a** was also carried out in the presence of $AgNO_3$ (2 equiv). Under these conditions the reaction went to completion in a relatively very short time. Again, however, **2a** was the only bromosulfoxide formed together with some sulfone (20%).[19] Since in the case at hand $AgNO_3$ merely accelerates the reaction without altering its course, all further experiments were carried out in the presence of $AgNO_3$.

The question of the steric course was approached through the use of specifically deuterium labeled derivatives of **1,** as described in the following (Schemes I–III). Bromosulfoxide **2a** was subjected to reductive debromination by Zn in methanol-*O*-*d* in the presence of acid catalyst (D_2SO_4). Previously, on an open-chain substrate, complete inversion of configuration had been found by Montanari and co-workers.[7,20] On this basis, the product expected with our substrate was **1b,** where the D atom is quasi-axial and trans to S–O. Instead (Scheme I) a mixture was obtained of **1b** (60%) and **1c** (40%) corresponding to the reductive debromination occurring with 80% racemization and 20% net inversion.

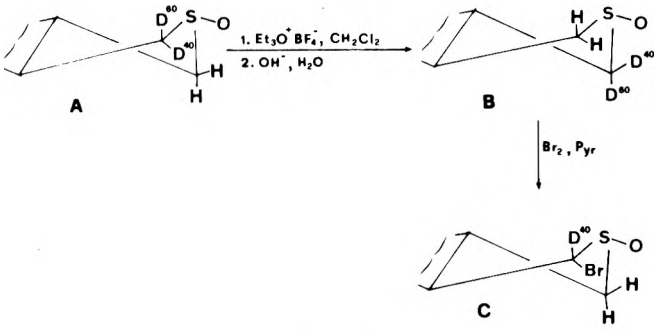
This material, subjected to bromination under the usual conditions, gave a bromosulfoxide containing 100% protium at the R_3 position (geminal to Br), but only about 60 and 40% protium respectively at R_4 and R_1. In other words, the product was made up of a mixture of **2b** and **2c** (Scheme I). This finding demonstrates that bromination of **1a** occurs completely regiospecifically at C_3 and stereospecifically at sulfur with steric course inversion.

In order to ascertain the steric course at the α carbon, one needs to know which of the protons at C_3 was replaced by

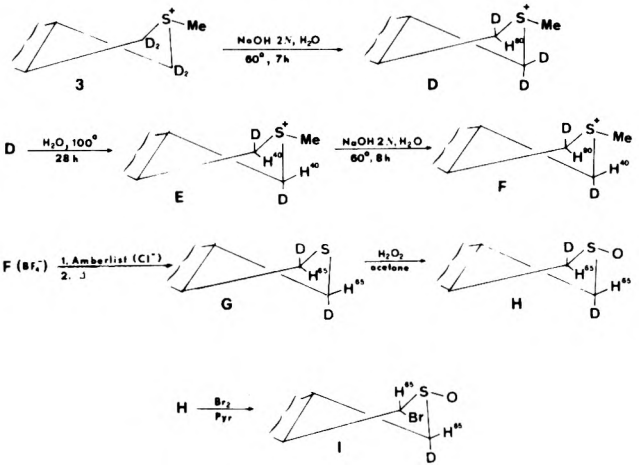
Scheme I



Scheme II



Scheme III



bromine, and this requires differential labeling at R_1 and R_4. A preliminary experiment was carried out starting with the 60:40 mixture of deuteriosulfoxides **1b** and **1c,** obtained as described above, by reductive debromination of **2a** (Scheme II).[21] Treatment of this mixture (**A**) with triethyloxonium fluoborate in CH_2Cl_2, followed by basic hydrolysis, inverted the configuration at sulfur[22] producing **B,** partially deuterated at R_1 and R_4. Bromination of **B** gave a bromosulfoxide **C** with a protium content of 100% at both R_1 and R_4, but only about 40% at R_3, the position geminal to Br. This result, while confirming the inversion steric course at sulfur, is indicative of at least predominant inversion of configuration at the α carbon as well.

It was felt, however, that the differential deuterium labeling at R_1 and R_4 was insufficient to unambigously establish the stereoselectivity of removal and consequently the stereochemistry at C_3. A method was therefore sought to label only one of the positions at C_3. Since the experiment of Scheme II

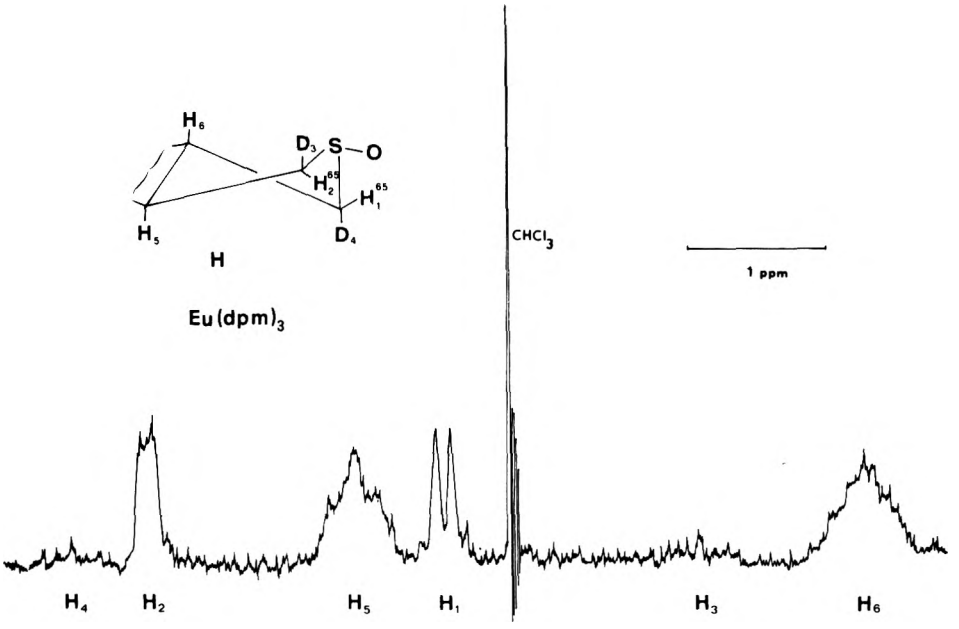


Figure 4. Proton NMR spectrum of specifically deuterated 2-thiahydrindan 2-oxide (**H**, Scheme III) in $CDCl_3$ in the presence of $Eu(dpm)_3$ 1.2:1 molar ratio.

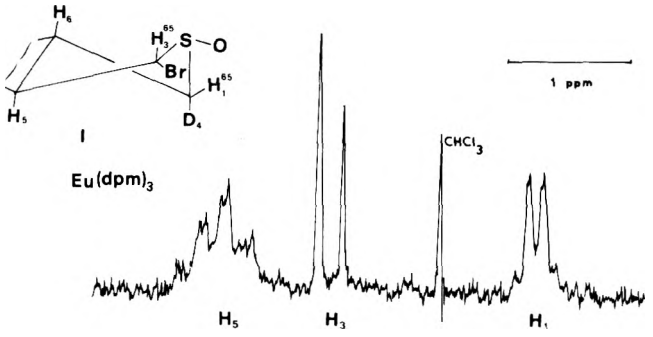


Figure 5. Proton NMR spectrum of the specifically deuterated bromosulfoxide **I** (see Scheme III) in $CDCl_3$ in the presence of $Eu(dpm)_3$ 1:1 molar ratio.

seemed to indicate preferential removal of H_4, it appeared desirable to deuterate precisely this position so that proton removal during bromination would eventually work against the kinetic isotope effect.[23] To this end the sequence of Scheme III was applied.

The S-methyl derivative of thiahydrindan-*1,1,3,3-d*$_4$ (**3**) was prepared as previously described.[24] From previous work this sulfonium salt was known to undergo highly stereoselective base-catalyzed H/D exchange at position R_2.[24] Treatment of **3** with 2N NaOH in H_2O (7 h, 60 °C) resulted in 80% exchange at the R_2 position giving **D**. This was subjected to thermal pyramidal inversion at sulfur, a process which exchanges corresponding positions across the sulfur atom.[24] Indeed the material (**E**) obtained through thermal equilibration of **D** had the H label equally divided between the quasi-equatorial α positions. This material was once more subjected to H/D exchange to obtain **F**. This was ion exchanged to obtain the chloride salt which was subsequently pyrolyzed to eliminate gaseous CH_3Cl, leaving behind the labeled sulfide **G**. This material was oxidized to the sulfoxide **H**, whose NMR spectrum in the presence of shift reagent is reported in Figure 4. As shown, the protium content at the quasi-equatorial positions R_1 and R_2 appears to be approximately 65%, while that at the quasi-axial positions was still practically negligible.

Bromination of **H** gave bromosulfoxide **I** whose NMR spectrum is reported in Figure 5. No protium appears to have been lost in bromination; it has switched place, however, as 65% protium now appears at R_3, the axial position geminal to Br. Recalling that bromination occurs with complete inversion at sulfur, this result demonstrates that the deuterium atom has been removed at R_4 (in spite of the unfavorable isotope effect),[23] implying essentially complete inversion at the α carbon.

In conclusion, α-bromination of **1a** is completely regio- and stereospecific and involves complete inversion of configuration at both sulfur and α carbon.

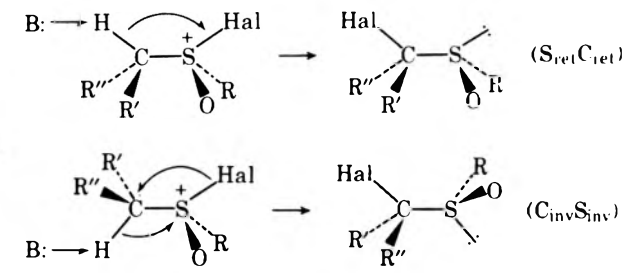
Discussion

All available evidence consistently indicates that the halogenation of sulfoxides with halogen or halogen sources (X_2) in the presence of bases (B:) proceeds through the initial formation of a halooxosulfonium intermediate, whose base-promoted collapse eventually leads to the α-halosulfoxide product.[23]

$$RS(O)CHR_1R_2 \xrightarrow{X_2} \underset{\displaystyle O}{\overset{\displaystyle X}{RS^+CHR_1R_2}}\ X^- \xrightarrow[\text{one step or more}]{B:} RS(O)CXR_1R_2 + BH^+X^-$$

A sizable deuterium isotope effect, $k_H/k_D \geq 5.5$, has been found for an open-chain substrate,[23] indicating proton abstraction occurs in the rate-determining transition state. In the absence of contrary evidence, this mechanism may be reasonably assumed to have general validity. Kinetic studies cannot provide information about the step in which halogen is attached to the α carbon, since this occurs after the rate-determining step. This is precisely the question that stereochemical studies have sought to answer.

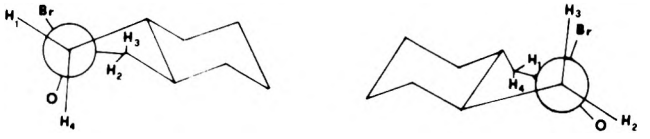
Fundamentally two types of mechanism have been proposed. In one, by Montanari and co-workers,[7] hydrogen abstraction and halogen migration were considered to occur in the same transition state. Such concertedness was assumed specifically in view of the close correlation, which in open-chain substrates was observed between the stereochemical course at sulfur and α carbon, $S_{inv}C_{inv}$ or $S_{ret}C_{ret}$.[7] However, in order to explain the occurrence of various blends of $S_{inv}C_{inv}$



and $S_{ret}C_{ret}$, these authors suggested two processes were competing with each other.

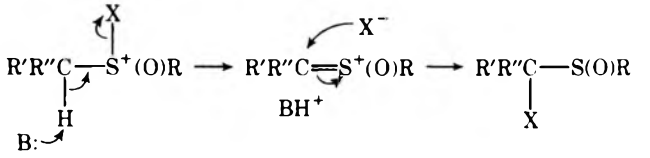
In the first, the halogen would migrate with a *cation* from a syn coplanar conformation, producing retention of configuration at both sulfur and α carbon. In the second, the halogen would migrate as an *anion* from an anti coplanar conformation, involving inversion of configuration at both reaction centers. According to Montanari and his students,[7] the competition between the two paths I and II would be decided by the relative stability of the syn and anti conformers and ultimately by a steric factor: increasing bulk of the groups (R, R_1, and R_2) at the ends of the S–C_α bond destabilizes the syn conformation required for process I, thus shifting the balance toward process II and its attendant $S_{inv}C_{inv}$ steric course.

To visualize how the Montanari mechanism would apply to our substrate it is useful to examine the Newman projections (along the S–C_α bonds) of the key intermediate, the bromooxosulfonium cation.



Protons H_2 and H_4 (trans to bromine) appear to deviate considerably from anti coplanarity with the bromine atom; from Dreiding models, the dihedral angles the S–Br bonds make with C–H_4 and C–H_2 are on the order of 140 and 110°, respectively. On the other hand, protons H_1 and H_3 (cis to bromine) deviate less from syn coplanarity, the corresponding dihedral angle being about 20°. Although neither anti or syn coplanarity can be easily achieved in this very rigid system, the geometry is unquestionably more suitable for the occurrence of process I rather than II. Indeed, if the two processes comparably compete in open-chain systems, as proposed by Montanari,[7] process I would be expected to prevail strongly in our system, leading to removal of H_1 and/or H_3 and preferential steric course $S_{ret}C_{ret}$. This expectation is not fulfilled by the experiment, as the proton removed is H_4, one of the protons trans to bromine, and the steric course is $S_{inv}C_{inv}$. Thus Montanari's mechanism, though not rigorously disproved by our results, does not receive support from them.[25]

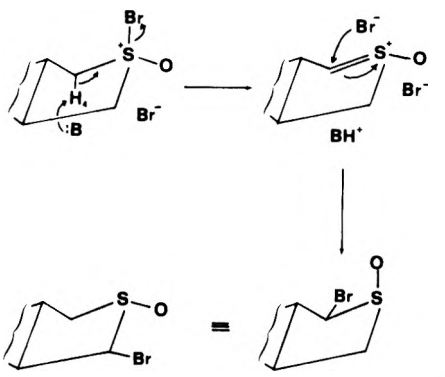
The second mechanism was proposed by Klein and Stollar[10] and independently by Marquet and co-workers,[9] specifically for explaining the results obtained in the halogenation of six-membered cyclic sulfoxides. It is a two-step process of elimination–addition from the halooxosulfonium ion, in which a rate-determining anti β elimination of HX to form a posi-



tively charged "sulfene" is followed by fast halide attack at the α carbon of the sulfene to produce the halosulfoxide.

Applied to our system, this mechanism requires the first step to be the anti elimination of proton H_4 and Br^- (Scheme IV).

Scheme IV



As noted above, the H_4–C–S–Br torsion angle is ~140°; i.e., the C–H_4 and S–Br bonds deviate considerably from the condition of anti coplanarity which is most suitable for trans elimination. This stereoelectronic requirement could be overcome by the elimination occurring via the carbanion mechanism, E1cb, but it may be unnecessary to go as far as that, since concerted anti β eliminations are known to occur without great difficulty even in rigid systems which deviate considerably from anti coplanarity. For example, a case of an essentially exclusive base-catalyzed anti elimination has been reported involving the five-membered ring of a steroidal bromide, 3α-acetoxy-16α-deuterio-17α-bromopregnane-11,20-dione,[26] where the geometrical situation of the groups being eliminated is comparable to that of our bromooxosulfonium intermediate. Moreover, even in norbornyl derivatives, where the anti coplanar arrangement is essentially unaccessible, anti eliminations do occur to some extent.[26] In such cases the E2 transition state may be shifted somewhat toward the E1cb extreme,[27] a requirement which could be accommodated in the elimination from the bromooxosulfonium ion, where substantial carbanion character may be easily achieved.

As far as the second step of the Marquet mechanism is concerned, however, the observed steric course demands that bromide attack on the sulfene occurs exclusively, or very nearly so,[28] on one of the two sides, precisely that where bromide was expelled from the bromooxosulfonium intermediate (equatorial attack). Since, at least in the absence of ionic silver, bromide ions are likely to face both sides of the sulfene, this result is very surprising. It is nevertheless admissible, since the faces of the "sulfene", being diastereotopic, have intrinsically different reactivities. In this connection it may be recalled that in the chlorination of *trans*-4-R-thiane 1-oxide, the observed steric course would require attack on the sulfene to occur preferentially (20:1) on the side opposite to that where chloride was expelled.[9-11]

In conclusion our findings, though not providing additional evidence, may not be incompatible with the Marquet[9] "sulfene" mechanism.

One aspect of the halogenation reaction that this mechanism does not consider explicitly is the role silver ions can play in changing, sometimes very drastically, the steric course (though this was not the case of the present study). We feel this capacity of ionic silver, and perhaps of other electrophiles, may provide the key to a better understanding of the product-forming steps of the halogenation mechanism. We are currently testing the idea that the effect of silver ion may be related to its ability to bind halide ions in solution which might otherwise function as counterion of the halooxosulfonium intermediate. The results of this study will be reported in a forthcoming paper.

Experimental Section

Bromination of *trans*-2-Thiahydrindan 2-Oxide. A solution of bromine (2.01 g, 13 mmol) in anhydrous acetonitrile (15 mL) was added dropwise to a stirred solution of *trans*-2-thiahydrindan 2-oxide[16] (1 g, 6.3 mmol) in a mixture of anhydrous pyridine (3.6 mL) and acetonitrile (20 mL) cooled at −20 °C. The reaction mixture was stirred at room temperature for 48 h. Acetonitrile was removed under reduced pressure; the oily residue was dissolved in chloroform (200 mL) and washed, in order, with aqueous sodium thiosulfate, aqueous sulfuric acid, and saturated aqueous sodium chloride. After drying with anhydrous sodium sulfate, chloroform was evaporated to leave an oil which, analyzed by TLC, resulted in a mixture of bromosulfoxide, starting sulfoxide, and sulfone. The oil was dissolved in ethyl ether (3 mL) and precipitated at −30 °C with light petroleum ether (15 mL) to give 450 mg (30%) of a white crystalline solid. Recrystallized from acetone/ethyl ether at −20 °C, it appeared to be a pure compound (TLC). Unfortunately neither melting point nor elemental analysis could be obtained, since this compound, stable in solution at low temperature, spontaneously and unpredictably undergoes sudden decomposition in the solid. However, mass spectral analysis gave the expected molecular peaks at *m/e* 236 and 238 and a fragmentation pattern consistent with the assigned structure (**2a**). The NMR (60 MHz, 38 mg in 0.5 mL of $CDCl_3$) is shown in Figure 2. The low-field doublet at δ 4.18, due to the methyne proton geminal to bromine, is characterized by an 11-Hz coupling which establishes its quasi-axial setting (trans diaxial vicinal coupling); hence the bromine atom must be quasi-equatorial.

The geometric relation with respect to the S–O function was obtained by lanthanide-induced shift experiments. For instance, the spectrum obtained at the maximum shift reagent to bromosulfoxide molar ratio (1:1) shows (Figure 3) how the methyne proton doublet has moved downfield much less rapidly than the triplet of the axial proton at C_3. Thus the methyne proton is trans and the axial methylene proton at C_3 is cis with respect to S–O.

Bromination in the Presence of Silver Nitrate. A solution of bromine (2 g, 12 mmol) in anhydrous acetonitrile (15 mL) was added dropwise at −20 °C to a stirred solution of sulfoxide (1 g, 6.3 mmol) and silver(I) nitrate (4.2 g, 25 mmol) in a mixture of anhydrous pyridine (3.8 mL) and acetonitrile (30 mL). The reaction mixture was further stirred at −20 °C for 1 h, then at room temperature for 1 h. Filtration of silver bromide and removal of acetonitrile under reduced pressure left a crude oily product which (TLC and NMR) appeared to be made up of bromosulfoxide **2a** (80%) and sulfone (20%). No unreacted sulfoxide could be detected. Workup as described above gave 1.2 g of pure **2a**.

This bromination procedure was applied to the deuterium labeled compounds for which, however, the reaction time was 4 h at −20 °C and 1 h at room temperature.

Reductive Debromination of 2a. Zinc (20 g, 0.3 mol) and a few drops of concentrated deuteriosulfuric acid were added to a stirred solution of bromosulfoxide **2a** (10 g, 0.042 mol) in methanol-*O*-*d* (55 mL). Continuous TLC monitoring of the reaction mixture, stirred at room temperature, showed complete disappearance of the starting sulfoxide after 6 h. Zinc was filtered off and methanol removed under reduced pressure. The residue was dissolved in chloroform (300 mL) and washed with aqueous sodium carbonate and saturated aqueous sodium chloride. After drying with sodium sulfate and removal of chloroform, the residue was purified by column chromatography (silica; chloroform–acetone). The recovered sulfoxide (2 g, 28% yield) was finally distilled at reduced pressure, bp 126 °C (1.5 mm). NMR in the presence of $Eu(dpm)_3$ indicated a 60% protium content at the H_2 position and a 40% protium content at the H_3 position.

Inversion of A to B. The inversion of **A** to obtain **B** was achieved according to the procedure by Johnson and McCants.[22] NMR of the inverted sulfoxide **B** in the presence of $Eu(dpm)_3$ showed protium contents of 51 and 62% at the positions corresponding to H_4 and H_1, respectively.

D/H Exchange of 3 and Pyramidal Inversion. The sulfonium salt **3** (4.5 g, 0.018 mol) was heated at 60 °C for 7 h in 2 N NaOH (70 mL). The recovered salt (4.5 g) was twice crystallized from 95% ethanol, containing a few drops of diluted hydrochloric acid, and ethyl ether.

The NMR of the undeuterated sulfonium salt in D_2O has been previously described.[24] The recovered material, **D**, had 80% protium content at δ 3.40 corresponding to H_2.

A solution of **D** (4 g) in water (50 mL) was refluxed for 28 h. The sulfonium salt **E**, recovered after removal of water under reduced pressure and analyzed by NMR, showed 40% protium contents at δ 3.85 and 3.4 corresponding to H_1 and H_2, respectively.[24]

Four grams of this material was dissolved in 2N NaOH (70 mL) and kept at 60 °C for 8 h. The recovered sulfonium salt (3.5 g) **F** was twice crystallized from 95% ethanol, containing a few drops of diluted hydrochloric acid, and ethyl ether. The protium content (NMR) was found to be 90% at δ 3.4 (H_2) and 40% at δ 3.85 (H_1).[24]

Sulfonium Tetrafluoroborate Anion Exchange and Pyrolysis. The sulfonium tetrafluoroborate **F** (3.5 g) was dissolved in water (50 mL) and the solution eluted through a column of Amberlist 26 (Cl^-). The sulfonium chloride, obtained as a semisolid compound by removal of water under reduced pressure, was decomposed to sulfide and methyl chloride at 160 °C. The resulting crude sulfide was dissolved in chloroform and washed with aqueous sodium thiosulfate and saturated aqueous sodium chloride. After drying with sodium sulfate and removal of chloroform, the residue was distilled under reduced pressure to give 1.6 g (78%) of sulfide **G**, whose NMR spectrum in $CDCl_3$ showed 65% protium content at δ 2.8, corresponding to the pseudoequatorial positions.[2c]

Oxidation of Sulfide G to Sulfoxide H. To a solution of 1.5 g of sulfide **G** in acetone (15 mL) at 0 °C, 1.3 mL of 31% hydrogen peroxide in acetone (10 mL) was added dropwise. The solution was stirred at room temperature for 3 days. Workup gave 1.5 g of pure sulfoxide, whose NMR is reported in Figure 4, containing 65% protium at the positions corresponding to H_1 and H_2.

NMR. All spectra were recorded at 60 MHz (C-60 Jeol). The addition of $Eu(dpm)_3$ shift reagent to chloroform solutions of sulfoxides and bromosulfoxides allowed the complete resolution of the resonances of the heterocyclic ring protons (see, for example, Figures 1 and 3). Assignment of the different resonances to each individual proton was done on the basis of coupling constants and rates of chemical shift changes in the presence of $Eu(dpm)_3$. The percentages of protium at the various positions for the partially deuterated compounds were determined (±10% approximation) using as standard the intensities of the two bridgehead protons (H_5, H_6) for the sulfoxide and of one bridgehead proton (H_5) for the bromosulfoxide.

Acknowledgment is made to Professors A. Marquet, F. Montanari, and E. Casadevall for stimulating discussions, and to C.N.R. Roma for financial support (A.F.).

Registry No.—**1a**, 51066-12-7; **2a**, 63640-73-3.

References and Notes

(1) Sulfoxides can also be halogenated, in the presence as well as in the absence of base, by a variety of other reagents (SO_2Cl_2,[2] tosyl chloride,[3] NOCl,[4] *t*-BuOCl,[5] *N*-chloro- or *N*-bromosuccinimide[6]) which, however, are likely not to act merely as halogen sources.
(2) (a) K. C. Tin and T. Durst, *Tetrahedron Lett.*, 4643 (1970); (b) G. Tsuchihashi, K. Ogura, S. Iriuchijima, and S. Tomisawa, *Synthesis*, 89 (1971); (c) E. Casadevall and M. M. Bouisset, *Tetrahedron Lett.*, 2975 (1973).
(3) M. Hojo and Z. Yoshida, *J. Am. Chem. Soc.*, **90**, 4496 (1968).
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(5) S. Iriuchijima and G. Tsuchihashi, *Tetrahedron Lett.*, 5259 (1969).
(6) (a) G. Tsuchihashi and K. Ogura, *Bull. Chem. Soc. Jpn.*, **44**, 1726 (1971); (b) S. Iriuchijima and G. Tsuchihashi, *Synthesis*, 588 (1970); (c) F. Jung, K. C. Tin, and T. Durst, *Int. J. Sulfur Chem.*, **8**, 1 (1973).
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(8) (a) S. Iriuchijima, M. Ishibashi, and G. Tsuchihashi, *Bull. Chem. Soc. Jpn.*, **46**, 921 (1973); (b) S. Iriuchijima and G. Tsuchihashi, *ibid.*, **46**, 929 (1973).
(9) S. Bory, R. Lett, B. Moreau, and A. Marquet, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **276**, 1323 (1973).
(10) J. Klein and H. Stollar, *J. Am. Chem. Soc.*, **95**, 7437 (1973).
(11) M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc., Perkin Trans. 1*, 1723 (1974).
(12) M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc., Perkin Trans. 1*, 1719 (1974).
(13) Several authors have used conformationally biased 4-substituted thiane 1-oxides for halogenation studies.[8-11] In these systems, however, the biasing substituent at C_4, if it fixes the ground-state conformation, does not at all guarantee against major skeletal deformations that may occur in the transition state at around the reaction centers (S–C_α).
(14) E. Casadevall and co-workers [2c,15] have reported on the chlorination of this sulfoxide. Under the conditions employed by these authors, however (SO_2Cl_2 as chlorinating agent), the reaction appears not to be stereospecific. (See also footnote 1.)
(15) (a) E. Casadevall and M. M. Bouisset, *Tetrahedron Lett.*, 2023 (1975); (b) M. M. Bouisset and E. Casadevall, *ibid.*, 299 (1977).
(16) G. Barbarella, A. Garbesi, and A. Fava, *J. Am. Chem. Soc.*, 97, 5883 (1975).
(17) Each of the four α-bromosulfoxides which in principle may be formed from **1a** are expected to exhibit a low-field doublet due to the methine proton geminal to Br, and are characterized by either a large (11–12 Hz) or a medium (5–6 Hz) coupling according to whether the geminal halogen is equatorial or axial, respectively.
(18) See, for instance: (a) J. Uebel and R. M. Wing, *J. Am. Chem. Soc.*, **94**, 8910

(1972); (b) R. Lett and A. Marquet, *Tetrahedron*, **30**, 3379 (1974); (c) I. Sataty, *Org. Magn. Reson.*, **6**, 8 (1974).
(19) The formation of sulfone may be minimized by careful exclusion of moisture.
(20) M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J. Chem. Soc., Perkin Trans. 1*, 1886 (1972).
(21) In Schemes II and III partially labeled products are indicated as single products rather than mixtures, as they actually are. Formulas representing such mixtures are indicated by capital letters. The percent deuterium or protium at a given position (as obtained from NMR) is indicated by a figure at the upper right of the symbol. Thus the 60:40 mixture of **1b** and **1c** obtained by reductive debromination of **2a** is indicated by structure **A** in Scheme III.
(22) C. R. Johnson, *J. Am. Chem. Soc.*, **85**, 1020 (1963); C. R. Johnson and D. McCants, *ibid.*, **87**, 5404 (1965).
(23) M. Cinquini, S. Colonna, and D. Landini, *J. Chem. Soc., Perkin Trans. 2*, 296 (1972).
(24) G. Barbarella, A. Garbesi, A. Boicelli, and A. Fava, *J. Am. Chem. Soc.*, **95**, 8051 (1973).
(25) Previously, the halogenation of conformationally biased sulfoxides, *trans*-4-R-thiane 1-oxides (R = Ph, *t*-Bu), had also been found to give results incompatible with the concerted mechanism.[8-11]
(26) N. L. Wendler, D. Taub, and N. Kuo, *J. Am. Chem. Soc.*, **82**, 5701 (1960).
(27) C. H. De Puy, C. G. Naylor, and J. A. Beckman, *J. Org. Chem.*, **35**, 2750 (1970).
(28) A small percentage (<5) of the isomeric bromosulfoxide formed by collapse from the opposite side could have escaped detection, however.

Syntheses of and Structural Assignments for Some *N*-Phosphono-2-iminoimidazolidines (Cyclic Guanidines)[1]

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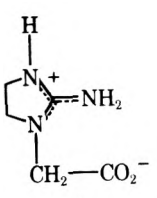
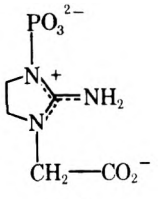
Phosphorylated derivatives of 1-carboxymethyl-2-iminoimidazolidine (1) with phosphorus attached to the primary and secondary nitrogen positions, respectively, were prepared. Dilithium 1-carboxymethyl-3-phosphono-2-iminoimidazolidine (2) was obtained by treatment of 1 with $POCl_3$ in aqueous LiOH solution. Compound 2 was shown to be identical with the product of phosphorylation of 1 by adenosine 5′-triphosphate, catalyzed by creatine kinase. Thus, the previous structural assignment for this compound [G. L. Rowley, A. L. Greenleaf, and G. L. Kenyon, *J. Am. Chem. Soc.*, **93**, 5542 (1971)] is incorrect. 1-Carboxymethyl-2-(diphenoxyphosphinylimino)imidazolidine sodium salt (**13**), the diphenyl ester of the isomeric substance, was obtained by coupling of *N*-(2-aminoethyl)-glycine sodium salt with *S,S*-dimethyl-*N*-(diphenoxyphosphinylimino) dithiocarbonimidate. Structural assignments for both 2 and 13 were made using NMR spectroscopy; especially valuable were measurements of $J_{^{31}P-^{15}N}$ values of appropriate selectively ^{15}N-enriched compounds. Some model 2-iminoimidazolidines, unequivocally phosphorylated on either the primary or secondary nitrogen, were synthesized for use in spectral comparisons. The measured apparent first-order rate constant for the hydrolysis of the P–N bond of 2 at pH 2.96 was found to be consistent with the structural assignment given here.

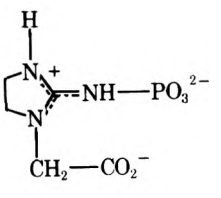
The synthetic creatine analogue 1-carboxymethyl-2-iminoimidazolidine (**1**)[5] is an excellent substrate for the enzyme creatine kinase, having a maximal velocity of 90% of that of creatine itself.[6] The two possible products of this enzymatic phosphorylation are salts of 1-carboxymethyl-3-phosphono-2-iminoimidazolidine (**2**) and 1-carboxymethyl-2-(phosphonoimino)imidazolidine (**3**). After an exhaustive analysis of the products of this enzymatic process, only one of these was detected, and it was tentatively identified as **3**.[5] This identification was based upon examination of the proton NMR spectrum of the isolated product and its observed minimal $^{31}P-N-C-^{1}H$ coupling of phosphorus to the protons of one of the ring methylene groups. Such coupling had been anticipated to be relatively pronounced in structure **2**, but not in **3**.[7] The present work includes the chemical syntheses and structural assignments for **2**, the diphenyl ester of **3**, and several other *N*-phosphono-2-iminoimidazolidines. As a result of this work, the structural assignment given previously[5] for the product of the creatine kinase catalyzed phosphorylation of 1 has been shown to be incorrect; that is, this product has structure **2**, not **3**.



1



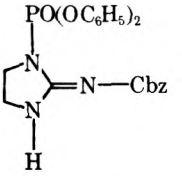
2



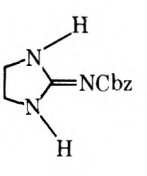
3

Results and Discussion

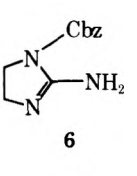
In the course of this work, synthetic routes to both **2** and **3** were sought so that the chemical and biochemical behaviors of each could be examined. One of the compounds synthesized as a potential precursor to **2** was 1-diphenoxyphosphinyl-2-(benzyloxycarbonylimino)imidazolidine (**4**). The precursor to **4**, 2-(benzyloxycarbonylimino)imidazolidine (**5**), and the isomeric **6** had both been prepared and characterized by Matsumoto and Rapoport.[8] Using proton NMR spectroscopy, the distinction between **5** and **6** is straightforward, since **5** is symmetrically substituted and **6** is not.



4



5

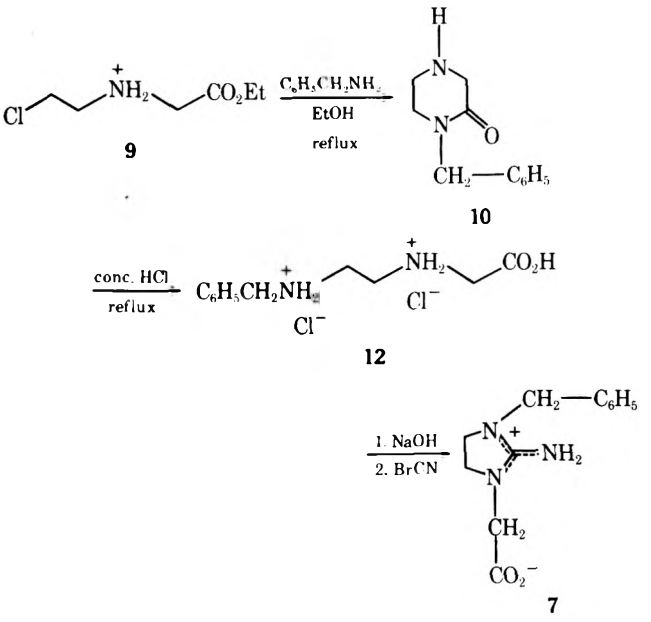


6

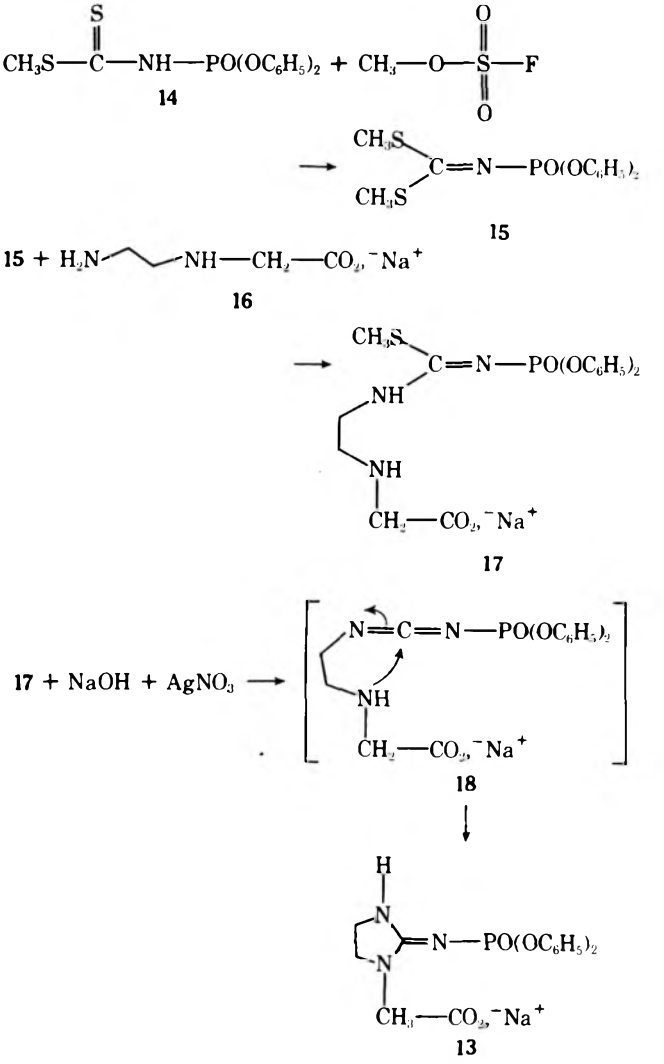
Where Cbz = $-CO_2CH_2C_6H_5$

When **5** was treated with diphenyl chlorophosphate and triethylamine in tetrahydrofuran solution, product **4** was generated. Consistent with the structural assignment, the proton NMR spectrum clearly indicated asymmetric substitution, since the two ring methylene groups were now in different magnetic environments. Attempts to carboxymethylate **4** at the N-3 position were unsuccessful,[9] precluding its use as a precursor to **2**. The proton NMR spectrum was valuable, however, since **4** *unequivocally* possesses the structure with

Scheme I

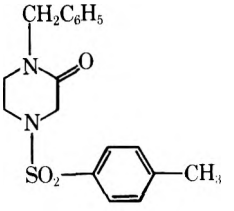


Scheme II



phosphorus attached to the *secondary* nitrogen in the ring. At 220 MHz the $-CH_2CH_2-$ proton region (for spectrum, see ref 9) was remarkably similar to the AA'BB' spectrum previously seen for the product of the creatine kinase catalyzed phosphorylation of **1**.[5] Thus, determination of the J_{PNCH} value for coupling of phosphorus to one of the ring methylene groups is not a reliable method of determining structure for this type of compound.

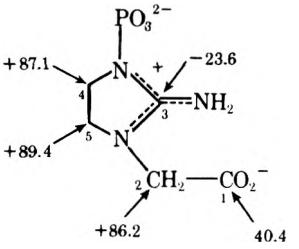
A potential route to the unequivocal synthesis of **3**, centered on the preparation of **7**, is outlined in Scheme I. The use of Na/liquid NH_3, a successful procedure employed in similar syntheses,[10] was proposed for the ultimate removal of the *N*-benzyl blocking group. For the synthesis of **7**, 2-hydroxyethylaminoacetonitrile (**8**) was converted to ethyl-*N*-(2-chloroethyl)glycine hydrochloride (**9**), by modification of the methods of Jones and Wilson.[11] In our hands, the conditions reported by Jones and Wilson were too severe and resulted in intractable tars. When **9** was treated with benzylamine in refluxing ethanol, spontaneous cyclization to 1-benzyl-2-ketopiperazine (**10**) occurred. Isolated as a viscous oil, **10** was characterized as its crystalline *N*-tosyl derivative **11**. When



either **10** or **11** were hydrolyzed, *N*-(2-benzylaminoethyl)-glycine dihydrochloride (**12**) was produced. In analogy to the synthesis of **1**,[5] intermediate **12** was then converted to **7** by treatment with cyanogen bromide in aqueous solution. A variety of conditions, described elsewhere,[9] were used in unsuccessful attempts to phosphorylate **7**.

Scheme II shows a successful route to the unequivocal synthesis of 1-carboxymethyl-2-(diphenoxyphosphinylimino) imidazolidine (**13**), the diphenyl ester of **3**. The scheme was patterned after syntheses of other cyclic guanidines by Bosin *et al.*[12] The use of the powerful methylating agent, methyl fluorosulfonate,[13] was found to be necessary for the conversion of **14** to **15**. Intermediate **17** was purified by the unusual procedure of chromatography over silica gel of its sodium salt, using methanol as eluent. The final ring-closure presumably proceeds *via* the hypothetical carbodiimide **18**. Despite several attempts,[9] including catalytic hydrogenation under a variety of non-acidic conditions, efforts to remove the phenyl groups from **13** to generate **3** have so far been fruitless.

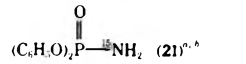
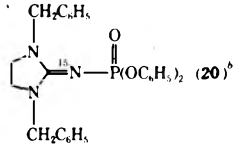
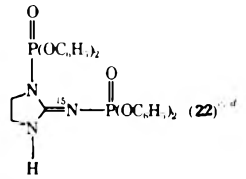
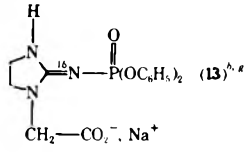
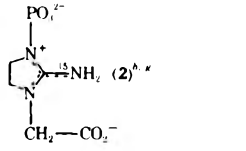
Compound **1** was phosphorylated in aqueous base with $POCl_3$, using a slight modification of the procedure which Ennor and Stocken[14] used for the conversion of creatine to phosphocreatine. Surprisingly, only one phosphorylated product could be detected and isolated, and it was identical to the sole product of the creatine kinase-catalyzed phosphorylation of **1**.[5] The natural abundance, proton-decoupled carbon-13 NMR spectrum of this product was examined. The chemical shift assignments are shown below (relative to dioxane):



^{13}C NMR of **2**

The spectrum was consistent with the structure of **2**, not **3**. The carbons furthest removed from phosphorus (C-1, C-2, and C-5) appeared as singlets. Both C-3 and C-4, however, appeared as doublets with *J* values of 4 ± 1 Hz, consistent with

Table I. ^{31}P NMR Data for Some ^{15}N-Enriched Phosphoramidates

Structure	Registry no.	$J_{^{15}N-^{31}P}$ (Hz)
	63784-03-2	45
	63784-04-3	35
	63784-05-4	~50[e], 0[f]
	63784-06-5	11
	63784-07-6	0[h]

[a] Solvent = acetone-d_6. [b] 99% ^{15}N enriched. [c] Solvent = $CDCl_3$. [d] 96% ^{15}N enriched. [e] Since this measurement was made using only 96% ^{15}N-enriched material, the resolution of the doublet was not complete. The value given is an estimate based on the width at half-height. [f] As expected, a second ^{31}P peak was observed as a sharp singlet. [g] Solvent = D_2O. [h] This ^{31}P peak appeared 5.33 ppm downfield from trimethyl phosphate which was included in the sample at a concentration of 0.10 M.

$J_{^{31}P^{15}N^{13}C}$ coupling. Nevertheless, since very few similar coupling constants have ever been determined, this evidence was considered insufficient for a definitive structural assignment.

More convincing evidence for the structural assignments given to **2** and **13** came from measurement of $J_{^{31}P-^{15}N}$ values for some selectively ^{15}N-enriched phosphoramidates using phosphorus-31 NMR. The data are shown in Table I. Compound **20**, owing to appropriate substitution, unequivocally has phosphorus attached to the 2-imino nitrogen. As expected,[15] the ^{31}P NMR spectra of both **20** and **21** showed large $J_{^{31}P-^{15}N}$ values. Because its ring methylene groups are in different magnetic environments as determined by proton NMR,[9] compound **22** must have one phosphorus attached to a secondary nitrogen and one phosphorus attached to the 2-imino nitrogen. This latter example provides direct evidence that J_{NCNP} values must be relatively small in systems of this type.

Within experimental error, selectively ^{15}N-enriched **2** shows no evidence of coupling to phosphorus, whereas selectively enriched **13** does. This lack of observed coupling of ^{15}N to phosphorus provides evidence that the product of creatine kinase catalyzed phosphorylation of **1** is **2**, not **3** as previously proposed.[5]

Further evidence for the structure of **2** is provided by a comparison of the rate of removal of phosphorus from **2** by hydrolysis to the rate of removal of phosphorus from a phosphoguanidine where the bond is between phosphorus and a primary nitrogen. The apparent first-order rate constant for appearance of inorganic phosphate when **2** undergoes hydrolysis in acetate buffer (30.5 °C, pH 2.96, μ 0.2) was found to be 1.39 (±0.08) × 10^{-3} min^{-1}. Assuming that the apparent pK_a' values for **2** are similar to those for phosphocreatine,[16] then the species here would be monoprotonated on the phosphate moiety and electronically comparable to the phosphocreatine species present in solution at pH 1–3.5.[17] Under the conditions described above, the apparent first-order rate constant for the hydrolysis of this species of phosphocreatine[16] is 1.5–1.65 × 10^{-2} min^{-1}. This 11- to 12-fold difference in rates could be due to a pK_a' difference in the guanidines of about 1 unit (if the phosphorus were joined to a primary nitrogen in both cases).[18] However, such a difference in pK_a' is unlikely and a more plausible explanation of the difference in rate constants is that the compounds are of different types. Benkovic and Sampson[18] found that various phosphorylpyridinium ions have a rate of hydrolysis 50-fold lower than phosphoramidates formed from primary alkyl amines. A similar situation could be present here where the difference in rate constants may be due to the fact that phosphorus is bound to a primary nitrogen in one case and a secondary in the other.

A preliminary report[19] of the x-ray crystal structure of the product from the creatine kinase catalyzed phosphorylation of **1** confirms the structural assignment made here. Moreover, there is evidence[10,20] which indicates that **2** can substitute for phosphocreatine in the creatine kinase catalyzed reaction in the direction of adenosine 5′-triphosphate formation. Further studies on the biochemical properties of **2** will be reported at a later date.

Experimental Section[21]

Dilithium 1-Carboxymethyl-3-phosphono-2-iminoimidazolidine Dihydrate (2). A solution of 0.5 g (3.5 mmol) of 1-carboxymethyl-2-iminoimidazolidine (**1**)[5] in 0.5 mL of 3.7 N LiOH and 5 mL of H_2O was cooled in an ice–salt bath. While using vigorous mechanical stirring, 1.6 mL (17.5 mmol) of freshly distilled $POCl_3$ and 32 mL of 3.7 N LiOH were added in 16 portions at appropriate time intervals over a period of 2 h. At the end of the 2-h addition period, the pH of the solution was carefully adjusted to 7.2 with 6 N HCl. Solids in the reaction mixture were removed by either centrifugation or filtration and washed with 30% methanol–water (v/v). The filtrate (or supernatant) and washings were combined, and an aliquot was analyzed by polyethylenimine (PEI) cellulose thin-layer chromatography, as previously described.[22] Only one phosphorus-containing spot was in evidence, and its R_f value corresponded favorably to that of other phosphocreatine analogues.[22] To complete the purification of the product, the solution was reduced in vacuo at room temperature to a volume of 5 mL. The resulting solution, slightly turbid due to a small amount of insoluble material, was filtered through a fine-grade sintered-glass funnel to give a clear filtrate. Absolute ethanol was added to this filtrate until it became slightly turbid. After standing overnight, crystals had formed. They were collected by filtration and recrystallized once more from H_2O–EtOH. This resulted in 400 mg of colorless crystals. Addition of more EtOH to the mother liquor until it turned turbid gave an additional 168 mg of product. The combined yield amounted to 568 mg (57%). Both the IR and 220-MHz NMR spectra were identical with those of the product obtained from the creatine kinase catalyzed phosphorylation of **1**.[5] PEI-cellulose thin-layer chromatography and NMR analyses of the mother liquors at various stages of purification of **2** gave no evidence for the presence of a second isomer.

Anal. Calcd for $C_5H_8N_3O_5PLi_2 \cdot 2H_2O$: N, 15.50; P, 11.43. Found: N, 15.36; P, 11.56.

The hydrolysis of compound **2** in acetate buffer was followed by measuring inorganic phosphate using the method of Jencks and Gilchrist[23] (developed for use with labile phosphoramidates). A 10 mM solution of **2** in sufficient acetate buffer to give an ionic strength of 0.2 and a pH of 2.96 was heated at 30.5 °C (±0.2 °C) until no further hydrolysis occurred. The pH changed no more than ±0.02 unit. With the sample of **2** used here the initial concentration of inorganic phosphate was 0.3 mM and the final concentration (>6 half-lives) was 7.4 mM. Duplicate sets of data were plotted on graphs of ln $(P_\infty - P_t)$ vs. time, and the slope and standard deviation were derived by the method of least squares.

1-Diphenoxyphosphinyl-2-(benzyloxycarbonylimino)imidazolidine (4). To a stirred solution of 1.00 g (4.56 mmol) of 2-(benzyloxycarbonylimino)imidazolidine (5)[8] and 1.20 mL (8.72 mmol) of triethylamine in 80 mL of tetrahydrofuran (THF) under an atmosphere of N_2 was added a solution of 2.32 g (8.72 mmol) of diphenylchlorophosphate (Aldrich) in 80 mL of THF. Addition was carried out over a period of 10 min. Following completion of addition, the mixture was evaporated to dryness. The resulting material was dissolved in a minimal amount of 5% Et_3N–$CHCl_3$ (v/v) and applied to a silica gel column. The column was eluted with 5% Et_3N–$CHCl_3$ (v/v), and the fractions containing the component with an R_f value of 0.6 on silica gel thin-layer plates were pooled and the solvent was removed. The white solid thus obtained was recrystallized from $CHCl_3$–ether. A total of 1.54 g of product was obtained (75% yield): mp 141–142 °C; IR (Nujol) 6.02, 6.26, 6.78, 7.78 μm; NMR ($CDCl_3$) δ 3.63 (m, 1), 5.22 (s, 2), 7.18 (s, 5), 8.40 (br s, 1).

Anal. Calcd for $C_{23}H_{22}N_3O_5P$: C, 61.23; H, 4.93; N, 9.33; P, 6.88. Found: C, 60.93; H, 4.80; N, 9.29; P, 6.72.

Ethyl-*N*-(2-chloroethyl)glycine Hydrochloride (9). This compound was prepared by the method of Jones and Wilson,[11] modified as follows. While stirring in a water bath at room temperature, 51.1 g (0.9 mol) of cyanohydrin[24] was added dropwise to 54.7 g (0.90 mol) of ethanolamine over a period of 2 h. The mixture was stirred overnight. A distillation head was fitted to the flask, and the reaction system was evacuated to a pressure of ca. 8 mm while stirring and cooling. After 5–10 min of pumping, the material in the flask turned into a wet, white, crystalline mass. Pumping was continued for an additional 30–45 min. This intermediate, 2-hydroxyethylaminoacetonitrile (8), was not purified further and was stored at 4 °C until used. A flask containing 200 g of absolute ethanol containing 65 g of HCl was stirred on an ice bath. To this was added cautiously 30.8 g (0.308 mol) of 8. Stirring was continued for 30 min while still cooling in an ice bath. The mixture was then heated at reflux for ca. 2 h. Following filtration of the reaction mixture, the filtrate was evaporated to remove all of the ethanol. The remaining residue was taken up in 45 mL of $CHCl_3$. This solution was cooled in ice while 100 g (0.84 mol) of $SOCl_2$ was added dropwise. Stirring at room temperature was continued for 14 h. The solvent was then removed. A large amount of ether was poured over the residue, and the crude product was collected by filtration. The product melted between 150 and 156 °C (lit.[11] 152 °C).[25] The material failed to recrystallize under the conditions reported by the original authors.[11] No straightforward method of further purification could be found, but the material was used successfully in its somewhat impure form in subsequent reactions.

1-Benzyl-2-ketopiperazine (10). To a solution of 21 g (0.10 mol) of ethyl-*N*-(2-chloroethyl)glycine hydrochloride (9) in 1400 mL of refluxing 95% ethanol was added dropwise a solution of 39.2 g (0.366 mol) of benzylamine (Aldrich, 99%) in 350 mL of 95% ethanol. Heating at reflux was continued overnight. The ethanol was removed, and the residue which remained was triturated with $CHCl_3$. Filtration removed the insoluble benzylammonium chloride. The excess benzylamine was removed by vacuum distillation. Once again $CHCl_3$ was added to the residue, and a small amount of benzylammonium chloride which remained was removed by filtration. Removal of solvent yielded a red, viscous oil which was further purified by one of the following two procedures:

(a) Purification by tosylation. The crude oil was dissolved in 60 mL of 3 N NaOH. While cooling in a water bath, 22.8 g (0.122 mol) of *p*-toluenesulfonyl chloride, dissolved in acetone, was added with stirring. After standing overnight, the crude, crystalline tosyl derivative, 1-benzyl-4-*p*-toluenesulfonyl-2-ketopiperazine (11), was collected by filtration. After recrystallization from 95% ethanol, 7.3 g (21%) of the pure derivative was obtained: mp 153–155 °C; IR (Nujol) 6.03, 8.61 μm.

Anal. Calcd for $C_{18}H_{20}N_2O_3S$: C, 62.70; H, 5.86; N, 8.13. Found: C, 62.58; H, 5.76; N, 8.36.

(b) Purification by silica gel chromatography. The crude oil was chromatographed on silica gel by eluting with either 50% MeOH–EtOAc (v/v) or MeOH–$CHCl_3$ (2:3, v/v). The pure, hygroscopic oil was obtained in a yield of 30–40%, and it had an R_f value of 0.4 on silica gel thin-layer plates when chromatographed with 50% MeOH–$CHCl_3$ (v/v). Due to its extremely hygroscopic nature, a satisfactory elemental analysis was not obtained for this product. Conversion of the chromatographically pure oil to the tosyl derivative gave a crystalline material identical to the one described above.

***N*-(2-Benzylaminoethyl)glycine Dihydrochloride (12).** This compound was obtained by hydrolysis of either 1-benzyl-2-ketopiperazine (10) itself (method 1) or its *N*-tosyl derivative 11 (method 2).

Method 1. A solution of 0.6 g of (10) was heated at reflux in 14 mL of 6 N HCl for 30 h. After cooling to room temperature, a mass of colorless crystals had formed. They were collected by filtration and washed with 3 mL of cold water. A total of 0.60 g of product was obtained (72% yield): mp 215–216.5 °C; IR (Nujol) 3.55, 5.74 μm; NMR (D_2O) δ 3.50 (s, 4), 4.00 (s, 2), 4.25 (s, 2), 7.45 (s, 5).

Anal. Calcd for $C_{11}H_{18}Cl_2N_2O_2$: C, 46.98; H, 6.47; N, 9.97; Cl, 25.22. Found: C, 47.14; H, 6.38; N, 10.16, Cl, 25.14.

Method 2. A solution of 5.9 g of (11) was heated at reflux for 72 h in 80 mL of 6 N HCl. The hydrolyzed product crystallized upon cooling of the solution. Collection of the product by filtration, followed by further workup of the mother liquors, resulted in 3.3 g (69% yield) of product, identical to the material obtained by method 1.

1-Carboxymethyl-3-benzyl-2-iminoimidazolidine (7). To a solution of 2.3 g (8.2 mmol) of *N*-(2-benzylaminoethyl)glycine dihydrochloride (12) in 2.8 mL of 8.7 N NaOH was added dropwise with stirring a solution of 0.87 g (8.2 mmol) of BrCN in 1.2 mL of methanol. After 4.75 h of stirring at room temperature, the solvent was removed. The residue was triturated with warm absolute ethanol and filtered to remove the insoluble material. The ethanolic filtrate was reduced in volume and applied to a column of silica gel. It was washed onto the column with a small amount of $CHCl_3$, followed by 50% MeOH–$CHCl_3$ (v/v). Elution was completed using absolute methanol. The product had an R_f value on silica gel thin-layer plates of 0.5 when eluted with methanol. The white product began to discolor at 180 °C and melted with decomposition between 262 and 265 °C; IR (Nujol) 6.2 μm; NMR (D_2O) δ 3.25 (s, 4), 3.75 (s, 2), 4.40 (s, 2), 7.3 (s, 5).

Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.72; H, 6.53; N, 18.05. Found: C, 61.68; H, 6.49; N, 17.89.

***S,S*-Dimethyl-*N*-(diphenoxyphosphinylimino) Dithiocarbonimidate (15).** Methyl-*N*-(diphenoxyphosphinyl) dithiocarbamate (14)[27] was dissolved in the minimal amount of CH_2Cl_2 necessary to bring it into solution at room temperature. While stirring the solution at room temperature, a fivefold molar excess of methyl fluorosulfonate (Aldrich, 97%) was added. Stirring at room temperature was continued for ca. 6 h. At the end of this period the initial yellow tint had disappeared, and the solution was colorless. The solvent was removed, and the oil which remained was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with a portion of 5% $NaHCO_3$ solution followed by two portions of water. After drying the $CHCl_3$ layer over $MgSO_4$, it was filtered and the solvent was removed. The remaining oil was pure product. The oil was dried with mild heating over P_2O_5 before submitting for elemental analysis, and the product was analyzed as a monohydrate. The yield from this reaction was consistently in the range of 80–90%: IR (neat) 3.2, 6.29, 6.50, 6.84 μm.

Anal. Calcd for $C_{15}H_{16}NO_3PS_2 \cdot H_2O$: C, 48.49; H, 4.89; N, 3.78; P, 8.34; S, 17.27. Found: C, 48.34; H, 4.55; N, 4.02; P, 8.32; S, 17.06.

On one occasion a portion of the oil crystallized spontaneously. Ether was poured over the mixture of oil and crystals, and the crystals were collected by filtration, mp 75–77 °C. The crystals were dried over P_2O_5 and submitted for analysis; this time anhydrous product was obtained: NMR ($CDCl_3$) δ 2.4 (s, 6), 7.1 (s, 10).

Anal. Calcd for $C_{15}H_{16}NO_3PS_2$: C, 50.97; H, 4.57; N, 3.97; P, 8.76; S, 18.18. Found: C, 51.28; H, 4.41; N, 4.19; P, 8.63; S, 18.40.

***N*-[2-*N*-(Methylmercapto-*N*-diphenoxyphosphinylcarbonimidoyl)aminoethyl]glycine Sodium Salt Dihydrate (17).** A flask containing 0.45 g (3.2 mmol) of *N*-(2-aminoethyl)glycine (16), sodium salt, and 1.20 g (3.4 mmol) of *S,S*-dimethyl-*N*-(diphenoxyphosphinylimino) dithiocarbonimidate (15) in a total of 10 mL of absolute ethanol was stirred for 24 h at room temperature, and then the solvent was removed. The yellow oil which remained was dissolved in water, and the basic aqueous solution was carefully adjusted to pH 7.1 by the addition of 1 N HCl. The aqueous solution was then extracted with several portions of $CHCl_3$. The combined $CHCl_3$ extracts were dried over $MgSO_4$, the solution was filtered, and the solvent was removed. The crude oil which remained consisted of two components as could be observed on a silica gel thin-layer plate eluted with methanol. The two components had R_f values of 0.9 and 0.5, respectively. The crude oil was dissolved in $CHCl_3$ and applied to a column (2 × 80 cm) containing 70 g of silica gel. Elution of the column was carried out using methanol. The fractions containing the component of R_f 0.5 were pooled and the solvent was removed. Carbon tetrachloride was repeatedly poured over the oily material and removed. Following this treatment, 0.4 g (29% yield) of a white, glassy solid was obtained. After drying for several hours over P_2O_5, the product was submitted for analysis: IR (Nujol) broad peak at 6.3 μm; NMR ($CDCl_3$) δ 2.1–3.4 (br m, 9), 7.15 (s, 10).

Anal. Calcd for $C_{18}H_{21}N_3O_5PSNa \cdot 2H_2O$: C, 44.81; H, 5.24; N, 8.73; S, 6.65; P, 6.43. Found: C, 44.91; H, 4.88; N, 8.56; S, 6.42; P, 6.38.

1-Carboxymethyl-2-(diphenoxyphosphinylimino)imidazolidine Sodium Salt Hemihydrate (13). A solution of 0.39 g (0.81

mmol) of N-[2-N-(methylmercapto-N-diphenoxyphosphinylcarbonimidoyl)aminoethyl]glycine sodium salt dihydrate (17) in 13 mL of CH_3CN was cooled in an ice bath. While stirring, 0.43 mL (0.81 mmol) of 1.88 N NaOH was added, followed by a solution of 0.137 g (0.81 mmol) of $AgNO_3$ in 1.1 mL of CH_3CN. A precipitate of yellow silver mercaptide formed immediately upon addition of the $AgNO_3$ solution. Stirring of the reaction mixture was continued for an additional 2 h in an ice bath and for 1 h more at room temperature. The reaction mixture was then centrifuged. After spinning down the solid material, the supernatants were decanted and saved. A small amount of CH_3CN was added to each tube, the solid was resuspended, and the tubes were once again centrifuged. The supernatants were decanted from the tubes. All the decanted supernatants were combined and the solvents were removed. The residue was dissolved in $CHCl_3$ and filtered. The filtrate was evaporated. A glassy solid remained. A total of 0.26 g (79% yield) of product was obtained. After drying over P_2O_5 it was submitted for analysis: IR (Nujol) 6.15, 6.50, 7.28 μm; NMR (D_2O) δ 3.5 (s, 4) 3.7 (s, 2), 7.3 (s, 10).

Anal. Calcd for $C_{17}H_{17}N_3O_5PNa \cdot 0.5H_2O$: C, 50.21; H, 4.47; N, 10.35; P, 7.63. Found: C, 50.18; H, 4.82; N, 10.20; P, 7.62.

1,3-Dibenzyl-2-iminoimidazolidine Hydrobromide (19). To a solution of 11.0 g (46 mmol) of N,N'-dibenzylethylenediamine (99%, Aldrich) in 9.0 mL of methanol was added dropwise a solution of 5 g (46 mmol) of BrCN (97%, Aldrich) in 7 mL of methanol while cooling in an ice bath. About halfway through the addition a white mass precipitated from solution. The reaction flask was removed from the ice bath and placed in a water bath at room temperature while addition of the BrCN solution was completed. After stirring 1 h, the white crystalline material was collected by filtration, and the product was washed well with ether. A total of 15.1 g (94% yield) of crystalline hydrobromide was obtained. The analytically pure product melted between 253 and 258 °C: NMR [$(CD_3)_2SO$] δ 3.4 (s, 4), 4.6 (s, 4), 7.4 (s, 10), 8.6 (br s, 1).

Anal. Calcd for $C_{17}H_{20}N_3Br$: C, 58.91; H, 5.89; N, 12.12; Br, 23.05. Found: C, 58.71; H, 5.56; N, 12.28; Br, 22.84.

1,3-Dibenzyl-2-(diphenoxyphosphinylimino)imidazolidine (20). The free base of 1,3-dibenzyl-2-iminoimidazolidine was obtained by dissolving 1.5 g (4.4 mmol) of its hydrobromide salt (19) in 7.7 mL of 0.97 N NaOH and extracting with several portions of ether. The combined ether extracts were dried over Na_2SO_4, the solution was filtered, and the solvent was removed. The resultant clear oil was dissolved in 3.5 mL of dry THF. To the THF solution was added a solution of 0.56 g (2.0 mmol) of diphenyl chlorophosphate in 3.5 mL of dry THF. The mixture was stirred 12 h at room temperature. It was then filtered to remove precipitated salt, and the salt was washed with 3 mL of THF. The filtrate was evaporated, and the resultant oil was further purified by silica gel chromatography. The oil was applied to a column of 25 g of silica gel packed in 1% Et_3N–$CHCl_3$ (v/v), and the elution was carried out using Et_3N–MeOH–$CHCl_3$ (1:5:94, v/v). The fractions containing the component with R_f 0.9 on a silica gel thin-layer plate eluted with 5% MeOH–$CHCl_3$ (v/v) were pooled and the solvent was removed. This resulted in 0.44 g (44% yield) of a yellow oil. The oil was dried in vacuo over P_2O_5 and required no further purification: NMR ($CDCl_3$) δ 3.2 (s, 4), 4.5 (s, 4), 7.2 (s, 20); IR (neat) 6.15, 6.29, 6.74 μm.

Anal. Calcd for $C_{29}H_{28}N_3O_3P$: C, 70.02; H, 5.68; N, 8.45; P, 6.22. Found: C, 70.07; H, 5.76; N, 8.49; P, 6.35.

1-Diphenoxyphosphinyl-2-(diphenoxyphosphinylimino)imidazolidine (22). In a 100-mL three-neck flask, 2.4 g (14.5 mmol) of 2-iminoimidazolidine hydrobromide[28] was dissolved in a mixture of 15 mL of 0.97 N NaOH and 15 mL of THF. The flask was fitted with two dropping funnels, one of which contained 15 mL of 0.97 N NaOH and the other of which contained 3.9 g (14.5 mmol) of diphenyl chlorophosphate diluted to 15 mL with THF. The contents of the two funnels were added simultaneously over a period of 15 min while cooling the flask in an ice bath. The mixture was transferred to a 250-mL flask, and the THF was removed. The resulting aqueous solution was extracted with $CHCl_3$. After drying the combined extracts over $MgSO_4$, they were filtered and the solvent was removed. The resulting oil was applied to a column of 75 g of silica gel, and the column was eluted with a mixture of $CHCl_3$–CH_3OH–Et_3N (94:5:1, v/v). The product had an R_f value of 0.6 on silica gel thin-layer plates using the same solvent system. The fractions containing this component were pooled and the solvent was removed. Ether was poured over the resulting oil, and after several hours of standing at room temperature crystals began to form. A total of 1.3 g of crystals was collected (16% yield): mp 83–86 °C; IR (Nujol) 2.95, 6.07, 6.26 μm; NMR ($CDCl_3$) δ 3.5 (m, 4), 7.2 (s, 20).

Anal. Calcd for $C_{27}H_{25}N_3O_6P_2$: C, 58.97; H, 4.60; N, 7.65; P, 11.27. Found: C, 58.97; H, 5.02; N, 7.61; P, 11.07.

^{15}N-Diphenyl Phosphoramidate (21). The synthesis was based on the method of Chambers and Khorana.[29] A test tube containing 1 equiv of diphenyl chlorophosphate and an ampule containing 2.2 equiv of 99% enriched ^{15}N-NH_3 (Bio-Rad) were seated firmly against rubber seals on two closed stopcocks of a vacuum manifold. Both vessels were cooled in liquid N_2. After evacuation of the manifold, the system was closed. The stopcock to the ampule of ammonia was opened, and the liquid N_2 coolant was removed. The stopcock to the test tube containing the diphenyl chlorophosphate was opened, and the ammonia was allowed to distill into it. Gentle heating of the manifold was used to force all of the ammonia into the cooled test tube. The stopcock to the test tube was closed, and the liquid N_2 coolant was replaced with a dry ice–acetone bath. The test tube was removed from its rubber seal, and it was filled with water while still cooled. The product precipitated as a white crystalline material and was collected immediately by filtration. It was dried in vacuo over P_2O_5. The melting point of the product was in agreement with the value reported by Chambers and Khorana (148–149 °C).[29]

^{15}N-Cyanogen Bromide. The synthesis of enriched BrCN used 99% enriched ^{15}N-KCN (Bio-Rad) as starting material. The procedure of Hartman and Dreger[30] was modified for this preparation. In a 25-mL flask in a room-temperature water bath was placed 1.3 g (8.1 mmol) of Br_2 and one drop of water. A small dropping funnel containing a solution of 0.50 g (7.6 mmol) of 99% enriched ^{15}N-KCN dissolved in 2.5 mL of water was connected to the flask. The KCN solution was added slowly to the stirred Br_2 over a period of 10 min. Stirring was continued an additional 50 min. A short-path distillation head with a 10-mL receiving flask containing 1 mL of methanol was attached to the reaction flask in place of the dropping funnel, and the BrCN was distilled with heating on a steam bath. After distillation appeared complete, an additional 0.5 mL of methanol was added to the distillation pot, and the added methanol was distilled to chase the last traces of product into the receiving flask. The methanolic solution of ^{15}N-BrCN was used immediately in reaction with the appropriate diamine to obtain the desired labeled guanidine. All reactions were carried out assuming the presence of 7.6 mmol of BrCN.

In order to determine the yield of BrCN obtained from this procedure, several trial runs were made using unlabeled KCN as starting material. An excess of standard NaOH was added to the methanolic distillate, and the basic solution was back-titrated with standard HCl. The results of these determinations indicated a reliable yield of 99–100%.

^{15}N-Potassium Thiocyanate. Using 99% enriched ^{15}N-KCN (Bio-Rad) as starting material, the procedure was exactly the same as that used by Greenberg and Rothstein[31] for the synthesis of the analogous ^{14}C-labeled compound. The only change made in the procedure was the use of a potassium instead of a sodium salt.

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Registry No.—1, 35404-50-3; 2, 63784-08-7; 4, 63784-09-8; 5, 15230-93-0; 7, 63784-10-1; 8, 54961-35-2; 9, 63784-11-2; 10, 59702-21-5; 11, 63784-12-3; 12, 63784-13-4; 13, 63784-14-5; 14, 63784-15-6; 15, 63784-16-7; 16, 35404-68-3; 17, 63784-17-8; 19, 63784-18-9; 20, 63784-19-0; 22, 63784-20-3; LiOH, 1310-65-2; $POCl_3$, 10025-87-3; diphenyl chlorophosphate, 2524-64-3; benzylamine, 100-46-9; methyl fluorosulfonate, 421-20-5; N,N'-dibenzylethylenediamine, 140-28-3; 2-iminoimidazolidine hydrobromide, 33325-25-6.

References and Notes

(1) A preliminary account of this work was presented at the Pacific Conference on Chemistry and Spectroscopy, San Diego, Calif., Oct., 1973.
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Synthesis and Properties of Carbamate Derivatives of Tetrakis(hydroxymethyl)phosphonium Chloride

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Tetrakis(hydroxymethyl)phosphonium chloride (**1**) condenses with primary or secondary alkyl carbamates, forming stable quaternary phosphonium salts having the structure $(RO_2CNHCH_2)_4PCl$ (**3**) or $[EtO_2CN(R)CH_2]_4PCl$ (**6**). The alkyl carbamates are too feebly basic to cause the displacement of formaldehyde and HCl that characterizes the reaction of **1** with primary or secondary amines. The quaternary phosphonium salt **3a** (R = Me) undergoes halogen exchange, either by metathesis or by passage over an ion-exchange column, giving the corresponding iodide **9a** or bromide **11a**. Acid hydrolysis of **3a** unexpectedly regenerates **1**—a rare case of alkyl–nitrogen fission in a carbamate. The reaction of **3a** with sodium hydroxide is complicated by interaction of the product $(RO_2CNHCH_2)_3P$ (**13**) with the by-product $RO_2CN{=}CH_2$ (**16**), resulting in a different tertiary phosphine **15**, but this can be avoided by replacing the base by a reagent capable of reacting with the by-product, such as ammonium hydroxide, morpholine, or sodium sulfite. Oxide and sulfide derivatives of **13** are described.

The development of durable flame-retardant finishes for cotton based on the reaction of tetrakis(hydroxymethyl)-phosphonium chloride (**1**) with trimethylolmelamine and urea[2] has led to the investigation of many other nitrogen compounds as resin-forming substrates.[3] The alkyl carbamates are particularly appealing in this respect, for they are the substrates of another important set of cotton finishes, the durable-press finishes.[4] Some attempts have been made to combine these properties in a single finish, without notable success.[5–7] In this paper, we report our investigation of the reaction of **1** with alkyl carbamates, leading to a series of novel nitrogen-containing quaternary phosphonium salts and their tertiary phosphine, phosphine oxide, and phosphine sulfide *derivatives.*

Quaternary Phosphonium Salts. Condensation of the phosphonium salt **1** with the alkyl carbamates **2a–e** took place in refluxing toluene (bp 110 °C) with azeotropic removal of the water, giving tetrakis(*N*-carbalkoxylaminomethyl)-phosphonium chlorides (**3a–e**) in moderate to good yield (eq 1).[8,9]

$$\underset{\mathbf{1}}{(HOCH_2)_4PCl} + 4\underset{\mathbf{2}}{RO_2CNH_2} \rightarrow \underset{\mathbf{3}}{(RO_2CNHCH_2)_4PCl} + 4H_2O \quad (1)$$

a, R = Me
b, R = Et
c, R = *i*-Pr
d, R = *n*-Bu
e, R = $MeOCH_2CH_2$–

The methyl (**3a**), ethyl (**3b**), and isopropyl (**3c**) esters crystallized and were purified by recrystallization, giving yields of 86, 60, and 45%, respectively. The others were purified by adsorption on a cation-exchange resin, followed by displacement with hydrogen chloride, adopting a procedure developed for the analysis of tetramethylphosphonium chloride.[10,11] The 2-methoxyethyl ester **3e**, which is water soluble, was isolated in 53% yield as a viscous colorless oil. The *n*-butyl ester **3d**, which is not water soluble, was isolated in 38% yield as a viscous colorless oil, together with 21% of unreacted carbamate (**2d**) and 14% of di-*n*-butyl *N,N'*-methylenedicarbamate (**4d**).[12]

The products **3a–e** are air-stable, odorless compounds that, unlike **1**, are only mildly acidic in aqueous solution. Their infrared spectra are dominated by intense absorption bands at 1715 ± 10 (C=O, amide I) and 1525 ± 15 (NH, amide II) cm^{-1}, regions characteristic of secondary carbamates.[13] In the solid phosphonium salts **3a–c**, the amide I band appears as a sharp doublet in Nujol but as a singlet in solution. In KBr disks, the amide I band appears as a doublet in strong spectra and a singlet in weak spectra. This concentration dependence is ascribed to self-association (NH···OC) in the solid phase. Deuteration of **3b** with deuterium oxide shifts the free and hydrogen-bonded NH stretching bands and, to a lesser degree, the amide II band to lower frequencies in the expected manner.[14]

The ^1H NMR spectra of the phosphonium salts **3a–e** show that the four phosphorus substituents in each product are identical. Owing to coupling with NH, the PCH_2 protons appear as a triplet, which, upon shaking with D_2O, collapses to a doublet. The ^{31}P NMR spectra of **3a,b,d,e** all show a single peak at −30.5 ± 0.5 ppm, a region characteristic of phosphonium salts.[15] Molecular weight measurements on **3a** in water by vapor-phase osmometry give values that are just over half of the calculated value. These data are all consistent with the formulation of the compounds as phosphonium salts.

The condensation of **1** with **2b** also occurred in xylene (bp 139 °C), but not in benzene (bp 80 °C). Upon further investigation, it was found that removal of the water by azeotropic distillation was unnecessary. The phosphonium salt **3a** was prepared in 41% yield by heating **1** with **2a** in *n*-butyl alcohol (bp 117.5 °C), and in 80% yield by heating technical 80% **1** with **2a** to 110 °C in the absence of any solvent other than the water in the reagent.

Condensation of **1** with ethyl *N*-methylcarbamate (**5a**), a secondary carbamate, also took place in refluxing toluene with azeotropic removal of the water, giving tetrakis(*N*-carbethoxy-*N*-methylaminomethyl)phosphonium chloride (**6a**) in 31% yield (eq 2).

$$\underset{\mathbf{5}}{1} + 4EtO_2CNHR \rightarrow \underset{\mathbf{6}}{(EtO_2CN[R]CH_2)_4PCl} + 4H_2O \quad (2)$$

a, R = Me f, R = Ph

The product, a mobile liquid, showed an unchanging PCH_2 doublet in the ^1H NMR, and no NH stretching or amide II absorption bands in the IR. The C=O, amide I bond at 1690 cm^{-1} was within the limits assigned to tertiary carbamates.[13] The ^{31}P NMR spectrum showed a single peak at −31.0 ppm, in the same region as **3**.

Ethyl carbanilate (**5f**) failed to react with **1**, either in toluene or xylene.

Condensation of (hydroxymethyl)triphenylphosphonium chloride (**7**) with methyl carbamate (**2a**) took place under the same conditions as with **1**, giving (*N*-carbomethoxylaminomethyl)triphenylphosphonium chloride (**8a**) as a white, crystalline solid in 73.1% yield (eq 3).

$$\underset{\mathbf{7}}{[Ph_3PCH_2OH]Cl} + \mathbf{2a} \rightarrow \underset{\mathbf{8a}}{[Ph_3PCH_2NHCO_2Me]Cl} + H_2O \quad (3)$$

The ^1H NMR spectrum of **8a** exhibits long-range coupling (2.0 Hz) between the NH and aromatic protons.[16] Similar coupling (3.5 Hz) is observed between OH and aromatic protons in **7**, but not in urea derivatives which have no NH proton in this position.[17]

Efforts to characterize the phosphonium salts **3a**, **3e**, or **6a** as the picrates[18] yielded only uncrystallizable yellow oils. Metathesis of the phosphonium chloride **3a** with sodium iodide in ethanol, however, gave the corresponding iodide, tetrakis(*N*-carbomethoxylaminomethyl)phosphonium iodide (**9a**), in 49.1% yield. Attempts to prepare **9a** directly from tetrakis(hydroxymethyl)phosphonium iodide (**10**) and **2a** were unsuccessful.

The corresponding bromide, tetrakis(*N*-carbomethoxylaminomethyl)phosphonium bromide (**11a**), was prepared from **3a** by adsorption on the ion-exchange column followed by displacement with hydrogen bromide instead of hydrogen chloride. The yield was 70.2%.

The foregoing experiments established beyond doubt that the products **3a–e**, **6a**, **8a**, **9a**, and **11a** are all quaternary phosphonium salts. The alkyl carbamates are too feebly basic to cause the characteristic displacement of formaldehyde and HCl that occurs when hydroxymethylphosphonium salts such as **1** or **7** react with primary, secondary, or tertiary amines.[19]

Acid Hydrolysis. Hydrolysis of the phosphonium salt **3a** with 6 N HCl at 110 °C gave, unexpectedly, a 68.0% yield of **1**, together with 92.0% of ammonium chloride (eq 4).

$$\mathbf{3a} + 8HCl + 4H_2O \rightarrow \mathbf{1} + 4CO_2 + 4RCl + 4NH_4Cl \quad (4)$$

Carbamates, like amides, decompose by acyl- rather than alkyl–nitrogen fission, except when the alkyl substituent possesses unusual carbonium ion stability, as, for example, *t*-Bu.[20,21] We suggest that protonation of a nitrogen in **3a** renders the methylene group, flanked by positive charges on both sides, highly electron deficient and susceptible to nucleophilic attack by water:

$$\mathbf{3a} \overset{H^+}{\rightleftharpoons} RO_2\overset{+}{C}—\underset{H_2O}{\overset{\curvearrowleft}{\overset{\curvearrowright}{NH_2}}}—CH_2\overset{+}{P}— \rightleftharpoons RO_2CNH_2$$

$$+ H_2\overset{+}{O}—CH_2\overset{+}{P}— \overset{-H^+}{\rightleftharpoons} HOCH_2\overset{+}{P}—$$

The alkyl carbamate displaced in this reaction is subsequently hydrolyzed to RCl, CO_2, and ammonium chloride;[21] the other product, through successive reactions, ultimately yields **1**.[22]

The hydrolysis of **3a** also yielded a small amount (7.3%) of bis(hydroxymethyl)methylphosphine oxide (**12**), a by-product of the acid degradation of **1**.[23]

Alkaline Hydrolysis. Hydrolysis of the phosphonium salt **3a** with aqueous sodium hydroxide was expected to give tris(*N*-carbomethoxylaminomethyl)phosphine (**13a**), together with methyl (hydroxymethyl)carbamate (**14a**) (eq 5).

$$\mathbf{3} + NaOH \rightarrow \underset{\mathbf{13}}{(RO_2CNHCH_2)_3P} + \underset{\mathbf{14}}{RO_2CNHCH_2OH} + NaCl \quad (5)$$

Some **13a** separated from the reaction mixture as a white, crystalline solid, but the major product was a water-soluble tertiary phosphine **15a** which could not be induced to yield any **13a** after workup.[24] The yield of **13a** varied from 0 to 29%, depending on the reaction conditions. Barium hydroxide, the preferred catalyst for condensing carbamates with formaldehyde,[25,26] gave a 21% yield of **13a**. Other moderately strong bases, such as sodium bicarbonate, disodium phosphate, trisodium phosphate, or triethylamine, gave yields in the 40 to 60% range. Sodium hydroxide buffered with borax or phosphate also gave yields in this range. Yields of 87 to 92%, approaching the quantitative, were only attained with reagents that were capable of reacting with the by-product **14a**, viz., ammonium hydroxide,[19] morpholine, or sodium sulfite (Table I).[27]

The (hydroxymethyl)carbamate **14a**, which is prone to undergo self-condensation[25] or reaction with formaldehyde[28] in the presence of alkaline catalysts such as sodium hydroxide, did not react with **13a** at room temperature but did upon

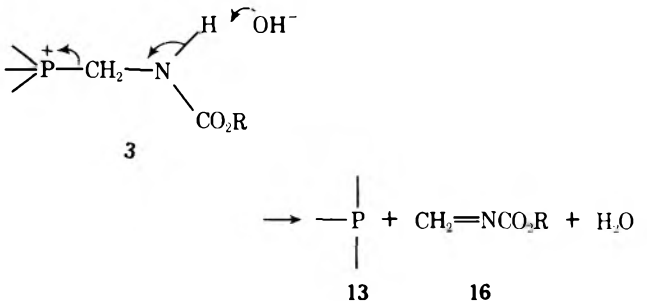
Table I. Hydrolysis of 3a with Various Bases

Base	Conditions	13a (% yield)
NaOH	100 °C, 15 min	29.1[a]
NaOH (borax)	100 °C, 15 min	42.7
NaOH (Na_2HPO_4)	100 °C, 15 min	43.7
NaOH (Na_2HPO_4)	60 °C, 90 min[b]	45.0
$Ba(OH)_2$[c]	100 °C, 1 h	21.0
$NaHCO_3$	100 °C, 1 h	60.1[d]
Na_2HPO_4	100 °C, 1 h	60.3
Na_3PO_4[c]	100 °C, 30 min	48.2
Et_3N	100 °C, 30 min	53.4
Et_3N	25 °C, 3 h	54.1[e]
Morpholine	100 °C, 1 h	46.7
Morpholine	25 °C, 2 h	90.6[f]
NH_4OH	25 °C, 2 h	87.0
Na_2SO_3	100 °C, 1 h	92.5

[a] Yield raised to 51.3% by subsequent treatment with ammonium hydroxide. [b] Sodium hydroxide solution added dropwise to the buffered 3a solution during the first 45 min. [c] Mixture yellowed when the amount of base was doubled. [d] Subsequent treatment with 6 N HCl regenerated only 24.4% of the 3a. [e] Yield unaffected by subsequent treatment with ammonium hydroxide or sodium bisulfite. [f] Together with 93.5% of morpholine hydrochloride, mp 175–176 °C (lit.[31] mp 175–176 °C).

heating to 100 °C, giving a colorless, neutral oil having the same properties (IR, solubility) as those of **15a**.

We suggest that the reactive species in these reactions is not **14a** but its anhydro precursor, methyl *N*-methylenecarbamate (**16a**), which is formed from **3a** by β-elimination of **13a**.



3

13 **16**

The reactive intermediate, if not trapped, reacts with **13a** in the presence of the alkaline catalyst giving an N-substituted tertiary phosphine **15a** from which no **13a** can be recovered.[29,30]

The tertiary phosphine **13a** is an air-sensitive white, crystalline solid. It dissolves readily in 6 N HCl, and precipitates unchanged upon neutralization. Oxidation of **13a** with hydrogen peroxide in acetone gave tris(*N*-carbomethoxylaminomethyl)phosphine oxide (**17a**) in 81.0% yield, and reaction with sulfur in benzene gave tris(*N*-carbomethoxylaminomethyl)phosphine sulfide (**18a**) in 73.4% yield. Both derivatives were crystalline. Their structures were confirmed by IR, NMR, and elemental analysis.

None of the carbamate derivatives described in this paper exhibited the sensitivity to base that is characteristic of the hydroxymethyl compounds 1,[32–34] tris(hydroxymethyl)-phosphine,[35,36] or tris(hydroxymethyl)phosphine oxide.[33,36] No hydrogen evolution was observed even when the carbamate derivatives were heated to boiling with concentrated sodium hydroxide solution. This could be used to advantage to detect and destroy any $HOCH_2P$-containing impurities that might be present in these substances.

Other Reactions. Several attempts were made to develop independent synthetic routes toward the carbamate derivatives **3**, **13**, or **17**. No reaction occurred between methyl (hydroxymethyl)carbamate (**14a**) and phosphine in the presence of hydrochloric acid[37] (to give **3a**), or cadmium chloride catalyst[38] (to give **13a**), nor between **14a** or **14b** and white phosphorus[39] (to give **17a** or **17b**).

Experimental Section[40,41]

Reagents. Tetrakis(hydroxymethyl)phosphonium chloride (**1**) was dried by azeotropic distillation with benzene and recrystallized from 2-propanol, mp 149–149.5 °C. (Hydroxymethyl)triphenylphosphonium chloride (**7**), mp 190–192 °C, was prepared from triphenylphosphine:[42] ^1H NMR (Me_2SO-d_6) δ 5.76 (s, 2 H, CH_2), 6.25 (s, ~1 H, OH), and 7.9 (m, 15 H, C_6H_5; doublet at δ 7.95, J = 3.5 Hz collapsing with D_2O to a singlet, δ 7.96). In $CDCl_3$: ^1H NMR δ 5.52 (lit.[43] δ 5.51), 6.62, and 7.8, respectively; same behavior in the aromatic region. Other reagents were used as obtained, except for **5a** and triethylamine, which were redistilled.

Tetrakis(*N*-carbomethoxylaminomethyl)phosphonium Chloride (3a). (A) From Crystalline 1. A mixture of **1** (47.64 g, 0.25 mol), **2a** (75.07 g, 1.00 mol), and toluene (200 mL) was heated to reflux in an apparatus fitted with a Dean–Stark trap for azeotropic removal of the water. The mixture was held at reflux until the evolution of water ceased; after 2.5 h, 18.5 mL (1.03 mol) had been collected. The product crystallized on standing to a hard mass and was broken up, triturated under ethyl acetate, filtered, and dried, giving 90.67 g (86.5%) of **3a**, mp 177 °C (dec). Two recrystallizations from ethanol afforded pure **3a** as a white, crystalline solid: mp 189 °C (dec); IR (Nujol) 1540 (vs; NH, amide II), 1700 and 1740 [s and vs; C=O, amide I; doublet in Nujol, but a singlet, 1730 (vs), in Me_2SO], 3220 (m; NH, bonded), and 3300 (m; NH, free) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.63 (s, 12 H, CH_3), 4.32 (t, 8 H, CH_2, J = 5.0 Hz, collapsing with D_2O to d, J = 4.0 Hz), and 8.05 (m, ~4 H, NH, vanishing with D_2O); ^{31}P NMR (Me_2SO), δ −30.7.

Anal. Calcd for $C_{12}H_{24}ClN_4O_8P$: C, 34.41; H, 5.78; Cl, 8.47; N, 13.38; P, 7.40; mol wt, 419. Found: C, 34.64; H, 5.66; Cl, 8.71; N, 13.24; P, 7.53; mol wt (osmometric in H_2O), 249, 259.

The phosphonium salt **3a** is partially soluble in water, Me_2SO (7 mL/g), and methanol, and insoluble in other common organic solvents. Its aqueous solution is mildly acidic (pH 4.5). It can be recrystallized from ethanol (20 mL/g) or 2-propanol (75 mL/g), and is air stable, nonhygroscopic, and odorless.

(B) From Technical 1. For large-scale preparation, it is more convenient to use the commercially available 80% aqueous **1** solution (THPC)[44] and omit the azeotropic distillation. A large flask was charged with 80% THPC (1191 g, 5 mol) and half of the **2a** (1501 g, 20 mol) was heated briefly to 100 °C, allowed to cool to 65 °C, charged with the remainder of the **2a**, and heated at gentle reflux (110 °C) for 3 h. The next day the crystalline mass was broken up, triturated in portions with ethanol, filtered, and allowed to air-dry in evaporating dishes. The product **3a**, 1472 g, was a white, crystalline solid, mp 189 °C (dec) (70.3%). Workup of the mother liquor raised the yield to 80.1%.

Tetrakis(*N*-carbethoxylaminomethyl)phosphonium Chloride (3b). Reaction of **1** (47.64 g, 0.25 mol) with **2b** [Caution: carcinogenic[45]] (89.10 g, 1.00 mol), following procedure A, gave 71.53 g (60.2%) of **3b** as a white, crystalline solid, mp 112–13 °C, after two recrystallizations from ethyl acetate: IR (Nujol) 1515 and 1535 (vs and s, NH, amide II), 1680 and 1730 (both s, C=O, amide I; doublet in Nujol or concentrated KBr changing to singlet in $CHCl_3$ or dilute KBr), 3230 (m, NH bonded), and 3360 (w, NH free) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, 12 H, CH_3, J = 7.0 Hz), 4.17 (q, CH_2C, J = 7.0 Hz), 4.42 (m, PCH_2, collapsing with D_2O to d, δ 4.46, J = 3.0 Hz; total CH_2, 16 H), and 7.43 (m, NH, vanishing with D_2O); ^{31}P NMR (Me_2SO) δ −31.2.

Anal. Calcd for $C_{16}H_{32}ClN_4O_8P$: C, 40.46; H, 6.79; Cl, 7.47; N, 11.80; P, 6.52. Found: C, 40.49; H, 6.80; Cl, 7.59; N, 11.60; P, 6.61.

The phosphonium salt **3b** is soluble in water, ethanol, chloroform, benzene, Me_2SO (1.5 mL/g), and acetone, and insoluble in ether, carbon tetrachloride, and cyclohexane. Its aqueous solution is mildly acidic. It is readily recrystallized from ethyl acetate (5 mL/g), but tends to oil out from hot carbon tetrachloride or toluene.

Upon deuteration, the free and H-bonded NH bands in the IR spectrum of **3b** were shifted from 3360 and 3230 cm^{-1} to 2500 and 2370 cm^{-1}, respectively, and the amide II doublet was shifted from 1515 and 1535 cm^{-1} to (Nujol-masked) and 1425 cm^{-1}. The hydrogens were exchanged by dissolving **3b** in D_2O, stripping in a rotary evaporator, and drying in a vacuum desiccator. This sequence was repeated twice.

Tetrakis(*N*-carbisopropoxylaminomethyl)phosphonium Chloride (3c). Reaction of **1** (9.53 g, 0.05 mol) with **2c** (20.62 g, 0.20 mol), following procedure A but using ether instead of ethyl acetate,

gave 9.32 g (45.6%) of **3c** as a white, crystalline solid, mp 140–41 °C, after two recrystallizations from water: IR (Nujol), 1510 (s, NH, amide II), 1720 and 1730 (s and vs, C=O, amide I), 3220 (m, NH bonded), and 3320 (m, NH free) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (d, 24 H, CH_3, J = 6.0 Hz), 4.44 (br s, CH_2, resolved with D_2O to d, δ 4.46, J = 3.0 Hz), 4.94 (m, CH, J = 6.0 Hz; combined CH_2 and CH, 12 H), and 7.31 (m, 4 H, NH, vanishing with D_2O).

Anal. Calcd for $C_{20}H_{40}ClN_4O_8P$: C, 45.24; H, 7.59; Cl, 6.68; N, 10.55; P, 5.83. Found: C, 45.11; H, 7.37; Cl, 6.63; N, 10.74; P, 5.94.

The phosphonium salt **3c** is soluble in ethanol, chloroform, carbon tetrachloride, and benzene, and insoluble in ether. It can be recrystallized from ethyl acetate (10 mL/g) or water (3 mL/g).

Ion-Exchange Method. Fifty grams of the resin (Bio-Rad AG 50W-X4), a high porosity nuclear sulfonic acid cation-exchange resin suitable for organic ions of mol wt 300–400 or over,[46] was charged into a 19 × 600 mm chromatographic column with a sealed-in coarse-fritted disk, backwashed thoroughly with water, and rinsed with water until the effluent was neutral and chloride free.

A solution of **3a** (4.19 g, 10.0 mmol) in warm water (30 mL) was transferred to the column and eluted with water, collecting the effluent in 50-mL fractions at a flow rate of 30 drops/min. The top 2 in. of the resin lightened noticeably. Titration of the first five effluent fractions with 0.1 N NaOH gave 2.42, 7.32, 0.04, 0.02 and 0.01 mmol of HCl for a total of 9.82 mmol (98.2%). The resin was then eluted with 6 N HCl at the same flow rate, causing the resin to contract from 12 to 8.5 in., and restoring its original color. The effluent, collected in 50-mL fractions and stripped carefully in a rotary evaporator at 50 °C/3 mm, yielded 0, 2.26, 1.31, 0.57, and 0.31 g of crystalline **3a**, totaling 4.45 g (106.2%) with melting points decreasing progressively from 177.5 (dec) to 165 °C (dec). The four fractions, combined and recrystallized from ethanol, yielded 3.25 g (77.5%) of pure **3a**, mp 189 °C (dec).

Tetrakis(*N*-carbo-*n*-butoxylaminomethyl)phosphonium Chloride (3d). Reaction of 1 (9.53 g, 0.05 mol) with **2d** (29.29 g, 0.25 mol), following procedure A, gave 37.67 g of a colorless oil that partly crystallized on standing. Attempts to separate the excess **2d** from the product by extraction with hot ligroin,[47] ether, or carbon tetrachloride were unsuccessful, for the two substances exhibit the same solubility behavior. Half of the mixture was therefore dissolved in ethanol (25 mL) and percolated through the ion-exchange resin described above, using ethanol as the eluent. The neutral fractions yielded 17.6 mmol (70.4%) of HCl, 3.10 g (21.2%) of **2d**, and 2.24 g (14.6%) of di-*n*-butyl *N,N'*-methylenedicarbamate (**4d**), mp 93–95 °C; the latter, a by-product of the original condensation, was identified by comparison of its IR, NMR, and mp with the authentic sample described below. The phosphonium salt fractions, eluted with ethanolic HCl, yielded 7.83 g of a viscous, colorless oil, $n^{20}D$ 1.4839, whose composition, determined by NMR and elemental analysis, comprised some unreacted 1 (11.2%) in addition to the product **3d** (38.4%). To remove the unreacted 1, the oil was taken up in chloroform (50 mL), extracted twice with water, filtered, stripped, and dried, giving 4.71 g (30.1%) of **3d** as a viscous, colorless oil: $n^{20}D$ 1.4951; IR (Nujol) 1515 (vs, NH, amide II), 1710 (vs, C=O, amide I), and 3230 (s, NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, 12 H, CH_3, J = 6.0 Hz), 1.1–2.0 (m, 16 H, CH_2C), 4.13 (t, 8 H, OCH_2, J = 6.0 Hz), 4.43 (m, 8 H, PCH_2), and 7.37 (m, ~4 H, NH, vanishing slowly with D_2O); ^{31}P NMR ($CHCl_3$) δ −30.0.

The phosphonium salt **3d** is soluble in all of the common organic solvents, including toluene and hot ligroin, and insoluble in water.

Di-*n*-butyl *N,N'*-Methylenedicarbamate (4d). This compound has been described as a crystalline solid, mp 97–98 °C,[48] and as a liquid.[49] A mixture of **2d** (5.86 g, 0.05 mol), paraformaldehyde (0.80 g, 0.025 mol of CH_2O), and 2-propanol (15 mL) was heated to reflux in an oil bath. When the solids had all dissolved, the solution was treated with 3 drops of concentrated HCl, refluxed for 30 min, allowed to cool, and stripped under reduced pressure. The residue (7.01 g) was recrystallized twice from hexane, giving 2.85 g (46.3%) of **4d** as a white, crystalline solid: mp 97–98 °C; IR (Nujol) 1530 (s, NH, amide II), 1690 (vs, C=O, amide I), and 3350 (s, NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 6 H, CH_3, J = 7.0 Hz), 1.1–1.8 (m, 8 H, CH_2C), 4.10 (t, 4 H, OCH_2, J = 6.5 Hz), 4.52 (t, 2 H, NCH_2, J = 6.5 Hz, collapsing with D_2O to s), and 6.05 (br s, ~2 H, NH, vanishing very slowly with D_2O).

Anal. Calcd for $C_{11}H_{22}N_2O_4$: C, 53.64; H, 9.00; N, 11.38. Found: C, 53.33; H, 9.18; N, 11.10.

The dicarbamate **4d** is soluble in ethanol, acetone, chloroform, carbon tetrachloride, ether, and benzene, and insoluble in water. It can be recrystallized from 2-propanol (6 mL/g, with water added to incipient turbidity) or from hexane (50 mL/g), in which it dissolves slowly and clumps out like cotton.

Tetrakis[*N*-carbo(2-methoxyethoxyl)aminomethyl]phosphonium Chloride (3e). Reaction of 1 (9.53 g, 0.05 mol) with **2e** (35.74 g, 0.30 mol), following procedure A, gave 40.71 g of a viscous, almost colorless oil that resisted efforts at crystallization or conversion to a crystalline oxalate or picrate. Half of the oil was therefore dissolved in water (10 mL) and percolated through the ion-exchange resin described above, using water as the eluent. The neutral fractions yielded 16.9 mmol (67.6%) of HCl. The phosphonium salt fractions yielded 11.10 g of oil which was taken up in chloroform, filtered, stripped and dried [omitting the extraction with water, since the partition is unfavorable], giving 9.05 g (53.7%) of **3e** as a viscous, colorless oil: $n^{20}D$ 1.5094; IR (neat), 1515 (s, NH, amide II), 1720 (vs, C=O, amide I), and 3240 (m, NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.38 (s, 12 H, CH_3), 3.61 (m, 8 H, 2-CH_2), 4.29 (m, 8 H, 1-CH_2), 4.53 (m, 8 H, PCH_2), and 7.42 (m, ~4 H, NH, vanishing slowly with D_2O); ^{31}P NMR ($CHCl_3$) δ −31.0.

The phosphonium salt **3e** is soluble in water, ethanol, acetone, chloroform, ethyl acetate, and hot toluene.

Tetrakis[*N*-carbethoxy-*N*-methylaminomethyl]phosphonium Chloride (6a). Reaction of 1 (9.53 g, 0.05 mol) with **5a** (20.62 g, 0.20 mol), following procedure A, gave 29.86 g of a mobile, colorless oil that, unlike the products of the primary carbamates, was not at all viscous. The oil was dissolved in ethanol (25 mL) and percolated through the ion-exchange resin described above, using ethanol as the eluent. The neutral fractions yielded 35.1 mmol (70.2%) of HCl. The phosphonium salt fractions, eluted with ethanolic HCl, yielded 12.42 g of a colorless oil, $n^{20}D$ 1.4985, which, from the elemental analysis and NMR, was calculated to contain some unreacted 1 (3.8%) in addition to the product **6a** (31%): IR (neat), 1690 (vs, C=O, amide I), and 3000 (m) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.42 (t, 12 H, CH_3C, J = 7.0 Hz), 3.22 (d, 12 H, NCH_3, J = 1.0 Hz), 4.33 (q, 8 H, CH_2C, J = 7.0 Hz), and 4.61 (d, 8 H, PCH_2, J = 4.0 Hz); ^{31}P NMR ($CHCl_3$) δ −31.3.

The phosphonium salt **6a** is soluble in ethanol, acetone, chloroform, and hot toluene, and insoluble in water.

(*N*-Carbomethoxylaminomethyl)triphenylphosphonium Chloride (8a). Reaction of 7 (3.29 g, 0.01 mol) with **2a** (0.75 g, 0.01 mol), following procedure A but using benzene instead of ethyl acetate, gave 2.82 g (73.1%) of **8a** as a white, crystalline solid, mp 198.5–199 °C (dec), after recrystallization from 2-propanol: IR (Nujol) 994 (w, P–C_6H_5), 1430 (s, P–C_6H_5), 1540 (m, NH, amide II), 1580 (w, C=C), 1720 (vs, C=O, amide I), and 3170 (m, sh, NH) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.36 (s, 3 H, CH_3), 4.39 (d pair, 2 H, CH_2, J = 3.0 Hz, collapsing with D_2O to d, δ 4.31, J_{PCH} = 3.0 Hz), 6.87 (m, 15 H, C_6H_5; doublet at δ 6.92, J = 2.0 Hz collapsing with D_2O to s, δ 6.90), and 7.67 (m, 1 H, NH, vanishing with D_2O); ^{31}P NMR ($CHCl_3$) δ −20.0.

Anal. Calcd for $C_{21}H_{21}ClNO_2P$: C, 65.37; H, 5.49; Cl, 9.19; N, 3.63; P, 8.03. Found: C, 65.04; H, 5.67; Cl, 9.35; N, 3.47; P, 8.07.

The phosphonium salt **8a** is soluble in water, ethanol, and chloroform, and insoluble in ether, carbon tetrachloride, acetone, and ethyl acetate. It can be recrystallized from 2-propanol (5 mL/g).

Tetrakis(*N*-carbomethoxylaminomethyl)phosphonium Iodide (9a). **3a** (8.38 g, 0.02 mol) was added to a solution of sodium iodide (3.00 g, 0.02 mol) in ethanol (30 mL), heated at reflux for 1 h, cooled, and filtered, giving 3.23 g of granular solid consisting of sodium chloride and unreacted **3a**. The latter was removed by stirring with dimethyl sulfoxide, leaving 0.67 g (57.3%) of sodium chloride. The ethanol filtrate was stripped, taken up in hot chloroform, filtered to remove unreacted sodium iodide (0.22 g, giving a positive test with acidified iodate), and stripped again. The residue (8.45 g) was recrystallized from ethanol, giving 5.01 g (49.1%) of **9a** as a white, crystalline solid: mp 142.5–143 °C; IR (Nujol) 1535 (vs, NH, amide II), 1690 and 1730 (s and vs, C=O, amide I), 3230 (m, NH bonded), and 3300 (m, sh, NH free) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.67 (s, 12 H, CH_3), 4.33 (t, 8 H, CH_2, J = 5.0 Hz, collapsing with D_2O to d, J = 4.0 Hz), and 7.67 (m, 4 H, NH, vanishing with D_2O); ^{31}P NMR (Me_2SO) δ −30.3.

Anal. Calcd for $C_{12}H_{24}IN_4O_8P$: I, 24.87; P, 6.07. Found: I, 24.50 (gravimetric), 25.05 (by iodometric titration[50]); P, 6.12.

Tetrakis(*N*-carbomethoxylaminomethyl)phosphonium Bromide (11a). A solution of **3a** (8.38 g, 0.02 mol) in methanol (200 mL) was percolated through the ion-exchange resin described above, giving 18.6 mmol (93.0%) of hydrogen chloride. It was necessary to wrap the column in heating tape and warm it to 40–50 °C to prevent the salts from crystallizing. The column was then eluted with hydrogen bromide in methanol, yielding four liquid fractions (6.79 g) followed by eight solid fractions (19.19 g). The solids were combined, shaken with ethanol, and filtered, giving 6.50 g (70.2%) of **11a**, mp 180–184.5 °C (dec). One recrystallization from ethanol (75 mL/g) afforded pure **11a** as a white, crystalline solid: mp 185–186 °C (dec); IR (Nujol) 1550 (vs, NH, amide II), 1700 and 1730 (s and vs, C=O, amide I), 3220 (s, NH bonded), and 3320 (m, NH free) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.65 (s, 12 H, CH_3), 4.35 (t, 8 H, CH_2, J = 5.0 Hz, col-

lapsing with D_2O to d, J = 4.0 Hz), and 7.75 (br t, 4 H, NH, vanishing with D_2O); ^{31}P NMR (Me_2SO) δ −30.0.

Anal. Calcd for $C_{12}H_{24}BrN_4O_8P$: Br, 17.25; P, 6.69. Found: Br, 17.71; P, 6.93.

The product suffered no loss in weight when heated in a drying pistol for 2 h at 100 °C/0.5 mm.

Acid Hydrolysis of 3a. A solution of **3a** (8.38 g, 0.02 mol) in 6 N HCl (100 mL) was heated to reflux under argon in an oil bath, held at 110 °C for 17 h, and then stripped under vacuum. The residue (7.51 g) was extracted with boiling ethanol, giving 3.94 g (92.0%) of ammonium chloride, identified by IR, by a positive Beilstein test, and by the liberation of ammonia upon treatment with 10% NaOH solution. The ethanol extract yielded 3.23 g of a colorless oil, n^{20}_D 1.5514, which was separated by passage over the ion-exchange resin into a neutral fraction (0.18 g, 7.3%), consisting solely of bis(hydroxymethyl)-methylphosphine oxide, **12**, ^1H NMR (D_2O) δ 1.59 (d, 3 H, CH_3, J = 13.0 Hz) and 4.08 (d, 4 H, CH_2, J = 3.5 Hz), and a phosphonium salt fraction containing 2.59 g (68.0%) of **1**, ^1H NMR (D_2O) δ 4.73 (d, 8 H, CH_2, J = 1.5 Hz), together with other impurities. The phosphonium salt fraction showed residual amide I and II bands in the IR.

Alkaline Hydrolysis of 3a. A slurry of **3a** (20.94 g, 0.05 mol) in water (50 mL) was treated dropwise under argon with a solution of sodium hydroxide (2.00 g, 0.05 mol) in water (25 mL).

During the addition, which took 15 min, the mixture cleared, turned milky, and then cleared again. After heating to 100 °C to complete the reaction, the solution, which had a pH of 8.4 and gave a strongly positive iodine test, abruptly crystallized, giving 4.30 g (29.1%) of the tertiary phosphine **13a**, identical to the product of the ammonium hydroxide reaction (mp, IR). The filtrate was extracted with chloroform, leaving an iodine-negative aqueous solution which, on workup, yielded 2.90 g (99.3%) of sodium chloride. The chloroform extract, which gave a strongly positive iodine test, was filtered under argon and concentrated, giving 16.49 g (65.7%) of the tertiary phosphine **15a** as a colorless oil: n^{20}_D 1.5011; IR (neat) 750 (m, $CHCl_3$), 1530 (vs, NH, amide II), 1710 (vs. C=O, amide I), and 3350 (m, br) cm^{-1}. The phosphine **15a** is soluble in acetone, chloroform, and water, and its aqueous solution is neutral.

The other alkaline hydrolyses listed in Table I were performed in the same manner, using 0.05 mol of **3a** and 0.05 mol of the base for each experiment, except for the experiments with barium hydroxide (0.025 mol), triethylamine (0.10 mol), morpholine (0.10 mol), and ammonium hydroxide (excess, described in detail below). The buffer experiments were each performed with 0.05 mol of base and 0.01 mol of buffer.

Tris(*N*-carbomethoxylaminomethyl)phosphine (13a). Concentrated ammonium hydroxide (10 mL) was added to a well-stirred slurry of **3a** (20.94 g, 0.05 mol) in water (50 mL) in an apparatus previously purged with argon. There was no exotherm nor gassing, but the mixture gradually thickened. After 30 min, more water (50 mL) was added to facilitate stirring. The mixture was then stirred for 2 h and filtered, and the filter cake was washed with water and dried in a vacuum desiccator, giving 12.85 g (87.0%) of **13a** as a white, crystalline powder, mp 100–125 °C. All of these operations were performed under argon, for the product becomes hot and sticky when exposed to air. One recrystallization from 2-propanol raised the melting point (sealed tube) to 137–140 °C: IR (Nujol) 1535 (vs, br, NH, amide II), 1700 and 1735 (vs and s, C=O, amide I), and 3350 (m, NH) cm^{-1}.

The phosphine **13a** is soluble in ethanol, chloroform, and acetone, and insoluble in water, ether, carbon tetrachloride, and benzene. It can be recrystallized from water (8 mL/g) or 2-propanol (7 mL/g).

Tris(*N*-carbomethoxylaminomethyl)phosphine Oxide (17a). Thirty percent hydrogen peroxide (57.0 g, 0.5 mol) was added dropwise to a vigorously stirred slurry of **13a** (147.6 g, 0.5 mol) in 500 mL of acetone under an argon atmosphere. Ice-bath cooling was applied as necessary to counter the strongly exothermic reaction. The **13a** gradually dissolved, and was all in solution when two-thirds of the peroxide had been added. About 10 min after the addition was completed, the product started to crystallize. The next day the solid was collected on a filter, washed with acetone, and dried, giving 98.9 g (63.5%) of **17a**, mp 179–180 °C. Workup of the filtrate raised the yield to 126.0 g (81.0%). Two recrystallizations from ethanol afforded pure **17a** as a white, crystalline solid: mp 189–190 °C; IR (Nujol) 1540 (s, NH, amide II), 1710 (vs, br, C=O, amide I), 3250 (w, NH bonded), and 3400 (w, NH free) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.60 (s, CH_3), 3.47 (t, CH_2, J = 9.0 Hz, blending into the CH_3 peak with D_2O; combined CH_3 and CH_2, 15 H), and 7.34 (m, 3 H, NH, vanishing with D_2O).

Anal. Calcd for $C_9H_{18}N_3O_7P$: C, 34.73; H, 5.83; N, 13.50; P, 9.95. Found: C, 34.69; H, 5.70; N, 13.48; P, 10.00.

The phosphine oxide **17a** is soluble in chloroform and insoluble in water, acetone, and the common organic solvents. It can be recrystallized from ethanol (25 mL/g) or water. When heated above its melting point, **17a** gasses without discoloration at 200 °C and froths to a tan-colored resin at 260 °C.

Tris(*N*-carbomethoxylaminomethyl)phosphine Sulfide (18a). A mixture of **13a** (2.95 g, 0.01 mol), sulfur (0.32 g, 0.01 g-atom), and benzene (25 mL) was heated to reflux under an argon atmosphere. After 1 h, most of the solids had dissolved. The mixture was cooled and stripped of benzene under reduced pressure. The residue was taken up in hot acetone, filtered hot to remove the unreacted sulfur (0.12 g), and stripped again under reduced pressure, leaving 2.40 g (73.4%) of **18a** as a white, crystalline solid. Two recrystallizations from ethanol afforded pure **18a**: mp 136.5–137 °C; IR (Nujol) 1520 (vs, br, NH, amide II), 1710 and 1740 (vs and s, C=O, amide I), and 3400 (s, NH) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.61 (s, CH_3), 3.72 (t, CH_2, J = 3.0 Hz, collapsing with D_2O to d, J = 3.0 Hz; combined CH_3 and CH_2, 15 H), and 7.39 (m, 3 H, NH, vanishing with D_2O).

Anal. Calcd for $C_9H_{18}N_3O_6PS$: C, 33.03; H, 5.54; N, 12.84; P, 9.46; S, 9.80. Found: C, 33.08; H, 5.49; N, 12.82; P, 9.60; S, 9.80.

The phosphine sulfide **18a** is soluble in chloroform, and insoluble in water or ethanol. It can be recrystallized from ethanol (6 mL/g), 2-propanol, or water.

Reaction of 13a with 14a. A mixture of **13a** (4.79 g, 0.01 mol), **14a**[29] (1.05 g, 0.01 mol), water (25 mL), and 50% sodium hydroxide (1 drop) was heated under argon for 15 min at 100 °C, cooled, and filtered, giving 1.55 g (32.4%) of recovered **13a**. The filtrate, extracted with chloroform and worked up as described above, yielded 1.68 g (44%) of a colorless, neutral oil, n^{20}_D 1.4788, identified by IR as **15a**. The presence of less chloroform in the product accounts for the lower refractive index.

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Registry No.—**1**, 124-64-1; **2a**, 598-55-0; **2b**, 51-79-6; **2c**, 1746-77-6; **2d**, 592-35-8; **2e**, 1616-88-2; **3a**, 63833-04-5; **3b**, 63833-05-6; **3c**, 63833-06-7; **3d**, 63833-07-8; **3e**, 63833-08-9; **4d**, 2533-21-3; **5a**, 105-40-8; **6a**, 63833-09-0; **7**, 5293-83-4; **8a**, 62779-17-3; **9a**, 63833-10-3; **11a**, 63833-11-4; **12**, 17919-49-2; **13a**, 63833-12-5; **14a**, 6092-56-4; **17a**, 63833-13-6; **18a**, 63833-14-7; paraformaldehyde, 30525-89-4.

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Derivatives of 6β-Methylpenicillanic Acid

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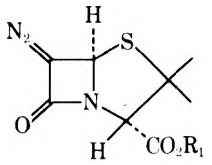
Diazo compounds **1** have been converted to intermediates **2** by two methods: reaction with aqueous *N*-bromosuccinimide, and treatment with triphenylphosphine and nitrous acid. Reaction of **2** with Wittig reagents gives a series of C_6 carbon analogues **6** and, after Curtius rearrangement, C_6 penicillin homologues **8**.

The C_6 carbon analogue of penicillin V has been synthesized and found to have interesting antibiotic activities.[1] The synthetic method for such analogues has therefore been improved and extended to make a series of carbon analogues available for further study.

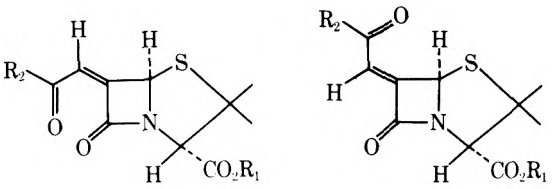
The starting intermediates for these syntheses are the 6-diazopenicillanates **1** (R_1 = CH_2CCl_3, CH_2Ph) which were synthesized according to a known method.[2] Compounds **1**



1

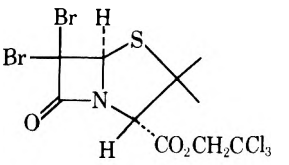
react with *N*-bromosuccinimide in aqueous solvents or Ph_3P followed by nitrous acid[3] to give keto compounds **2**.[4] Compounds **2** are relatively unstable and are not usually isolated, but used directly for further reactions.

For example, compound **2** (R_1 = CH_2CCl_3), as a crude oil derived from the treatment of **1** with aqueous NBS, reacted with $Ph_3P{=}CHCO_2CH_2Ph$ to give the syn and anti isomers **3** (R_1 = CH_2CCl_3; R_2 = OCH_2Ph). These isomers were isolated in 32 and 3% yield [based on diazo compound **1** (R_1 = CH_2CCl_3)]. The major product was assigned the sterically less hindered anti structure. A major by-product of this series of reactions is the dibromide **4**, isolated in yields ranging from 13 to 32%. The triphenylphosphine–nitrous acid method of



3

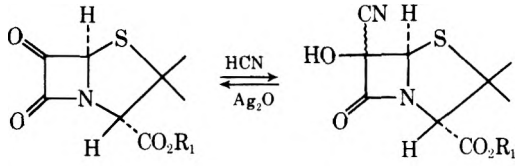
synthesizing compound **2** followed by reaction with the same Wittig reagent gave compounds **3** (R_1 = CH_2CCl_3; R_2 =



4

OCH_2Ph) in 60% yield. Similarly, ketone **2** (R_1 = CH_2CCl_3) reacted with $Ph_3P{=}CHCOCH(Ph)NH$-*tert*-Boc to give **3** (R_1 = CH_2CCl_3; R_2 = $CH(Ph)NH$-*tert*-Boc), mostly in the anti form. The yields, based on **1**, were 9% for the NBS method and 26% for the triphenylphosphine–nitrous acid method.

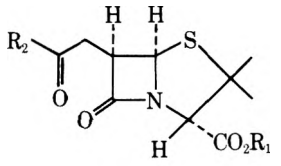
Addition of HCN to compound **2** (R_1 = CH_2Ph) gives a crystalline cyanohydrin **5** which can be used to regenerate the pure keto compound or react with other reagents.[5] For instance, cyanohydrin **5** (R_1 = CH_2Ph) reacts directly with an ylide such as $Ph_3P{=}CHCO_2$-*tert*-Bu or $Ph_3P{=}CHCOCH(Ph)NH$-*tert*-Boc to give compounds **3** (R_1 = CH_2Ph; R_2 = *O*-*tert*-Bu or $CH(Ph)NH$-*tert*-Boc) in 97 and



2 5

80% yields, respectively. Both isomers are also observed spectroscopically but were not isolated separately. The condensation of a Wittig reagent with a cyanohydrin can only proceed if enough of the ketone form is available. This seems to be the case with compound **4** (R_1 = CH_2Ph).

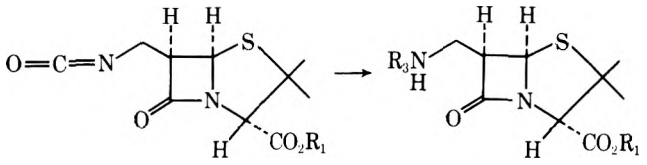
Hydrogenation of **3** (R_1 = CH_2CCl_3; R_2 = OCH_2Ph or CH(Ph)NH-*tert*-Boc, or R_1 = CH_2Ph; R_2 = *O*-*tert*-Bu) in the presence of rhodium on alumina gave only one isomer **6**. The carboxyl-protecting group of R_2 was removed by hydrogenolysis over Pd on charcoal (R_2 = OCH_2Ph) or trifluoroacetic acid treatment (R_2 = *O*-*tert*-Bu) to give the half-esters. Compound **6** (R_1 = CH_2Ph; R_2 = OH) was isolated as a solid material.



6

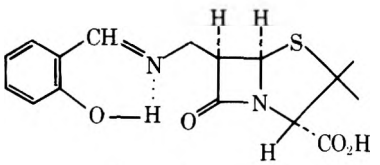
Half-esters **6** (R_1 = CH_2CCl_3 or CH_2Ph; R_2 = OH) were esterified and treated with amines to give a series of esters and amides. All reactions were done with diisopropylcarbodiimide with the exception of benzylamine which was coupled with carbonyldiimidazole. Removal of protecting groups gave penicillin C_6 carbon analogues with the following R_2 groups: PhCH(CH_2NHCHO)O, $PhCH_2O$, PhNH, $PhCH_2NH$, PhCH(CO_2H)NH, HCl·$H_2NCH_2CH_2S$ and $H_3{}^+NCH(Ph)$, $C_4H_3SCH_2O$, naphthyl-O.

Compound **6** (R_1 = CH_2Ph; R_2 = OH) was treated with sodium azide and rearranged to give **7**. Treatment of **7** (R_1 = CH_2Ph) with *tert*-butyl alcohol gave the penicillin homologue **8** (R_1 = CH_2Ph; R_3 = COO-*tert*-Bu). Compound **8** (R_1 = CH_2Ph; R_3 = COO-*tert*-Bu) is easily deblocked at the C_6 side chain to give the free amine, isolated as the trifluoroacetate salt.



7 8

Acylation of **8** (R_1 = CH_2Ph; R_3 = H) and removal of the benzyl group gave the following penicillin C_6 homologues: R_1 = H; R_3 = $PhCH_2CO$, EtOCO, $PhCH(NH_2)CO$, PhNHCO, CH_3PhSO_2, $PhCH_2SO_2$. Reaction of **8** (R_1 = R_3 = H) with salicylaldehyde gave the Schiff base **9**.



9

We have consistently observed a low β-lactam infrared frequency (1740–1750 cm^{-1}) for the penicillin homologues **8** (R_1 = CH_2Ph). However, the NMR spectra were consistent with a β-lactam structure. On deblocking the C_3 carboxyl, the infrared frequency appeared again at 1775 cm^{-1}. We have no explanation for this anomaly, although hydrogen bonding or solvation are the most likely explanations. Some of our compounds have coupling constants, $J_{5,6}$, of 6 Hz. Such a high $J_{5,6}$ value is not usually observed for penicillin compounds, although it is not unusual for β-lactam structures[6] in general.

All compounds were tested for biological activity. C_6 carbon analogues derived from **6** showed some gram-positive activity. Homologues **8** and **9** were inactive against gram-positive or gram-negative organisms.

Experimental Section

General. Melting points were determined on a Fisher-Johns melting point apparatus. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. IR spectra were recorded on a Perkin-Elmer 237 spectrophotometer. NMR spectra were taken on a Varian T-60 spectrometer and are reported in parts per million downfield from tetramethylsilane.

Synthesis of β,β,β-Trichloroethyl 6-Oxopenicillanate 2 (R_1 = CH_2CCl_3) and β,β,β-Trichloroethyl 6,6-Dibromopenicillanate (4). Method 1. *N*-Bromosuccinimide (0.54 g, 2.8 mmol) was added all at once to an ice-cold solution of the diazo ester **1** (R_1 = CH_2CCl_3; 1.0 g, 2.8 mmol) and 1 mL of pyridine in 25 mL of acetone and 5 mL of H_2O. After the addition, there was an immediate evolution of nitrogen. The solution was stirred at 0 °C for 1 h, diluted with CH_2Cl_2, washed with H_2O and ice-cold dilute HCl, and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was chromatographed on silicic acid initially using CH_2Cl_2 as an eluent. Isolation of the faster moving fraction gave 438 mg (32%) of β,β,β-trichloroethyl 6,6-dibromopenicillinate (**4**) as an oil. Further purification by chromatography gave an analytically pure sample: IR (neat) 1790 and 1755 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.73 (s, 3 H), 4.70 (s, 1 H), 4.84 (s, 2 H), 5.84 (s, 1 H).

Anal. Calcd for $C_{10}H_{10}Br_2Cl_3NO_3S$: C, 24.49; H, 2.06; N, 2.86; Br. 32.59; Cl, 21.69; S, 6.54. Found: C, 24.68; H, 2.11; N, 2.94; Br, 32.57; Cl, 21.82; S, 6.62.

The polarity of the eluting system was increased with ether. Isolation of the slower moving fraction gave β,β,β-trichloroethyl 6-oxopenicillanate (**2**) (R_1 = CH_2CCl_3) as an impure oil, 0.48 g: IR ($CHCl_3$) 2960, 1830, 1775, 1750 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (s, 3 H), 1.70 (s, 3 H), 4.84 (s, 2 H), 4.94 (s, 1 H), 5.80 (s, 1 H).

Synthesis of β,β,β-Trichloroethyl 6-Oxopenicillanate 2 (R_1 = CH_2CCl_3). Method 2. Diazo ester **1** (R_1 = CH_2CCl_3; 7.16 g, 0.02 mol) and triphenylphosphine (5.24 g, 0.02 mol) were dissolved in 550 mL of CH_2Cl_2 at 0 °C. A solution of $NaNO_2$ (6.80 g, 0.10 mol) and F_3AcOH (8.90 g, 0.12 mol) in 250 mL of Me_2SO at 0 °C was added to the above mixture and stirred at 0 °C for 1.75 h. The solution was washed extensively with water, 5% sodium bicarbonate, and saturated salt solution. The organic layer was dried ($MgSO_4$) and evaporated to give 12.1 g of an oil containing the keto compound **2** (R_1 = CH_2CCl_3) and triphenylphosphine oxide. Spectra were identical with those obtained from the NBS method except for the presence of Ph_3PO. The keto compound was used directly without further purification.

Synthesis of 3 (R_1 = CH_2CCl_3; R_2 = CH_2Ph). In the same manner as described above, treatment of the diazo ester **1** (R_1 = CH_2CCl_3) with NBS in aqueous acetone containing pyridine gave a mixture of dibromo and keto esters. The mixture was dissolved in benzene. Benzyloxycarbonylmethylenetriphenylphosphorane (2–3 equiv) was added and the mixture refluxed for 30 h. After removal of the solvent under reduced pressure, the dark-brown residue was chromatographed on silicic acid using methylene chloride as an eluent. Isolation of the fastest moving fraction gave β,β,β-trichloroethyl 6,6-dibromopenicillinate (**4**) (13.7%) as an oil. Isolation of a slower moving fraction gave the anti unsaturated ester **3** (R_1 = CH_2CCl_3, R_2 = OCH_2Ph) in 32% yield based on starting diazo ester. Further purification by chromatography gave an analytically pure sample: IR ($CHCl_3$) 1780 and 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (s, 3 H), 1.63 (s, 3 H), 4.67 (s, 1 H), 4.77 (s, 2 H), 5.20 (s, 2 H), 5.97 (d, 1 H, J = 1.0 Hz), 6.30 (d, 1 H, J = 1.0 Hz), 7.35 (s, 5 H).

Anal. Calcd for $C_{19}H_{18}NO_5Cl_3S$: C, 47.66; H, 3.79; N, 2.93; Cl, 22.22; S, 6.70. Found: C, 47.40; H, 3.77; N, 2.77; Cl, 22.40; S, 6.72.

Isolation of the slowest moving fraction gave 3% yield of the syn unsaturated ester **3** (R_1 = CH_2CCl_3, R_2 = CH_2Ph) as an oil which crystallized on standing. Recrystallization from ether gave an analytically pure sample: mp 108–109 °C; IR ($CHCl_3$) 1780 and 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.72 (s, 3 H), 4.75 (s, 1 H), 4.80 (s,

2 H), 5.26 (s, 2 H), 5.76 (d, 1 H, J = 0.5 Hz), 6.04 (d, 1 H, J = 0.5 Hz), 7.38 (s, 5 H).

Anal. Calcd for $C_{19}H_{18}NO_5Cl_3S$: C, 47.66; H, 3.79; N, 2.93; Cl, 22.22; S, 6.70. Found: C, 47.76; H, 3.43; N, 2.93; Cl, 22.41; S, 6.71.

Synthesis of 3 [R_1 = CH_2CCl_3; R_2 = CH(Ph)NH-*tert*-Boc]. Two grams of Ph_3P=CHCOCH(Ph)NH-*tert*-Boc (3.9 mmol) and 3.4 g of crude **2** (derived from 4.0 g, 5.5 mmol **1** by the NBS method) (R_1 = CH_2CCl_3) were dissolved in 80 mL of dry benzene. The mixture was stirred under N_2 at room temperature for 22 h. The mixture was evaporated and rapidly chromatographed on silica gel with methylene chloride–ether (8:1). The oil obtained was crystallized from ether to give white crystals, 9%: mp 175–178 °C (dec); IR (CH_2Cl_2) 2975, 1770, 1705, 1670, 1485 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.57 (s, 3 H), 1.62 (s, 3 H), 4.65 (s, 1 H), 4.78 (s, 2 H), 5.50 (d, 1 H, J = 6 Hz), 5.85 (d, 1 H, J = 6 Hz), 6.03 (s, 1 H), 6.72 (s, 1 H), 7.40 (s, 5 H); R_f (methylene chloride–ether, 6:1) 0.7.

The same reaction was carried out with ketone **2** derived from the triphenylphosphine–nitrous acid method to give 0.83 g (26%) of light-yellow crystals. Spectra and physical constants were the same as described above.

tert-Butoxycarbonyl-α-amino-α-phenylacetylmethylenetriphenylphosphorane. The ylide was synthesized according to published methods[7,8] to give 7.91 g (71% based on D-*tert*-butoxycarbonylphenylglycine) of yellow crystals. Recrystallization from ether gave an analytical sample: mp 112.4–114 °C; IR (CH_2Cl_2) 3375, 3050, 2980, 1700, 1550–1560 cm^{-1}; NMR ($CDCl_3$) δ 1.19 (s, 9 H), 5.12 (d, 1 H, J = 3.5 Hz), 6.19 (d, 1 H, J = 3.5 Hz), 7.2–7.7 (m, 21 H).

Anal. Calcd for $C_{32}H_{32}NO_3P$ (509.56): C, 75.42; H, 6.34; N, 2.75; P, 6.08. Found: C, 75.26; H. 6.50; N, 2.72; P, 5.85.

Synthesis of 3 (R_1 = CH_2Ph; R_2 = *O-tert*-Bu). Cyanohydrin 5[5] (R_1 = CH_2Ph) (8.0 g, 0.024 mol) was dissolved in 240 mL of benzene. *tert*-Butoxycarbonylmethylenetriphenylphosphine (10.8 g, 0.029 mol) in 300 mL of benzene was added and the solution stirred at 20 °C. for 24 h. The solution was evaporated and the residue chromatographed on silica gel with methylene chloride–ethyl ether (50:1) to give 8.8 g (97%) of **3** (R_1 = CH_2Ph; R_2 = *O-tert*-Bu) as an oil: IR (film) 2970, 1775, 1725, 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.40 and 1.45 (s, 15 H), 4.58 (s, 1 H), 5.15 (s, 2 H), 5.95 (s, 1 H), 6.10 (s, 1 H), 7.33 (s, 5 H).

Compound **3** [R_1 = CH_2Ph; R_2 = CH(Ph)NH-*tert*-Boc] was synthesized in the same manner from 2 mmol of cyanohydrin **5** and 2 mmol of Ph_3P=CHCOCH(Ph)NH-*tert*-Boc to give 0.85 g (80%) of **3** as an oil: IR ($CDCl_3$) 2975, 1770, 1730–1760, 1670, 1485 cm^{-1}; NMR ($CDCl_3$) δ 1.42 (s, 12 H), 1.55 (s, 3 H), 4.56 (d, 1 H, J = 2 Hz), 5.19 (s, 2 H), 5.42 (m, 1 H), 5.79 (m, 1 H), 5.99 (s, 1 H), 6.49 (s, 1 H), 7.38 (s, 10 H).

Hydrogenation of 3. Compound **3** (R_1 = CH_2Ph; R_2 = *O-tert*-Bu; 8.5 g, 0.020 mol) was dissolved in 400 mL of ethyl acetate. Rhodium on alumina (5%, 17.2 g) was added and the mixture was hydrogenated at atmospheric pressure for 10 h at 20 °C. The solution was filtered, evaporated, and chromatographed on silica gel with methylene chloride–ethyl ether (50:1) to give **6** (R_1 = CH_2Ph, R_2 = *O-tert*-Bu) as a yellow oil, 6.0 g (70%); NMR ($CDCl_3$) δ 1.50 and 1.65 (s, 15 H), 2.70–2.90 (m, 2 H), 3.75–4.10 (m, 1 H), 4.40 (s, 1 H), 5.10 (s, 2 H), 5.57 (d, 1 H, J = 4 Hz), 7.35 (s, 5 H); IR (film) 2980, 1775, 1740, 1725 cm^{-1}.

Compound **3** (R_1 = CH_2CCl_3; R_2 = OCH_2Ph) was hydrogenated in the same way. Chromatography gave **6** (R_1 = CH_2CCl_3, R_2 = OCH_2Ph) as an oil (42%) which could be crystallized from ether–petroleum ether: mp 42–50 °C; IR ($CHCl_3$) 1775, 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.74 (s, 3 H), 2.8–3.1 (m, 2 H), 3.8–4.3 (m, 1 H), 4.50 (s, 1 H), 4.74 (s, 2 H), 5.10 (s, 2 H), 5.53 (d, 1 H, J = 4.0 Hz), 7.26 (s, 5 H).

Compound **3** (R_1 = CH_2CCl_3; R_2 = CH(Ph)NH-*tert*-Boc) was hydrogenated in the same manner to give 50% **6** (R_1 = CH_2CCl_3, R_2 = CH(Ph)NH-*tert*-Boc) as an oil: IR ($CDCl_3$) 2975, 2925, 1770, 1740, 1700, 1475 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.40 (s, 9 H), 1.55 (s, 3 H), 2.80–3.02 (m, 2 H), 3.75–4.10 (m, 1 H), 4.35 (s, 1 H), 5.20 (s, 2 H), 5.35 (d, 1 H, J = 4 Hz), 5.50 (d, 1 H, J = 5 Hz), 5.82 (d, 1 H, J = 5 Hz), 7.4 (s, 5 H).

Synthesis of 6 (R_1 = CH_2CCl_3; R_2 = OH). The ester **6** (R_1 = CH_2CCl_3; R_2 = OCH_2Ph; 303 mg, 0.63 mmol) was dissolved in EtOAc and hydrogenated in the presence of a 10% Pd-C catalyst for 2.5 h at room temperature and 1 atm of pressure. After removal of the catalyst by filtration through celite and washing of the surface with ether, the solvent was removed under reduced pressure using no heat. The residual oil was dissolved in methylene chloride and extracted with aqueous $NaHCO_3$. After separation of the organic layer and acidification of the aqueous layer with ice-cold dilute HCl, the acid was isolated as an oil (246 mg, 62%) by extraction with methylene chloride, drying ($MgSO_4$), and removal of the solvent under reduced pressure using no heat: NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.73 (s, 3 H), 2.8–3.2 (m, 2 H), 3.8–4.3 (m, 1 H), 4.53 (s, 1 H), 4.79 (s, 2 H), 5.56 (d, 1 H, J = 4.0 Hz), 8.40 (s, 1 H).

Synthesis of 6 (R_1 = CH_2Ph; R_2 = OH). The ester **6** (R_1 = CH_2Ph; R_2 = *O-tert*-Bu) (1.9 g, 4.7 mmol) was dissolved in 60 mL of trifluoroacetic acid at 0 °C and stirred for 0.5 h. F_3AcOH was evaporated at 0 °C and the resultant oil freeze dried from benzene to give a quantitative yield of an oil: IR (film) 3000, 1775, 1725, 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.42 and 1.57 (s, 6 H), 2.8–3.4 (m, 3 H), 4.65 (s, 1 H), 5.20 (s, 2 H), 5.72 (d, 1 H, J = 6 Hz), 7.40 (s, 5 H). Crystallization of the oil from ether gave a white solid which is probably a hydrate according to spectra: IR (KBr) 3000, 1725, 1670 cm^{-1}; NMR ($CDCl_3$) same as above plus δ 7.57 (s, 2 H).

Synthesis of 6 (R_1 = CH_2Ph; R_2 = $NHCH_2Ph$). Acid **6** (R_1 = CH_2Ph; R_2 = OH) (350 mg, 1.0 mmol) was dissolved in 5 mL of methylene chloride at 0 °C. 1,1′-Carbonyldiimidazole (178 mg, 1.1 mmol) was added and the solution stirred for 5 min. Benzylamine (107 mg, 1.0 mm) in 5 mL of methylene chloride was added and the solution was allowed to stand at 5 °C for 12 h. The solution was washed with cold HCl (0.05 N), saturated sodium bicarbonate solution, and water. After drying and evaporation, the oil obtained was chromatographed on silica gel with methylene chloride–ethyl ether (10:1) to give 88 mg (19%) of a yellow oil: IR (film) 3350, 2900, 1775, 1730, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.35, 1.50 (s, 6 H), 2.6–3.2 (m, 3 H), 4.40 (d, 2 H, J = 5 Hz), 4.55 (s, 1 H) 5.15 (s, 2 H), 5.63 (d, 1 H, J = 6 Hz), 6.75 (m, 1 H), 7.25, 7.32 (s, 10 H).

Synthesis of 6 [R_1 = CH_2Ph; R_2 = $NHCH(CO_2CHPh_2)Ph$]. Acid **6** (R_1 = CH_2Ph; R_2 = OH) (350 mg, 1 mmol) was dissolved in 20 mL of CH_2Cl_2 at 0 °C. Benzyhydryl phenylglycinate as the tosylate salt (982 mg, 2 mmol) was suspended in 20 mL of CH_2Cl_2 and pyridine (0.25 mL, 3 mmol) at 0 °C. The solutions were mixed and diisopropylcarbodiimide (0.31 mL, 2 mmol) was added. The mixture was stirred at 0 °C. for 1 h and at 20 °C for 24 h. The solution was washed with 0.05 N HCl, saturated bicarbonate solution, and water. After drying and evaporation, the residue was chromatographed on silica gel with methylene chloride–ethyl ether (10:1) to give 367 mg (55%) of oil: IR (film) 3300, 3000, 1745, 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.30, 1.45 (s, 6 H), 2.55–3.25 (m, 3 H), 4.45 (s, 1 H), 5.02 (s, 2 H), 5.45 (d, 1 H, J = 6 Hz), 5.65 (s, 1 H), 6.70 (s, 1 H). 7.15 (s, 20 H).

Synthesis of 6 (R_1 = CH_2CCl_3; R_2 = $OCH_2C_4H_3S$). Compound **6** (R_1 = CH_2CCl_3; R_2 = OH) (105 mg, 0.36 mmol) was esterified with 2-thiophenemethanol (57 mg, 0.50 mmol) in the presence of pyridine (35 μL, 0.43 mmol) and *N,N′*-diisopropylcarbodiimide (70 μL, 0.45 mmol). The product was isolated as an oil (45 mg, 32%) after chromatography on silica gel using 2% MeOH–$CHCl_3$ as an eluent: IR ($CHCl_3$) 2985, 1770, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.73 (s, 3 H), 2.8–3.1 (m, 2 H), 3.9–4.3 (m, 1 H), 4.53 (s, 1 H), 4.77 (s, 2 H), 5.27 (s, 2 H), 5.55 (d, 1 H, J = 4.0 Hz), 6.7–7.5 (m, 3 H).

Synthesis of 6 (R_1 = CH_2CCl_3; R_2 = CH_2CCl_3; R_2 = O-Naphthyl). In the same manner as described above, the 2-naphthol ester was isolated as a crystalline material (72%) after chromatography on silicic acid using methylene chloride as an eluent. The product was recrystallized from CH_2Cl_2–petroleum ether: mp 119–120 °C; IR ($CHCl_3$) 1780 (sh) and 1760 cm^{-1}; NMR ($CDCl_3$) δ 1.66 (s, 3 H), 1.80 (s, 3 H), 3.1–3.4 (m, 2 H), 4.0–4.5 (m, 1 H), 4.64 (s, 1 H), 4.80 (s, 2 H), 5.70 (d, 1 H, J = 4.0 Hz), 7.0–8.0 (m, 7 H).

Anal. Calcd for $C_{22}H_{20}NO_5SCl_3$: C, 51.13; H, 3.90; N, 2.71; Cl, 20.58; S, 6.20. Found: C, 51.40; H, 4.00; N, 2.58; Cl, 20.79; S, 5.99.

Synthesis of 6 [R_1 = CH_2CCl_3; R_2 = $PhCH(CH_2NHCHO)O$]. Prepared in the same manner as described above, the mixture of diastereomeric esters was separated by chromatography on silicic acid using 5:1 methylene chloride–ether (v/v) as an eluent.

Less polar isomer: NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.73 (s, 3 H), 2.85 (d, 2 H, J = 8.0 Hz), 3.3–4.4 (m, 3 H), 4.57 (s, 1 H), 4.81 (d, 2 H, J = 1 Hz, CH_2CCl_3),[9] 5.61 (d, 1 H, J = 4.0 Hz), 5.7–6.3 (m, 1 H), 6.3–6.6 (m, 1 H), 7.35 (s, 5 H), 8.16 (s, 1 H).

More polar isomer: NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.70 (s, 3 H), 2.87 (d, 2 H, J = 8.0 Hz), 3.2–4.4 (m, 3 H), 4.50 (s, 1 H), 4.79 (d, 2 H, J = 1 Hz, CH_2CCl_3),[9] 5.48 (d, 1 H, J = 4.0 Hz), 5.6–6.0 (m, 1 H), 6.3–6.8 (m, 1 H), 7.23 (s, 5 H), 8.00 (s, 1 H).

Synthesis of 6 (R_1 = CH_2CCl_3; R_2 = PhNH). In the same manner as described above, the amide was isolated as an oil (56%) after chromatography on silicic acid using 20:1 CH_2Cl_2–ether (v/v) as an eluent: IR ($CHCl_3$) 3405, 3305, 1775 (sh), 1755, 1685, and 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.75 (s, 3 H), 2.90 (d, 2 H, J = 8.0 Hz), 3.8–4.4 (m, 1 H), 4.54 (s, 1 H), 4.70 (d, 1 H, J = 12.0 Hz), 4.90 (d, 1 H, J = 12.0 Hz), 5.60 (d, 1 H, J = 4.0 Hz), 6.9–7.7 (m, 5 H), 8.32 (s, 1 H).

Deblocking of Benzyl Esters. An ester **6** (R_1 = CH_2Ph) (0.20 mmol) was dissolved in 10 mL of ethyl acetate. Palladium on carbon

(10%), 0.5 g, was added and the mixture hydrogenated at 20 °C for 1 h. After filtration, the solution was evaporated to 2 mL, and a solution of potassium 2-ethylhexanoate (0.10 g in 2 mL of ethyl acetate) was added if the free acid did not precipitate. Cooling usually gave a white solid in 40–50% yield. If an oil was obtained, the solution was concentrated and petroleum ether was added. In the case of **6** [R_1 = CH_2Ph; R_2 = CH(Ph)NH-*tert*-Boc] the solution was evaporated after filtration and the oil obtained dissolved in trifluoroacetic acid. The solution was freeze-dried, glacial acetic acid was added, and the solution freeze-dried again. The free acids and salts all had infrared frequencies at 1770–1780 cm^{-1} (β-lactam) and NMR spectra identical to the blocked ester minus a benzyl group.

Deblocking of Trichloroethyl Esters. The ester (100–200 mg) was dissolved in 10 mL of 90% HOAc (1–2 mL of DMF was added if the ester did not dissolve) and the solution cooled to 0 °C before 1–1.5 g of zinc dust was added. The mixture was stirred at 0 °C for 3–5 h. Removal of the zinc by filtration through Celite into a flask containing 100 mL of ice water and washing of the zinc with methylene chloride yielded a two-phase system. Separation of the organic layer, extraction of the cold aqueous layer with several methylene chloride–zinc washings, drying ($MgSO_4$), and removal of the solvent under reduced pressure (no heat) afforded the free acid.

Benzyl 6-*tert*-Butoxycarbonylaminomethylpenicillanate (8) (R_1 = CH_2Ph; R_3 = CO_2-*tert*-Bu). Acid **6** (R_1 = CH_2Ph; R_2 = OH) (1.80 g, 5.16 mmol in 120 mL of THF was cooled to −30 °C. Triethylamine (0.73 mL, 1 equiv) was added followed by ethyl chloroformate (0.49 mL, 1 equiv). The mixture was stirred at −30 °C for 90 min. Sodium azide (335 mg, 5.16 mmol) in 50 mL of water was added and the solution stirred at 0 °C for 30 min. The solution was diluted with methylene chloride, washed with water and saturated salt solution, dried, and evaporated to give an oil. The oil was dissolved in 50 mL of benzene and refluxed for 90 min. *tert*-Butyl alcohol (50 mL) was added and refluxing continued for 2 h. The solvents were evaporated and the residue was chromatographed on silica gel with methylene chloride–ethyl ether (10:1). Elution with ether gave a yellow oil, 0.87 g (40%): IR (film) 3400, 3000, 1750, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.37, 1.42, 1.52 (s, 15 H), 2.5–2.9 (m, 2 H), 4.1–4.5 (m, 1 H), 4.63 (s, 1 H), 5.18 (s, 2 H), 5.30 (d, J = 5 Hz, 1 H), 7.35 (s, 5 H).

Anal. Calcd for $C_{21}H_{28}O_5N_2S$: C, 59.97; H, 6.71; N, 6.66; S, 7.62. Found: C, 59.37; H, 6.71; N, 6.43; S, 7.35.

Benzyl 6-Aminomethylpenicillanate 8 (R_1 = CH_2Ph; R_3 = $H_2^+CF_3CO_2^-$). Compound 8 (R_1 = CH_2Ph; R_3 = CO_2-*tert*-Bu) (200 mg, 0.48 mmol) was dissolved in 10 mL of trifluoracetic acid and stirred for 30 min at 0 °C. The solution was freeze-dried from benzene to give a quantitative yield of salt: IR (film) 3000, 1775–1700 (br) cm^{-1}; NMR (Me_2SO-d_6) δ 1.15, 1.55 (s, 6 H), 2.75–3.0 (m, 2 H), 3.8–4.05 (m, 1 H), 4.3 (s, 1 H), 5.10 (s, 2 H), 5.20 (d, J = 5 Hz, 1 H), 7.25 (s, 5 H).

Benzyl 6β-(*N*-Phenylacetyl)aminomethylpenicillanate 8 (R_1 = CH_2Ph; R_3 = $COCH_2Ph$). Triethylamine (138 mg, 2 equiv) in 5 mL of CH_2Cl_2 was dropped into phenylacetyl chloride (159 mg, 1.5 equiv) in 5 mL of CH_2Cl_2 at 0 °C. Compound 8 (R_1 = CH_2Ph; R_2 = $H_2^+CF_3CO_2^-$) (300 mg, 0.69 mmol) in 5 mL of CH_2Cl_2 was dropped into the cold mixture and stirring was continued for 3 h at 0 °C. The solution was washed with saturated bicarbonate and water, dried, and evaporated. The oil obtained was chromatographed on silica gel with methylene chloride–ether (1:1) to give an oil which can be crystallized from ethyl acetate–ether–petroleum ether: 60 mg (20%); mp 128–130 °C; IR (film) 3280, 1745, 1710, 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.50 (s, 3 H), 2.68 (dd, J_1 = 6 Hz, J_2 = 10 Hz), 3.50 (s, 2 H), 4.40 (m, 1 H), 4.52 (s, 1 H), 5.10 (s, 2 H), 5.20 (d, 1 H, J = 5 Hz). 6.61 (d, J = 6 H), 7.20 and 7.26 (s, 10 H).

Anal. Calcd for $C_{24}H_{26}O_4N_2S$ (438.53): C, 65.74; H, 5.98; N, 6.39; S, 7.31. Found: C, 65.25; H, 5.98; N, 6.36; S, 7.30.

Benzyl 6-Ethoxycarbonylaminomethylpenicillante 8 (R_1 = CH_2Ph; R_3 = $COCH_2CH_3$). Compound 8 (R_1 = CH_2Ph; R_3 = $H_2^+CF_3CO_2^-$) (0.77 g, 1.77 mmol) was coupled with PhCH(NH-*tert*-Boc)COOH using the mixed anhydride method. Chromatography on silica gel with CH_2Cl_2/ether (5:1) gave 0,41 g (35%) of compound 8 (R_1 = CH_2Ph; R_3 = $CO_2CH_2CH_3$) instead of the expected product; IR (film) 3300, 2960, 1750–1680 cm^{-1}; NMR ($CDCl_3$) 1.25 (t, 3 H), 1.35, 1.50 (s, 6 H), 2.5–2.9 (m, 2 H), 4.10 (q, 2 H), 4.35–4.60 (s on m, 2 H), 5.15 (s, 2 H), 5.35 (d, J = H Hz, 1 H), 6.15 (J = 8 Hz, 1 H), 7.30 (s, 5 H).

Compound 8 [R_1 = CH_2Ph; R_3 = $COCH(NHCO_2CH_2Ph)Ph$]. Compound 8 (R_1 = CH_2Ph; R_3 = $H_2^+CF_3CO_2^-$) (0.38 g, 0.87 mmol) in 10 mL of THF, *p*-nitrophenyl *N*-carbobenzoxyphenylglycinate (0.32 g, 1 equiv) and triethylamine (0.25 mL, 2 equiv) were stirred at 25 °C for 2.5 h. The solvent was evaporated and the oil obtained was chromatographed on silica gel with methylene chloride–ether (2:1). A foam was obtained which was rechromatographed with methylene chloride–ether (5:1) to give a white foam, 43%: IR (film) 3280, 1740–1675 (br) cm^{-1}; NMR ($CDCl_3$) 1.25, 1.40 (s, 6 H), 2.3–2.7 (dd, 2 H, J_1 = 8 Hz, J_2 = 6 Hz), 4.0–4.4 (m, 1 H), 4.45 (s, 1 H), 4.9 (s, 2 H), 4.95 (s, 2 H), 5.10–5.20 (s on d, J = 6 Hz, 2 H), 6.10 (d, J = 8 Hz, 2 H), 7.1 (s, 15 H).

Benzyl 6-Tosylamidomethylpenicillanate 8 (R_1 = CH_2Ph; R_2 = SO_2PhCH_3). To compound 8 (R_1 = CH_2Ph; R = $H_2^+CF_3CO_2^-$) (0.22 g, 0.51 mmol) in 5 mL of CH_2Cl_2 was added tosyl chloride (0.10 g, 0.51 mmol) in 5 mL of CH_2Cl_2 and triethylamine (0.14 mL, 2 equiv). The solution was stirred at 25 °C for 16 h, washed with saturated bicarbonate and water, and evaporated. The residue was chromatographed on silica gel with methylene chloride–ether (5:1). Elution with ether gave a white foam, 65 mg (27%): IR (film) 3250, 2975, 1750, 1700, 1600 cm^{-1}; NMR ($CDCl_3$) 1.38, 1.50 (s, 6 H), 2.45–2.73 (s on m, 5 H), 3.7–4.2 (m, 1 H), 4.56 (s, 1 H), 5 15 (s, 2 H), 5.38 (d, J = 6 Hz, 1 H), 6.25 (d, J = 8 Hz, 1 H), 7.2–7.8 (m, 9 H).

Synthesis of 9. Compound 8 (R_1 = H; R_3 = $H_2^+CF_3CO_2^-$) (0.141 g, 0.40 mmol) was dissolved in 10 mL of ethanol. Triethylamine was added to pH ~8.5, followed by *o*-hydroxybenzaldehyde (0.49 g, 10 equiv). The solution was stirred at 25 °C for 45 h, acidified with dilute HCl to pH ~6.5, and evaporated. After addition of ether, the mixture was filtered and evaporated. The yellow oil was dissolved in CH_2Cl_2 and 1.6 equiv of potassium 2-ethylhexanoate was added. Addition of petroleum ether gave a yellow solid, 110 mg, 72%: IR (nujol) 3350, 1775, 1700 (br), 1765 cm^{-1}; NMR (acetone-d_6) δ 1.40 (s, 6 H), 2.7–3.0 (m, 2 H), 3.8–4.2 (s on m, 2 H), 5.55 (d, J = 6 Hz, 1 H), 6.8–7.4 (m, 4 H), 8.5 (s, 1 H).

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Registry No.—**1** (R_1 = CH_2CCl_3), 51056-24-7; **2** (R_1 = CH_2CCl_3), 63784-21-4; *anti*-**3** (R_1 = CH_2CCl_3; R_2 = OCH_2Ph), 63784-22-5; *syn*-**3** (C_1 = CH_2CCl_3; R_2 = OCH_2Ph), 63784-23-6; *anti*-**3** (R_1 = CH_2CCl_3; R_2 = CH(Ph)NH-*tert*-Boc), 63784-24-7; *syn*-**3** (R_1 = CH_2Ph; (R_2 = O-*tert*-Bu), 63784-25-8; *anti*-**3** (R_1 = CH_2Ph; R_2 = O-*tert*-Bu), 63784-26-9; *syn*-**3** (R_1 = CH_2 Ph; R_2 = CH(Ph)NH-*tert*-Boc, 63784-27-0; *anti*-**3** (R_1 = CH_2Ph; R_2 = CH(Ph)NH-*tert*-Boc, 63784-28-1; **4**, 63797-55-7; **5** (R_1 = CH_2Ph), 39486-17-4; **6** (R_1 = CH_2Ph; R_2 = O-*tert*-Bu), 63784-29-2; **6** (R_1 = CH_2CCl_3; R_2 = OCH_2Ph), 63200-60-2; **6** (R_1 = CH_2CCl_3; R_2 = CH(Ph)NH-*tert*-Boc, 63784-30-5; **6** (R_1 = CH_2CCl; R_2 = OH), 63784-31-6; **6** (R = CH_2Ph; R_2 = OH), 63784-32-7; **6** (R_1 = CH_2Ph; R_2 = $NHCH_2Ph$), 63784-33-8; **6** (R = $CH_2Ph_1R_2$ = $NHCH(CO_2CHPh_2)Ph$), 63784-34-9; **6** (R_1 = CH_2CCl_3; R_2 = $OCH_2C_4H_3$), 63784-35-0; **6** (R_1 = CH_2CCl_3; R_2 = *O*-naphthyl, 63784-36-1; **6** (R_1 = CH_2CCl_3; R_2 = $PhCH(CH_2NHCHO)O$) isomer 1, 63784-37-2; **6** (R_1 = CH_2CCl_3; R_2 = $PhCH(CH_2NHCHO)O$) isomer 2, 63784-38-3; **6** (R_1 = CH_2CCl_3; R_2 = PhNH), 63784-39-4; **8** (R_1 = CH_2Ph; R_3 = CO_2-*tert*-Bu), 63784-40-7; **8** (R_1 = CH_2Ph; R_3 = $H_2^+CF_3CO_2^-$), 63784-42-9; **8** (R_1 = CH_2Ph; R_3 = $COCH_2Ph$), 63784-43-0; **8** (R_1 = CH_2Ph; R_3 = $CO_2CH_2CH_3$), 63784-44-1; **8** [R_1 = CH_2Ph; R_3 = $COCH(NHCO_2CH_2Ph)Ph$], 63797-57-9; **8** (R_1 = CH_2Ph; R_3 = SO_2PhCH_3), 63784-45-2; **9**, 63784-46-3; Ph_3P=$CHCO_2CH_2Ph$, 15097-38-8; Ph_3P=CHCOCH(Ph)NH-*tert*-Boc, 63784-47-4; Ph_3P=CHCO2Bu^t, 35000-38-5; $PhCH(CH_2NHCHO)$-OH, 58644-57-8; PhCH(NH-*tert*-Boc)COOH, 3601,66-9; benzylamine, 100-46-9; benzhydrylphenylglycinate tosylate salt, 63784-48-5; 2-thiophenemethanol, 636-72-6; 2-naphthol, 135-19-3; phenylamine, 62-53-3; *tert*-butyl alcohol, 75-65-0; phenylacetyl chloride, 103-80-0; *p*-nitrophenyl-*N*-carbobenzoxyphenyglycinate, 63784-49-6; tosyl chloride, 98-59-9; *o*-hydroxybenzaldehyde, 90-02-8.

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Ipso Nitration of 4-Iodo-o-xylene

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Nitration of 4-iodo-o-xylene with mixed acid affords mixtures of 4-nitro-o-xylene, 5-iodo-3-nitro-o-xylene, and 4-iodo-5-nitro-o-xylene. Under certain nitration conditions substantial amounts of 4,5-diiodo-o-xylene were also formed. Because of the inefficiency of the nitrodeiodination reaction and the faster rate of nitration of o-xylene relative to 4-iodo-o-xylene, iodine cannot be used as a catalyst to effectively alter the substitution pattern for nitration of o-xylene. Nitration of 4-iodoxy-o-xylene was found to give an iodoxynitroxylene.

Introduction

There is considerable interest in methods of altering isomer distribution in products of electrophilic aromatic substitutions. Recent approaches have included clathration of the aromatic to induce additional steric influence on selectivity[1] and rearrangement of the undesired initial product of electrophilic attack on the aromatic to give the desired one.[2] The nitration of o-xylene typifies the problems encountered in attempting to alter product isomer distribution. A wide variety of nitrating agents have been found to give a 4-nitro-o-xylene (4-NOX) to 3-nitro-o-xylene (3-NOX) product ratio which could not be made to exceed 3:1.[2] Since 4-nitro-o-xylene is a useful reagent for further reactions, increasing this ratio without increasing the extent of side reactions would provide a higher yield of a less contaminated material.

As indicated by eq 1 and 2, another method by which selectivity in products of electrophilic substitution may be altered is through the intermediacy of another electrophilic reagent, E_1^+, which exhibits a different, more desirable selectivity in substitution of the aromatic. Ipso (self-directed) substitution of E_1^+ by the desired electrophile E_2^+ as in eq 2 would give the product ArE_2 with a more desirable isomer ratio than that obtained by direct attack of E_2^+ on ArH (eq 3). If the rates k_1 and k_2 are fast relative to k_3, and if side reactions do not interfere, the system can obviously be effectively catalytic in E_1^+.

$$E_1^+ + ArH \xrightarrow{k_1} ArE_1 + H^+ \quad (1)$$

$$E_2^+ + ArE_1 \xrightarrow{k_2} ArE_2 + E_1^+ \quad (2)$$

$$E_2^+ + ArH \xrightarrow{k_3} ArE_2 + H^+ \quad (3)$$

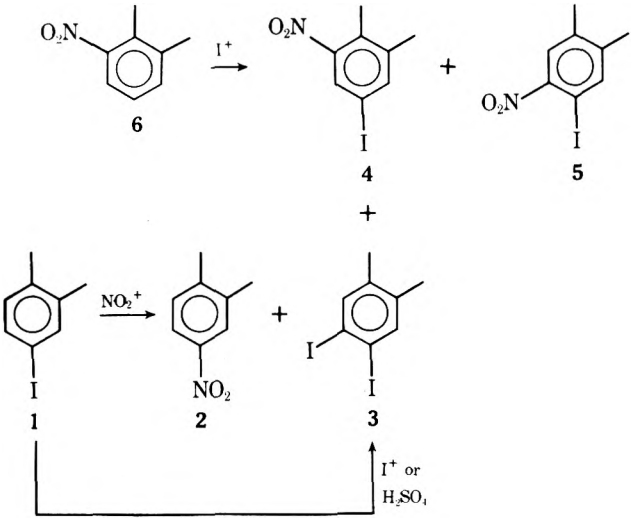
Exactly such a scheme has been achieved by thalliation of o-xylene with thallium(III) trifluoroacetate followed by treatment of the thalliated product with nitrogen dioxide.[3] This process produced an 84% yield of 4-NOX together with 4% 3-NOX. This type of scheme would have greater utility if it could be accomplished in a catalytic manner with a nonmetallic electrophilic intermediate. Since iodine is known to be one of the better ipso leaving groups under electrophilic substitution conditions,[4] our attention turned to its utilization.

It has been noted in the literature that iodination of o-xylene proceeds in high yield to give 4-iodo-o-xylene (4-IOX) and 3-iodo-o-xylene (3-IOX) in an 84:16 ratio.[5] A particularly attractive feature of this reaction is that the reported experimental procedure employs iodine in the presence of mixed nitric and sulfuric acids. A number of instances are known where I^+ is displaced from aromatics by such a nitrating mixture under somewhat more severe conditions. Iodo aromatics for which such ipso displacements have been reported include 4-iodoanisole,[6,7] 2-iodomesitylene,[8] and 2-iodo-1,3,5-trineopentylbenzene.[8] Nitrobenzene could not be detected, however, from nitration of iodobenzene with nitric acid in nitromethane,[8] and while iodo appears to be one of the better ipso leaving groups,[9] nitrodeiodination can also be complicated by the liberated I^+ (or equivalent species) iodinating either the iodo- or nitro-substituted aromatics.[6-8] Recognizing the potential for such side reactions, we examined the nitration of 4-iodo-o-xylene with the view of determining if iodine could be used effectively as a catalyst in directing the selectivity of the nitration of o-xylene.

Results and Discussion

Iodination of o-xylene according to the literature procedure[5] afforded a 93% yield of distilled mixed monoiodo isomers which could not be separated by distillation or GLC. Analysis by NMR showed this mixture to contain 80% 4-IOX and 20% 3-IOX. Pure 4-IOX (1) was obtained by fractional crystallization from hexane at −78 °C.[5]

Nitration of 4-IOX was run under several sets of conditions (Table I) and products were analyzed by GLC. The desired 4-NOX (2) was formed in each case in yields ranging from 6 to 13%; however, ordinary nitration (nitrodeprotonation) to give 5-iodo-3-nitro-o-xylene (4) and 4-iodo-5-nitro-o-xylene[10] (5) was found to be the predominant reaction, and under



certain conditions (cf. Table I) relatively large amounts of 4,5-diiodo-o-xylene (3) were formed as well.

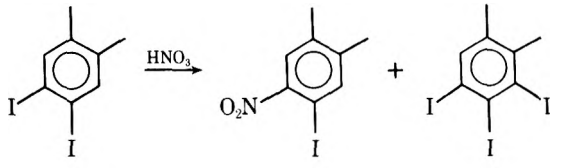
The ipso product 4-NOX was identified by GLC and infrared comparison with an authentic sample. Both 4-iodo-5-nitro-o-xylene (5) and 4,5-diiodo-o-xylene (3) were isolated from the nitration experiments and were characterized by NMR, mass spectrometry, and infrared analysis. The diiodo compound 3 and 5-iodo-3-nitro-o-xylene (4) were independently synthesized by iodination of 4-IOX and 3-NOX, respectively. Attempted iodination of 4-NOX gave no reaction.

Table I. Nitration of 4-Iodo-*o*-xylene

Expt. no.	Reagents: 4-IOX, mol	70% HNO_3, mol	Nitrating agent, mol	H_2SO_4, mol	H_2SO_4, %	Solvent, mL	Conditions: Temp, °C	Time, h	Products, mol %[c]: 4-IOX	4-NOX	4,5-di-IOX	5-I-3-NOX	4-I-5-NOX	?[d]
1	0.020	0.022	—	0.020	96	5[a]	50	4	60%	8%	24%	3%	3%	—
2	0.020	0.088	—	0.040	96	5[a]	60	8	0	13%	25%	17%	42%	—
3	0.010	—	N_2O_4 0.040	0.023	87	—	25	2	8%	9%	19%	21%	28%	—
4	0.0050	—	NO_2BF_4 0.010	—	—	5[a]	25	½	0	8%	6%	23%	54%	9%
5	0.010	0.020	$NaNO_2$ 0.001	0.022	90	—	25	4	3%	7%	20%	23%	47%	—
6	0.010	0.050	$NaNO_2$ 0.002	—	—	5[a]	70	22	25%	6%	41%	4%	22%	—
7	0.0043	—	$NOBF_4$ 0.0086	—	—	5[b]	60	6	0	10%	42%	16%	23%	9%
8	0.010	0.033	—	0.044	90	—	30	1	0	7%	0	26%	59%	7%
9	0.010	0.033	—	0.044	90	—	25	½	0	7%	0	28%	62%	3%
10	0.010	0.100 (90%)	—	—	—	10[b]	25	2	0	12%	0	23%	59%	6%

[a] HOAc. [b] CH_3NO_2. [c] As determined by GLC. [d] Unidentified; % estimated by GLC.

From the results presented in Table I and the separate iodination experiments, it is clear that nitrodeiodination accounts for only a small amount of the reaction products in the nitration of 4-IOX. Although the origins of the various products are not known with complete certainty, it is likely that **4** is formed entirely by nitrodeprotonation. Since 4-NOX does not iodinate readily, **5** cannot form via 4-NOX. It is most



3 **5** **7**

probably formed by nitrodeprotonation of 4-IOX, although to some extent it may also result from nitrodeiodination of **3**. In a separate experiment it was found that nitration of the latter at 65–75 °C for 12 h produced **5** in ca. 75% yield along with some 3,4,5-triiodo-*o*-xylene (**7**).

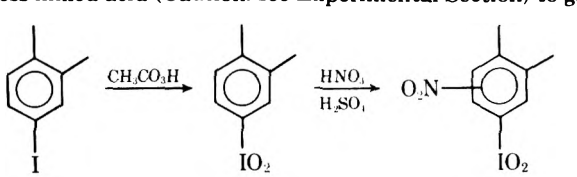
The origin of **3** is less certain. Although the nitrodeiodination reaction releases an equivalent amount of I^+, which is then available to iodinate 4-IOX, the yield of diiodo compound formed was frequently much greater than that of 4-NOX. A possible source of this excess **3** is the Jacobsen reaction of 4-IOX, in which 4-IOX, upon heating with sulfuric acid, produces **3**.[11] The other product of the Jacobsen reaction is presumably a sulfonic acid which would not be detected in our workup or GLC procedures. In a recent study of Friedel–Crafts acylations of iodoaromatics, excesses of diiodoaromatic over ipso substitution product were observed.[12] Whatever the origin of **3**, its formation could be suppressed by modification of the experimental conditions (Table I, experiments 8 and 9). Thus, in reactions of 4-IOX with excess mixed acid at 25 °C for short periods of time, no **3** was detected, and the product distribution was 7% 4-NOX, 28% **4**, 62% **5**, and 3% unidentified (probably dinitrated) material.

Several variations of the nitration procedure were attempted in an effort to increase the yield of 4-NOX (cf. Table I). These included use of N_2O_4, NO_2BF_4, and $NOBF_4$ as nitrating agents, addition of $NaNO_2$ to the nitric acid, and the use of nitromethane as a solvent. None of these conditions provided more than a 12% yield of 4-NOX. We had originally hoped that reaction of 4-IOX with NO^+ followed by oxidation would increase the amount of ipso substitution, based on the work of Butler and Sanderson,[7] who reported that nitrodeiodination of 4-iodoanisole proceeded via nitrosation rather than nitration. More recently, Olsson[13] reported that added $NaNO_2$ did not increase the amount of nitrodeiodination of 2-iodo-1,3,5-trineopentylbenzene relative to nitrodeprotonation. As seen in Table I, however, neither $NOBF_4$ nor nitric acid containing added $NaNO_2$ was effective in increasing the 4-NOX yields. Thus, the data indicate that NO^+ and NO_2^+ produce comparable proportions of nitrodeiodination product from 4-IOX.

Competitive mixed acid nitration of an equimolar mixture of *o*-xylene and 4-IOX was studied in an effort to determine which was the more reactive substrate. At the end of the reaction no *o*-xylene could be detected but 44% of the original 4-IOX remained unreacted. Clearly, the relative rates are in the wrong order for iodine catalysis of nitration as discussed in the Introduction. Thus, even if the 4-IOX → 4-NOX conversion could be made more efficient, the directive effects of a catalytic amount of iodine would be minimal because most of the reaction would proceed by direct nitration of *o*-xylene.

As a final empirical test of the iodine catalysis scheme, the mixed acid nitration of *o*-xylene was carried out in the presence of 5 mol % added iodine and the GLC analysis was compared with that of a similar reaction run without added I_2. In the presence of I_2 an 88% combined yield of mononitro isomers was obtained with a 4-NOX/3-NOX ratio of 46:54. In addition about 4% of 4-IOX was detected. In the absence of I_2 an 89% combined yield of 4-NOX and 3-NOX was obtained and the isomer ratio was 44:56. Thus, no significant effect on isomer distribution was observed.

The possibility of converting 4-IOX to a derivative which might undergo electrophilic ipso substitution more readily than 4-IOX itself was also examined. Since oxidation of 4-IOX to a polyvalent iodine compound would be expected to weaken the C–I bond,[14] and may thus increase susceptibility to ipso substitution, 4-IOX was oxidized with peracetic acid to give 4-iodoxy-*o*-xylene (**8**). This new compound was reacted with excess mixed acid (Caution: see Experimental Section) to give



1 **8** **9**

a compound the elemental analysis and IR of which indicated a nitrodeprotonation product **9** in 53% yield, along with a small amount of 4-I-5-NOX. No 4-NOX was found. We have been unable to locate any reference to electrophilic substitution of iodoxy-substituted aromatics in the literature.

The position of the nitro group in the insoluble, explosive, new compound **9** could only be inferred from its infrared spectrum. Compound **8** shows bands at 882 cm^{-1} (lone H out-of-plane vibration) and 808 cm^{-1} (2 adjacent H out-of-plane vibrations), while **9** displays a band corresponding to the former (876 cm^{-1}) but no band corresponding to the latter. The absence of adjacent hydrogens excludes 4-iodoxy-3-nitro-*o*-xylene as the correct structure. Of the two remaining possibilities, we favor assigning 5-iodoxy-3-nitro-o-xylene to compound **9** on mechanistic grounds since its Hammett σ parameters suggest that the iodoxy substituent is meta directing[15,16] and also the 3-position is the less hindered one.

In another experiment 4-IOX was treated with peracetic acid under conditions for making iodosodiacetates.[17] Treatment of the crude product with excess mixed acid gave a complex mixture of products but 4-NOX could not be detected by GLC.

Experimental Section

General. The NMR spectra were run in $CDCl_3$ on a Varian HA-100 spectrometer. GLC analyses were performed on a Hewlett-Packard Model 5750 instrument equipped with a flame ionization detector. The column was a 10 ft × ⅛ in. SS 20% QF-1 on 90/110 mesh Anakrom ABS and the temperature was programmed from 150 to 225 °C at 30 °C/min followed by 10 min at 225 °C. The following retention times (in minutes) were observed under these conditions: 4-IOX (2.8), 4-NOX (4.6), 4,5-di-IOX (5.5), 5-I-3-NOX (6.6), and 4-I-5-NOX (8.7). Quantitation was made from peak areas calibrated with known quantities of the compounds.

4-Iodo-o-xylene (1). To 500 mL of acetic acid was added slowly with stirring 140 mL of concentrated H_2SO_4 (2.60 mol) followed by 376 g (3.54 mol) of *o*-xylene and 210 g of finely divided iodine. The stirred mixture was heated to 50 °C, the heating bath was removed, and 140 mL of 70% HNO_3 (2.24 mol) was added dropwise at a rate to keep the temperature below 55 °C. After most of the iodine had reacted, an additional 210 g was added (total 420 g, 3.32 g-atoms) and addition of HNO_3 was completed. Stirring at 50 °C was continued for 40 min and the mixture was then cooled and poured over crushed ice. The organic layer was separated and the aqueous layer was extracted twice with methylene chloride. The combined organic material was washed twice with dilute NaOH and once with water, dried, and evaporated. Distillation of the resulting oil gave 719 g (93%) of iodo-*o*-xylenes, bp 96–102 °C (7 mm), which was determined to consist of 80% 4-iodo-*o*-xylene and 20% 3-iodo-o-xylene by NMR analysis.

Pure 4-iodo-*o*-xylene (1) was obtained by three crystallizations from hexane at −78 °C, decanting the mother liquor from the filter cake after each crystallization, and evaporating in vacuo to remove the residual hexane after the last crystallization. This procedure gave 440 g (57%) of pure 4-iodo-*o*-xylene, the ^1H NMR of which showed a singlet methyl at δ 2.14, containing no detectable amount of the 3-isomer (doublet methyl centered at δ 2.33).

Nitration of 4-Iodo-o-xylene in Mixed Acid. Isolation of 4-Iodo-5-nitro-o-xylene (5). Mixed acid was prepared from 0.3 mL of water, 2.4 mL of 96% H_2SO_4 (0.044 mol) and 2.1 mL of 70% HNO_3 (0.033 mol). The acid solution was added dropwise with stirring to 2.3 g (0.010 mol) of 4-iodo-*o*-xylene cooled in an ice bath to keep the reaction temperature ≤25 °C. After stirring for 20 min at 25 °C the mixture was poured into ice water and extracted with methylene chloride. The extracts were washed with dilute NaOH and water, dried, and evaporated to give 2.5 g of orange oil. GLC analysis of the oil showed 7% 4-NOX, 28% 5-I-3-NOX, 62% 4-I-5-NOX, and 3% of an unknown product. The oil was partially crystallized from ethanol to give 0.55 g of **5**, mp 62–66 °C. Successive recrystallization from ethanol and petroleum ether afforded yellow flakes, mp 65.5–67.5 °C.

Anal. Calcd for $C_8H_8NO_2I$: C, 34.61; H, 2.91; N, 5.06; mol wt, 277. Found: C, 34.47; H, 2.88; N, 4.86; *m/e* 277. ^1H NMR δ 7.78 (s, ArH), 7.68 (s, ArH), 2.26 (s, CH_3).

5-Iodo-3-nitro-o-xylene from Iodination of 3-Nitro-o-xylene. A mixture of 1.8 mL of 96% H_2SO_4 (0.032 mol), 6.0 g of 3-nitro-*o*-xylene (0.040 mol), 5.1 g of iodine (0.020 mol) and 1.8 mL of 70% HNO_3 (0.028 mol) in 10 mL of acetic acid was stirred at 80–85 °C for 24 h. The reaction mixture was poured into ice water containing sodium thiosulfate and extracted three times with methylene chloride. The combined extracts were washed with dilute NaOH and water, then dried and evaporated. GLC analysis of this oil showed about 70% unreacted starting material and about 30% product. Chromatography over grade I neutral alumina gave a small amount of crystalline product, mp 56–60 °C, from petroleum ether, identified as **4** by analysis and NMR.

Anal. Calcd for $C_8H_8NO_2I$: C, 34.61; H, 2.91; N, 5.06. Found: C, 34.57; H, 2.88; N, 5.08. ^1H NMR δ 7.90 (s, ArH), 7.69 (s, ArH), 2.31 (s, CH_3).

4,5-Diiodo-o-xylene (3). A mixture of 4.65 g (0.020 mol) of 4-iodo-*o*-xylene, 2.55 g (0.010 mol) of iodine and 1.6 mL (0.030 mol) of 96% H_2SO_4 in 5 mL of acetic acid was heated with stirring to 50 °C and 0.9 mL (0.014 mol) of 70% HNO_3 was added dropwise. Stirring was continued at 50–55 °C for 3 h and the mixture was poured into ice water and worked up as in the above example to give 5.9 g (82%) of crude **3**, mp 70–85 °C. Three recrystallizations from ethanol gave faintly yellow prisms: mp 91–93 °C (lit.[18] mp 93–94 °C); ^1H NMR δ 7.59 (s, ArH), 2.13 (s, CH_3).

Nitration of 4,5-Diiodo-o-xylene. A stirred suspension of 1.8 g of 4,5-diiodo-o-xylene (0.0050 mol) in 10 mL of acetic acid was heated to 50 °C and a solution of 1.0 g of 96% H_2SO_4 and 1.5 g of 70% HNO_3 was added. The reaction mixture was stirred at 65 °C for 6 h and then another 0.25 g of H_2SO_4 (total 0.0125 mol) and 0.4 g of HNO_3 (total 0.030 mol) were added and stirring was continued at 75 °C for another 6 h. The cooled reaction mixture was poured into ice water and extracted with methylene chloride. The extracts were washed with dilute NaOH and water, dried, and evaporated to give a yellow solid. GLC analysis showed this to be approximately 75% **5**, 5% unreacted **3**, and 20% of a new product. Fractional crystallization from ethanol gave a few milligrams of pale yellow crystals, mp 111–113 °C, identified as 3,4,5-triiodo-*o*-xylene (**7**) by analysis, IR, and NMR.

Anal. Calcd for $C_8H_7I_3$: C, 19.86; H, 1.46. Found: C, 19.61; H, 1.46. ^1H NMR δ 7.73 (s, ArH), 2.55 (s, CH_3), 2.24 (s, CH_3).

4-Iodoxy-o-xylene (8). The general procedure of Sharefkin and Saltzman[17] was used. To 23.2 g (0.100 mol) of 4-iodo-*o*-xylene stirred at 35 °C was added dropwise 65 mL of 40% aqueous peracetic acid (0.500 mol). After addition was complete, 80 mL of water was added and the bath temperature was raised to 100 °C. Considerable frothing occurred during heating. The mixture was stirred at 100 °C for 45 min and then cooled and filtered. The white solid was washed with water and dried in a vacuum desiccator to give 22.1 g (84%) of **8**, mp 207 °C (explodes), impact sensitivity = 20 cm.

Nitration of 4-Iodoxy-o-xylene. Ten milliliters of mixed acid of composition 35% HNO_3, 63% H_2SO_4, and 2% H_2O (from combining the proper quantities of 90% HNO_3, 96% H_2SO_4, and fuming H_2SO_4, 20–23% SO_3) was stirred in an ice bath while 0.5 g of finely divided solid 4-iodoxy-o-xylene (**8**) was added in small portions. (When a small lump was added a sudden violent reaction occurred.) After the addition, the yellow solution was poured over ice and the white solid which formed was filtered and washed with acetone to give 0.31 g (53%) of **9**, mp 204 °C (explodes).

Anal. Calcd for $C_8H_8NO_4I$: C, 31.08; H, 2.61; N, 4.53; I, 41.06. Found: C, 31.32; H, 2.23; N, 4.75; I, 40.81. Insolubility precluded NMR analysis and prevented establishment of the isomeric structure of this product.

Acknowledgment. We thank Drs. J. Lancaster and N. B. Colthup of the Research Service Department of the Stamford Laboratories of the American Cyanamid Co. for their assistance with interpretation of NMR and IR spectra, respectively. We also thank Messrs. R. E. Evans and W. E. Mealmaker for the shock sensitivity measurement.

Registry No.—**1**, 31599-61-8; **2**, 99-51-4; **3**, 5182-67-2; **4**, 63689-70-3; **5**, 39763-72-9; **6**, 83-41-0; **7**, 51352-09-1; **8**, 63689-71-4; **9**, 63689-72-5; *o*-xylene, 95-47-6; 3-iodo-*o*-xylene, 31599-60-7; HNO_3, 7697-37-2.

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(15) Although very limited data are available, iodoxy appears to be a typical electron withdrawing group with Hammett σ parameters (σ_m = 0.70, σ_p = 0.76) very similar to those of the nitro group (σ_m = 0.71, σ_p = 0.78).[16]
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Rates and Products of the Reaction of a β,β-Dichlorobenzylic Alcohol and Its Derivatives in CF_3CO_2H–H_2SO_4. A 1,2-Chlorine Shift Giving an α-Chloro Ketone

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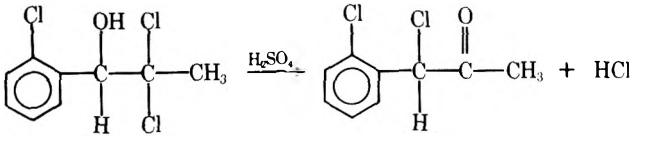
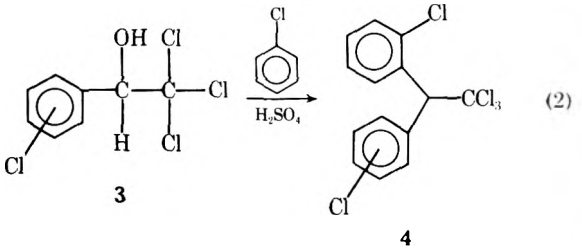
The *p*-toluenesulfonate and *p*-bromobenzenesulfonate of 1-(*o*-chlorophenyl)-2,2-dichloro-1-propanol (**1**) reacted at a conveniently measurable rate in 25 mL of CF_3CO_2H containing 1.127 g of 96% H_2SO_4. 1-(*o*-Chlorophenyl)-1-chloro-2-propanone and the trifluoroacetate of **1** were formed. The ketone, previously obtained from reaction of **1** in H_2SO_4, appears to be formed via a chloronium ion intermediate. The absence of rate effects of substituents in the leaving group is connected with acid catalysis.

Recently it was found[1] that the chlorine-containing alcohol **1** was converted exclusively to the α-chloro ketone **2** upon reaction with concentrated (96%) sulfuric acid. The formation



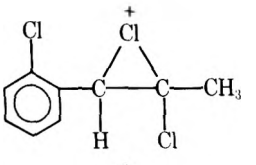
1 **2** (1)

of **2**, the apparent product of a 1,2-chlorine shift, was so facile that **1** formed no condensation product with chlorobenzene in the presence of H_2SO_4. Various alcohols related to **1** do undergo such condensation (e.g., that of eq 2) to give the



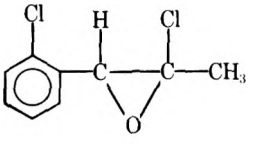
3 **4** (2)

pesticide DDT or related compounds.[2] Accordingly, we were prompted to further define the mechanism of the reaction of eq 1 and related processes. At the outset of our study, two main types of mechanism were considered. In one, mentioned previously,[1] the reaction of eq 1 is initiated by breaking the C–O bond, possibly with simultaneous chlorine participation to give a chloronium ion intermediate **5**. Another mechanism



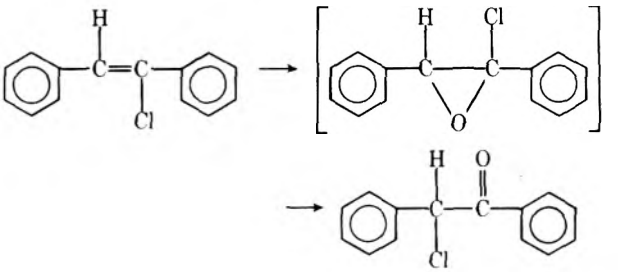
5

involves breaking of a C–Cl bond, presumably facilitated by electrophilic acid catalysis, with possible simultaneous hydroxyl participation to form a chloro epoxide intermediate, **6**. McDonald and co-workers have shown that chloro epoxides



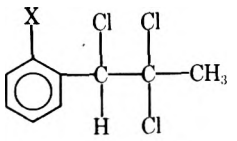
6

may rearrange with chlorine shift, to chloro ketones, probably via ketocarbonium ion intermediates.[3] The example[3a] of eq 3 is particularly relevant (cf. eq 1). The McDonald reaction typically occurs in neat liquid. Lewis acid catalysis may occur, but protonic acids tend to favor alternative reaction paths.[3b] Although the reaction of this paper occurs in protonic solvents, it appears that the McDonald mechanism should not be ruled out of consideration. A third type of mechanism for formation



(3)

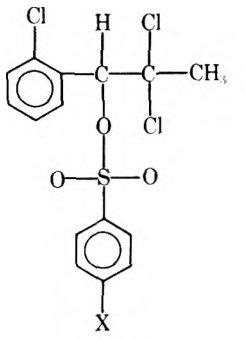
of **2** involves the intermediacy of chloride **7a**, formed in an intermolecular reaction from HCl evolved into the sulfuric acid solvent via side reactions or, after reaction has begun, via eq 1. Although reaction via **7** would involve no chlorine shift, hydrolysis of geminal halides is known to yield ketones. Furthermore, the reported isolation of **7b** from an experiment in H_2SO_4[1] suggested that the sequence involving **7** must be considered!



7
a, X = Cl
b, X = H

Description and Results

For mechanistic studies it was highly desirable to find conditions suitable for rate determinations. Presuming that a path involving initial C–O bond breaking was the most likely alternative, we elected to study the reactions of **8a**, the tosylate of **1**. Since trifluoroacetic acid was used by one of us as the



8
a, X = CH_3
b, X = Br

solvent in many previous studies of halogen participation in solvolysis,[4] we decided to add as much trifluoroacetic acid as possible to the sulfuric acid reaction medium. Encouragingly, in CF_3CO_2H–H_2SO_4 the tosylate **8a** gave ketone **2** and the trifluoroacetate ester of **1** in an approximate 1:1 ratio. Reaction occurred at a measurable rate at 35 °C in CF_3CO_2H containing 96% H_2SO_4 (see footnote, Table I, for concentrations). Hydrogen NMR at 90 MHz proved to be a sensitive, convenient method for following the course of reaction. With conditions suitable for kinetic studies at hand, we prepared the *p*-bromobenzenesulfonate of **1** and determined the reaction rates of both the tosylate and brosylate. Remarkably, the rates were almost identical, whereas we had expected to observe a substituent rate enhancement for the brosylate relative to the tosylate leaving group, $k_{Bs}/k_{Ts} = \sim 2.5$ We obtained a similar result for the tosylate and brosylate of isopropyl alcohol. The rate constants, to be discussed later, are given in Table I. It was noted that in the absence of H_2SO_4 the tosylate and brosylate solvolyzed in trifluoroacetic acid at a higher temperature (65 °C) with approximate half-lives of 180 and 85 min, respectively. However, little ketone **2** was formed, and several unidentified NMR peaks appeared instead. Unpublished observations in the laboratory of one of the authors indicate that the addition of strong acids to CF_3CO_2H lowers its nucleophilicity. Evidently a low nucleophilicity is required to obtain the product whose formation was the object of the present study.

Since the alcohol **1** forms ketone **2** in 96% H_2SO_4, it seemed likely that alcohol **1** would exhibit a similar reaction in the mixture of CF_3CO_2H and H_2SO_4 used for tosylate solvolysis. Actually, a new compound, presumably the bisulfate of **1**, formed rapidly (22% after 10 min), along with the trifluoroacetate of **1** (5% after 10 min). After 5 h, the composition was trifluoroacetate (63%), bisulfate (8%), and ketone **2** (6%). The ketone may have been derived from trifluoroacetate, since mixtures of trifluoroacetate and ketone derived from tosylate solvolysis were gradually converted to ketone upon prolonged reaction at 65 °C (76% ketone after 7.5 h). One might suppose that a bisulfate intermediate would give a ratio of ketone to trifluoroacetate comparable to that obtained from the tosylate. That it did not may be due to the lower nucleophilicity of the solvent in the reaction of alcohol **1** owing to an acid–base reaction between the alcohol and sulfuric acid.

Table I. Rates of Solvolysis in CF_3CO_2H–H_2SO_4[a]

	Registry no.	$10^4 k$, 35 °C, s^{-1}	Concn, mol L^{-1}
1-OTs	37610-59-6	1.9	0.125
1-OBs	63641-56-5	1.6	0.125
		$10^4 k$, 20 °C, s^{-1}	Concn, mol L^{-1}
i-PrOTs	2307-69-9	6.2	0.19
i-PrOBs	24767-70-2	6.4	0.14

[a] 1.127 g of 96% H_2SO_4 in 25 mL of CF_3CO_2H; molarity of H_2SO_4 = 0.446.

Table II. Rates of Trifluoroacetolysis of Tosylates, Brosylates, and a *p*-Nitrobenzenesulfonate

Compound	$10^5 k$, 25 °C, s^{-1}
Cyclohexyl brosylate	44.5[a]
Cyclohexyl tosylate	25.2[b]
Isopropyl nosylate	22[c]
Isopropyl brosylate	5.55 (est)[d]
Isopropyl tosylate	2.49[e]

[a] J. E. Duddey and P. E. Peterson, unpublished work. [b] D. M. Chevli and P. E. Peterson, unpublished work. [c] P. E. Peterson and J. F. Coffey, *J. Am. Chem. Soc.*, **93**, 5208 (1971). [d] Estimated using the Hammett equation, $\log k_x/k_y = \rho\Delta\sigma^n$. The σ^n value for *p*-NO_2 was incremented by 0.18 (to 0.96) to allow for the hydrogen-bonding effect of CF_3CO_2H. See P. E. Peterson, D. M. Chevli, and K. A. Sipp, *J. Org. Chem.*, **33**, 972 (1968) for further references. [e] P. E. Peterson, R. E. Kelley, and K. A. Sipp, *J. Am. Chem. Soc.*, **87**, 5169 (1965).

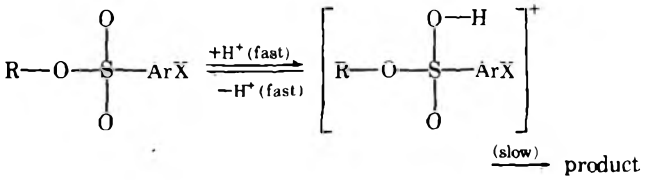
Discussion

The finding that the tosylate **8a** and brosylate **8b** yield 50% ketone **2** in CF_3CO_2H–H_2SO_4 and that reaction is faster than that of the presumed bisulfate or the alcohol provides further indication that neither the bisulfate or the epoxide **6** is an intermediate. The literature contains no indication that generation of a cationic center β to a tosyloxy group (e.g., in reactions of ditosylates) leads to epoxide intermediates. Under our conditions the chloride **7a** is also not an intermediate, since it was not observed by NMR, and a control experiment using 2-chloropentane showed that chlorides are, as expected, less reactive than tosylates of similar structure. Accordingly, the formation of ketone **2** from sulfonates **8a** and **8b** does seem to be initiated by breaking of the benzylic C–O bond. It may be argued that alcohol **1** may react in H_2SO_4 via an epoxide even if **8a** and **8b** in CF_3CO_2H–H_2SO_4 react by another mechanism. However, our study implies that a mechanism involving C–O bond breaking in alcohol **1** or its bisulfate should be readily accessible.

Initially, we expected the brosylate **8b** to react faster than the tosylate **8a**, based on other solvolytic data in the literature which suggested that the better leaving group (brosylate) would give evidence of rate determining C–O bond breaking by reacting faster.[5] Data gathered in part from unpublished results (Table II) show that trifluoroacetolyses do show a brosylate/tosylate rate ratio of 1.8 (for cyclohexyl) or 2.2 (estimated for isopropyl).

In sharp contrast, the results reported in Table I for the trifluoroacetolysis of isopropyl tosylate and brosylate (and for

Scheme I



8a and 8b) in CF_3CO_2H–H_2SO_4 show that the *sulfuric acid promoted* trifluoroacetolyses of our study are *insensitive to substituents in the leaving group.* It seems likely that substituted arylsulfonate is protonated in a rapid equilibrium prior to solvolysis (eq 1) (Scheme I). Opposing substituent effects in the two steps would explain the overall absence of substantial effects. A similar situation could occur if the intermediate is hydrogen bonded to H_2SO_4 instead of protonated. The situation is reminiscent of that which is found in acid-catalyzed ester hydrolyses,[6] in which substituent effects are small, presumably because of a comparable compensation of effects.

In retrospect, a decline in substituent effects as the solvent becomes more acidic (and presumably a stronger hydrogen-bonding solvent) is already evident from available brosylate/tosylate rate ratios. For the cyclohexyl compounds, the ratios are: acetolysis,[5] 3.5; formolysis,[5] 2.7; trifluoroacetolysis (Table II), 1.8.

The acid-catalyzed solvolysis of tosylates in pure sulfuric acid has received some study, particularly in Myhre's laboratory,[7] but the CF_3CO_2H–H_2SO_4 system used here is a promising alternative system for future work. It readily dissolves reactants, gives readily isolated trifluoroacetate or other products (ketone in the present instance), and is subject to control of acidity without addition of water through variation in the sulfuric acid concentration. At the concentration level of H_2SO_4 used here, the isopropyl tosylate rate at 35 °C is 27 times that found at 25 °C in the absence of H_2SO_4.

In the recent paper from Myhre's laboratory[7] it was found that the solvolysis of $CF_3CHOTsCH_3$ in H_2SO_4 occurs with probable cleavage at sulfur (and retention of configuration at the C–O bond). Since the effect of substituents in the leaving group is unknown for this new type of reaction, the possibility that our unusual substituent effects arise from this type of cleavage must be considered. However, in our system this cleavage should give alcohol 1, which reacts only slowly under the conditions used. The alcohol 1 (or its bisulfate) was not observed in our tosylate or brosylate solvolyses. Accordingly, our reaction is not initiated by reaction at sulfur.

Based on the considerations mentioned above, a mechanism for chlorine shift (for 8 and possibly for 1) involving the chloronium ion intermediate 5 is in the best accord with our observations. However, chlorine participation could occur in the rate-determining step (path a, Scheme II) or in a product-forming step which follows the initial heterolysis (path b, Scheme II).

Scheme II

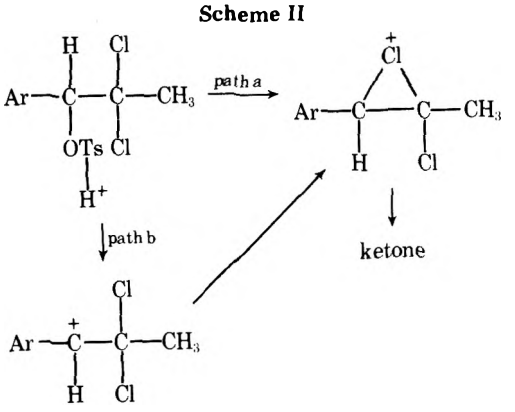


Table III. Chemical Shifts of Alcohol 1, Ketone 2, and Related Compounds

Functional group	Registry no.	δ, CH[a]	δ, CH_3[a]
OH (1)	35996-56-6	5.91	2.09
OTs		6.31	2.04, 2.33
OBs		6.28	2.08
OSO_3H	63641-57-6	6.48	2.13
O_2CCF_3	63641-58-7	6.89	2.12
Ketone (2)	37610-57-4	6.01	2.38

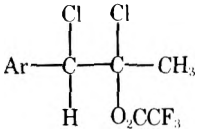
[a] Relative to a capillary of tetramethylsilane.

Neighboring group participation, including chlorine participation, has been detected by rate acceleration, compared to the expected rate for carbonium ion formation,[4,8] and by the net retention of configuration.[9] Accordingly, either path in Scheme II is compatible with our data, although we note that other halogen shifts in halotosylate solvolyses have invariably shown evidence for halogen participation in the rate-determining step.[4] An investigation into the halogen participation and steric course of this reaction is presently underway in our laboratories.[10]

The initial product of halogen shift in our system is presumably the chlorotrifluoroacetate. It is presumed that ionization of the chlorine on the potential ketone carbon occurs rapidly in CF_3CO_2H–H_2SO_4. Further transformations would afford ketone and trifluoroacetic anhydride.

Conclusion

By the use of the solvent CF_3CO_2H–H_2SO_4, the chlorine shift of alcohol 1 and its sulfonates has been brought under kinetic control. This solvent system has potential use for elucidation of the effect of structural modifications of structure 1, and for other studies of neighboring group participation.[10]



Experimental Section

Rate Determination. Products were identified by comparison of their 90-MHz NMR spectra with those of authentic materials previously prepared,[1] except for the presumed bisulfate of alcohol 1. The high signal to noise ratio of the Perkin-Elmer R-32 NMR instrument facilitated rate determinations based on relative peak heights or areas of the sharp singlets (Table III) of the side chain in 1, 2, and related compounds. The quality of rate plots was comparable to that of earlier methods. Since rates may be a sensitive function of the water content of the solvent, all rates in Table I were determined using a single batch of CF_3CO_2H–H_2SO_4. First-order rate constants were determined as the negative of the slope of plots of $\ln (1 - A_p/A_t)$ vs. time. Here A_p and A_t are areas of NMR peaks of the product and the total area (products plus reactant), respectively. Areas of the CH_3 singlets were used in the calculation. In the case of isopropyl derivatives, peak heights of the best-separated peaks of the CH_3 doublets were used instead of areas, since the heights were free from contributions of the tail of the adjacent peak.

1-(*o*-Chlorophenyl)-1-tosyloxy-2,2-dichloropropane. The compound was prepared according to the procedure of Jensen and Counsell.[1]

1-(*o*-Chlorophenyl)-1-brosyloxy-2,2-dichloropropane. The compound was prepared from 1-(*o*-chlorophenyl)-2,2-dichloro-1-propanol (1.2 g) by reaction with *p*-bromobenzenesulfonyl chloride (1.9 g) in pyridine (35 mL) at 45 °C for 3 days. The pyridine solution was quenched in cold 6 N hydrochloric acid and extracted with ether. The combined extracts were washed with dilute hydrochloric acid and water before drying over magnesium sulfate. Recrystallization from

hexane afforded colorless crystals, mp 109–111 °C.

Anal. Calcd for $C_{15}H_{12}BrCl_3O_3S$: C, 39.28; H, 2.63. Found: C, 39.20; H, 2.80.

Isopropyl Tosylate. The compound was prepared as previously described.[11]

Isopropyl Brosylate. The compound was prepared by the usual method.[12]

Acknowledgments. We thank the Summer Faculty Research Fund, University of Maine at Orono, for financial support of this work, and the University of South Carolina for providing its facilities.

Registry No.—CF_3CO_2H, 76-05-1; H_2SO_4, 7664-93-9; 1-(*o*-chlorophenyl)-2,2-dichloro-1-propanol, 355996-56-6.

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Equilibria in Reactions of Fluorocarbon Olefins, Imines, and Ketones with Fluoride Ion

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Rate and enthalpy measurements indicate that fluoride ion adds more easily to the C=O bond in $H(CF_2)_6COCF_3$ than to the C=C bond in $H(CF_2)_7OCF=CF_2$, at near ambient temperatures in a polar aprotic solvent. When both are present, however, there can be rapid fluoride exchange from the kinetically more favored to the less favored anion; the initial composition thus has little importance. In fluoride-catalyzed dimerization of C=C, C=O, and C=N compounds at 170–180 °C under equilibrium conditions, the final product will be the most thermodynamically stable one and can be predicted on the basis of relative acidities. The codimerization reaction is highly product specific.

Fluoride ion adds to highly fluorinated olefins and carbonyl compounds to form respectively carbanions and alkoxide ions which undergo many of the characteristic reactions of their nonfluorinated analogues.[1]

$$R_FCF=CF_2 + F^- \rightarrow R_FC^-FCF_3 \quad (1)$$

$$(R_F)_2C=O + F^- \rightarrow (R_F)_2CFO^- \quad (2)$$

In a mixed system containing olefin, carbonyl compound, and fluoride ion, two reaction possibilities exist: alkylation of the carbonyl compound or alkoxylation of the olefin

$$R_F'CF=CF_2 \xrightarrow{F^-} R_F'CF^- \xrightarrow{(R_F)_2C=O} R_F'CFC(R_F)_2 \quad (3)$$

(with CF_3 and O^- substituents)

$$(R_F)_2C=O \xrightarrow{F^-} (R_F)_2CFO^- \xrightarrow{R_FCF=CF_2}$$

$$(R_F)_2CFOCF_2C^-FR_F' \quad (4)$$

The first of these reactions has often been reported and the second never. Broadly speaking the question somewhat resembles the addition of an enolate ion to C=O in classical base-catalyzed carbonyl condensations, in which the new bond formed is C–C rather than C–O. The fluorinated carbanion and alkoxide ions are not ambident, as is the enolate ion, but it has heretofore been assumed that they are in some way interconvertible. The present work shows that this interconvertibility is real, that the overall reaction is apt to be thermodynamically rather than kinetically controlled, and that the product can be predicted in terms of relative acidities.

In order to study the C=O/C=C system shown in eq 3 and 4, two compounds of medium chain length, $H(CF_2)_6COCF_3$ (**1**) and $H(CF_2)_7OCF=CF_2$ (**2**), were prepared. A vinyl ether rather than an α-olefin was chosen since a terminal *F*-olefin[2] undergoes very facile double-bond migration in the presence of fluoride ion and this reaction would have interfered with the kinetic studies. A schematic diagram of the two syntheses is shown in Scheme I. No unusual difficulties were encountered. During identification of the vinyl iodide, an unexpected fragmentation pattern in the mass spectrum of the compound

Scheme I

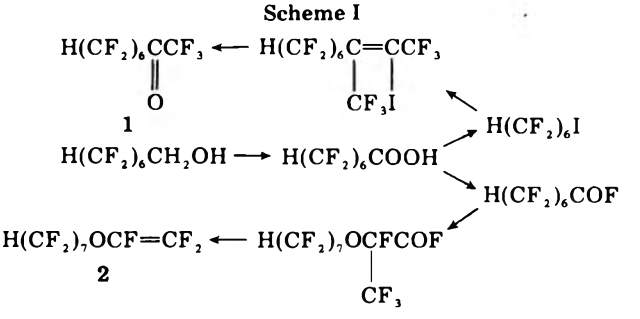

Table I. Variation of K_{eq} with Temperature for the Addition of Fluoride Ion to $H(CF_2)_6COCF_3$ and $H(CF_2)_7OCF{=}CF_2$

Substrate	Temp, °C	% anion	K_{eq}
$H(CF_2)_6COCF_3$	30	77.3	3.4
	10	56.8	1.4
	−10	45.5	0.8
$H(CF_2)_7OCF{=}CF_2$	30	50	1.0
	25	38	0.6
	5	25	0.3
	−15	0	

revealed a rearrangement rather similar to the McLafferty rearrangement. Details and supporting evidence for this phenomenon have been reported elsewhere.[3]

Preliminary tests of an infrared method for following the reaction of fluoride ion with substrate were carried out on a more easily accessible model compound, *F*-1-heptene, using potassium fluoride as fluoride source since cesium fluoride was found to react with ketones inconveniently rapidly for kinetic purposes. As followed by the disappearance of the terminal C=C infrared absorption, the reaction between *F*-1-heptene and fluoride ion always went to completion, even when the fluoride:olefin ratio was less than 1:1. This can be ascribed to fluoride-catalyzed rearrangement of the olefin, since with compounds 1 and **2**, which are incapable of rearranging, complete disappearance of the original IR band was not observed. Moreover, in the mass spectrum of the product recovered from the treatment of *F*-1-heptene with KF, fragments were noted (*m/e* 181, 212) which indicated respectively a cleavage β to the third carbon in the chain and a loss of two CF_3 groups, processes which would occur in *F*-2-heptene but not in the original *F*-1-heptene. It has been observed previously that rearrangement is a very facile process when it can occur.[1,4]

Plots of concentration vs. time showed zero-order kinetics. This fact and the large surface area effect noted with excess KF indicated that the reaction occurs on the crystal surface rather than in solution. Graham found a similar rate acceleration in the case of tetrafluoroethylene with fluoride ion.[5]

The reactions of the two principal test compounds with fluoride ion are shown below.

$$\underset{\mathbf{1}}{H(CF_2)_6COCF_3} + F^- \rightarrow \underset{\mathbf{3}}{H(CF_2)_6CF(CF_3)O^-} \quad (5)$$

$$\underset{\mathbf{2}}{H(CF_2)_7OCF{=}CF_2} + F^- \rightarrow \underset{\mathbf{4}}{H(CF_2)_7OC^-FCF_3} \quad (6)$$

Kinetic studies on these systems were run in diglyme at 30 °C with KF, using either IR or NMR to follow the reaction; the two methods gave fair agreement. In view of the heterogeneity of the reactions, rate constants are no more than relative, but since the same batch of KF was used throughout the average values should be significant for comparing the relative reaction velocities of the two compounds under those specific conditions. Average values for $t_{1/2}$ and K_{eq} respectively were 0.53 h and 4.1 for the ketone and 1.1 h and 1.3 for the vinyl ether, when followed by IR. Equilibrium constants at various temperatures, as found by NMR, are shown in Table I.

By plotting ln K_{eq} vs. T^{-1}, an approximate value for the enthalpy of anion formation was obtained. For the ketone $\Delta H = -5$ kcal/mol and for the vinyl ether $\Delta H = -9$ kcal/mol.

Competition for fluoride ion between vinyl ether and ketone was investigated by NMR for three cases: case I, preformed vinyl ether anion (carbanion) plus excess free ketone; case II, preformed ketone anion (alkoxide) plus excess free vinyl ether; case III, approximately equimolar quantities of ketone and vinyl ether, plus potassium fluoride in half this total molar quantity. The anions were prepared in diglyme as usual, the other reactant and $CFCl_3$ as internal standard were added in vacuo at −180 °C, and the tubes were sealed and stored at −80 °C until use. Each was then warmed rapidly to room temperature, spectra being taken immediately after warm-up and again after 1 and 2 h of mixing at room temperature. The two possible reactions of alkylation and alkoxylation are shown below.

$$R_FCOCF_3 + R_FCF_2O\bar{C}FCF_3 \rightarrow \underset{\mathbf{5}}{R_FC(O^-)(CF_3)-CFOCF_2R_F} \quad (7)$$

$R_F = H(CF_2)_6$

$$R_FCF_2OCF{=}CF_2 + R_FCF(CF_3)O^- \rightarrow \underset{\mathbf{6}}{R_FCF_2O\bar{C}FCF_2OCFR_F} \quad (8)$$

$$\underset{\mathbf{6}}{R_FCF_2O\bar{C}FCF_2OCFR_F} \xrightarrow{-F^-} \underset{\mathbf{7}}{R_FCF_2OCF{=}CFOCFR_F}$$

Although interpretation of the NMR spectra was difficult because of the possible presence of six different species and because differences in the chemical shift values of the various CF_3 groups were within or very near to the limits of reproducibility from sample to sample, the following conclusions seemed clear. In case I, the preformed carbanion originally present was absent even in the earliest spectrum taken. Free vinyl ether appeared in this spectrum but diappeared rapidly and was completely gone in the final spectrum. In case II, carbanion was detected in the first spectrum taken and persisted thereafter since vinyl ether was in excess. Since the carbanion disappears in the presence of free ketone, as shown by case I, the ketone formed in case II must have been consumed by reaction with the carbanion. In case III, neither the ether nor its carbanion was detected at any time. The final spectrum was virtually identical with that of case I.

These results are in accord with the reaction pattern vinyl ether **2** + alkoxide **3** ⇄ carbanion **4** + ketone **1** → condensation product **5**. Initial conditions are of minimal importance; in any system composed of the ketone, the vinyl ether, fluoride ion, and the respective anions, whether any of these be potential or real, the only end result is the formation of the carbanion and its addition to the ketone. Transfer of fluoride ion from the alkoxide ion **3** to the vinyl ether **2** is rapid and quantitative; the carbanion is apparently formed more effectively by this process than by simple addition of fluoride ion to the ether. In other words, the ketone acts as a very efficient carrier of fluoride ion.

The reaction pattern can be rationalized in terms of the relative strengths of the conjugate acids and bases involved. The alkoxide **3** is a weaker base than the carbanion **4** (i.e., $(R_F)_2CFOH$ is a stronger acid than $R_FOCHFCF_3$), therefore the ketone reacts more easily than the vinyl ether with fluoride ion. The alkoxide does not attack the C=C double bond as such an attack would lead to the more highly basic carbanion **6**, but the carbanion **4** can attack the C=O double bond to give **5**, the weakest base of all since it is the anion of a tertiary *F*-alkanol, with $pK_a \simeq 5$.

Considerations of equilibrium, anion stability, and relative acidity have similarly been found to be product determining in the fluoride-catalyzed codimerization of *F*-olefins and *F*-imines. When the three reactants $CF_3N{=}CF_2$, $CF_3CF{=}CF_2$, and $(CF_3)_2C{=}CF_2$ are treated separately with cesium fluoride the first dimerizes at 50 °C or less, the second dimerizes at 150 °C, and the third does not react. Presumably the lack of re-

action of $(CF_3)_2C{=}CF_2$ is due to poor accommodation of this bulky molecule or the related $(CF_3)_3C^-$ ion on the crystal surface, since the olefin can be dimerized by CsF at −20 °C even in diethyl ether.[6]

The dimerization or codimerization presumably occurs in three steps: (1) addition of fluoride ion to an olefin to form the anion, (2) addition of this anion to a second molecule of olefin to form a larger anion, and (3) expulsion of fluoride ion to form the most stable (i.e., most highly substituted) olefin.

$$CF_3CF{=}CF_2 + F^- \rightarrow (CF_3)_2CF^- \quad (9)$$

$$(CF_3)_2CF^- + CF_3CF{=}CF_2 \rightarrow (CF_3)_2CFCF_2C^-FCF_3 \quad (10)$$

$$(CF_3)_2CFCF_2C^-FCF_3 \rightarrow (CF_3)_2CFCF{=}CFCF_3 + F^- \quad (11)$$

In the presence of two different olefins, it would be expected that the more reactive of the pair should add fluoride ion to form an anion and that this anion would then attack a second molecule to give the codimer or the homodimer of the more reactive species. In short, the more reactive olefin should serve as addend and the less active (ignoring homodimerization) as receptor.

Given the aforementioned reactivities, crossed reactions of the three compounds should give the products predicted below, with possibly one homodimer in each case.

$$CF_3N{=}CF_2 + CF_3CF{=}CF_2 \rightarrow (CF_3)_2NCF{=}CFCF_3 \quad (12)$$
8

$$CF_3N{=}CF_2 + (CF_3)_2C{=}CF_2 \rightarrow (CF_3)_2NCF{=}C(CF_3)_2 \quad (13)$$
9

$$(CF_3)_2C{=}CF_2 + CF_3CF{=}CF_2 \rightarrow (CF_3)_3CCF{=}CFCF_3 \quad (14)$$
10

The actual results were exactly the opposite of those predicted. In every case, the less reactive species served as addend and the more reactive as receptor, to give high yields of the codimer and none of the homodimer. Results obtained are shown below.

$$CF_3N{=}CF_2 + CF_3CF{=}CF_2 \rightarrow (CF_3)_2CFCF{=}NCF_3 \quad (15)$$
11

$$CF_3N{=}CF_2 + (CF_3)_2C{=}CF_2 \rightarrow (CF_3)_3CCF{=}NCF_3 \quad (16)$$
12

$$(CF_3)_2C{=}CF_2 + CF_3CF{=}CF_2 \rightarrow (CF_3)_2CFCF{=}C(CF_3)_2 \quad (17)$$
13

Furthermore, the intervention of an equilibrium involving monomer, dimer, and anions was shown by heating the imine homodimer $(CF_3)_2NCF{=}NCF_3$ with $CF_3CF{=}CF_2$ and fluoride ion. The codimer **11** was produced.

The results show that the reaction is subject to thermodynamic rather than kinetic control. They can be rationalized on the same basis (anion stability and conjugate acid strength) as the preceding results on C=O vs. C=C activity. In the pair of reactions 12 and 15, the anionic intermediate is a conjugate base of either a C–H or an N–H acid. The latter is the stronger acid and therefore leads to the observed product.[7]

The same considerations hold for reactions 13 and 16. In the pair **14** and **17** the choice is between a secondary carbanion $(CF_3)_3CCF_2C^-CFCF_3$ and a tertiary carbanion $(CF_3)_2CFCF_2C^-(CF_3)_2$. Since a tertiary C–H bond in a hydrofluorocarbon is about 10^5 times as acidic as a secondary C–H,[8] the tertiary carbanion is the one which leads to product. In this last case the reluctance of $(CF_3)_2C{=}CF_2$ to add fluoride ion may also be a contributing factor, but it should be noted that the $(CF_3)_3C^-$ does form in reaction 16, possibly by a fluoride transfer mechanism such as that observed previously with the vinyl ether/ketone pair.

Scheme II

$$CF_3N{=}CF_2 + CF_3CF{=}CF_2 \rightleftharpoons \begin{cases} (CF_3)_2NCF_2\bar{C}FCF_3 \rightarrow 8 \\ (CF_3)_2CFCF_2\bar{N}CF_3 \rightarrow 11 \end{cases}$$

It is sometimes possible to change a regime of thermodynamic control to one of kinetic control by moderating the reaction conditions, as in the classic case of naphthalene sulfonation. In this regard, it is interesting to note that in the $(CF_3)_2C{=}CF_2/CF_3CF{=}CF_2$ reaction, only the kinetic dimer is obtained when the reaction is run at room temperature in a polar aprotic solvent.[9]

Experimental Section

General. The compounds $CF_3(CF_2)_4CF{=}CF_2$, $H(CF_2)_6CH_2OH$, $(CF_3)_2C{=}O$, $CF_3CF{=}CF_2$, and $CF_3C{\equiv}CCF_3$ were obtained from PCR, Inc. and used as received; $(CF_3)_2C{=}CF_2$ was made by reformation of $CF_3CF{=}CF_2$[10] and $CF_3N{=}CF_2$ by pyrolysis of $(CF_3)_2NCOF$.[11] Before use, the water content of the solvents glyme and diglyme was checked at 10 ppm or below, and CsF and KF were dried in vacuo at 50 °C for 10–15 h. Mass spectra were recorded on an AEI-MS12 instrument using 8 kV, 100 μA, source temperature 70 °C, inlet temperature 120 °C. NMR measurements were made using a Varian DP-60 at 56.4 MHz with $CFCl_3$ as internal standard.

Preparation of $H(CF_2)_6COCF_3$, 8-Hydryl-*F*-2-octanone, Compound 1. $H(CF_2)_6COOH$ was prepared by oxidation of $H(CF_2)_6CH_2OH$.[12] Reaction of its sodium salt with iodine was best carried out at 180–200 °C in sulfolane to give a 65% yield of $H(CF_2)_6$-I: bp 109 °C (630 mm); mass spectrum [*m/e* (rel intensity)] 428 (19), 301 (38), 231 (69), 177 (61), 131 (100). The iodide was added to hexafluorobut-2-yne by heating in a sealed Pyrex tube at 250 °C for 12–14 h to give $H(CF_2)_6C(CF_3){=}CICF_3$, bp 72—73 °C (7.5 mm), in 66% conversion and >90% yield: IR (C=C) 1580 cm^{-1}; mass spectrum 590 (12), 325 (64), 213 (78), 212 (100), 193 (32), 143 (52), 131 (42), 127 (34), 113 (36), 101 (26), 93 (64). The substituted vinyl iodide was oxidized with 2.2 mol of $KMnO_4$ in 1:1 acetone–water at 30 °C, treated with SO_2, separated, dried with P_2O_5, and fractionated to give 70% $H(CF_2)_6COCF_3$: bp 115 °C (630 mm); IR (C=O) 1790 cm^{-1}; mass spectrum 398 (2), 329 (12), 301 (24), 281 (24), 263 (28), 231 (52), 203 (14), 181 (34), 169 (50), 163 (28), 151 (24), 131 (100), 119 (75), 113 (74), 102 (62), 97 (35), 93 (46); NMR [ϕ^* (splitting, area)] 139.2 (d, 2 F), 131.1 (s, 2 F), 124.5 (s, 2 F), 122.4 (s, 4 F), 119.2 (s, 2 F), 76.4 (s, 3 F).

Preparation of $H(CF_2)_7OCF{=}CF_2$, 10-Hydryl-*F*-3-oxadecene, Compound 2. $H(CF_2)_6COOH$ was refluxed with excess benzoyl chloride for 3 h and fractionated to give 88% $H(CF_2)_6COCl$: bp 67 °C (70 mm); IR (C=O) 1780 cm^{-1}. The acid chloride was refluxed with NaF in diglyme and fractionated to give 78% $H(CF_2)_6COF$, bp 91 °C (630 mm) (lit. 88–91 °C (760 mm)[13]). Hexafluoropropylene epoxide, 0.020 mol, prepared by reaction of $CF_3CF{=}CF_2$ with alkaline hydrogen peroxide,[14] was added slowly to 0.017 mol of $H(CF_2)_6COF$ stirred with 0.01 mol of CsF in 25 mL of triglyme, followed by 5–6 h of reflux. Fractionation gave $H(CF_2)_7OCF(CF_3)COF$, bp 69 °C (30 mm), IR (C=O) 1870 cm^{-1}, in 22% average yield. The ether acid fluoride was converted to the sodium salt, which was pyrolyzed in vacuo at 250 °C over 3–5 h to give 81% yield $H(CF_2)_7OCF{=}CF_2$: bp 82 °C (88 mm); IR (C=O) 1830 cm^{-1}; mass spectrum 448 (3), 131 (48), 119 (20), 101 (28), 100 (19), 97 (16), 78 (100); NMR 138 (d, 2 F), 127.6 (s, 2 F), 123.5 (s, 2 F), 121.1 (s, 6 F), 84.1 (s, 2 F), 116 (m, 1 F), 122.8 (m, 1 F), 137.4 (m, 1 F). The ϕ^* values agreed well with those of a similar *F*-(vinyl ether) prepared by others.[15] All liquid intermediates and final products showed >98% purity by GC.

Utilization of NMR. The ϕ^* values for CF_3 in diglyme solution were surprisingly little affected by complex formation, $CF_3C(=O)$ 77, $CF_3CF(O^-)$ 78, CF_3C^-FO 82; a similarly slight change of about 2 ppm was noted for CF_3 in $(CF_3)_2CO$ and $(CF_3)_2CFO^-$. Spin–spin splitting was not observed except for that of the CHF_2 doublet and that among the vinyl fluorine atoms of the ether. The most reliable identification data were (1) distortion of the CHF_2 doublet due to superposition of the vinyl fluorine α to oxygen, which identified the free ether, and (2) a new peak at 54 ppm which appeared on treatment of the vinyl ether with fluoride ion, presumably OC^-FCF_3.

Codimizerations. Equimolar quantities (0.4–0.1 mol) each of the two reactants were heated in a steel bomb with 50 g of CsF for 6 days at 170–180 °C. After cooling, the bomb was evacuated for several hours and the condensate (dry ice trap) was fractionated. Chromatographic purity of all products was at least 99%. $(CF_3)_2CFCF{=}NCF_3$ (**11**), 4-(*F*-methyl)-*F*-2-aza-2-pentene: bp 28–31 °C (630 mm) (bp

$(CF_3N{=}CF_2)_2$ 34 °C (630 mm), bp $(CF_3CF{=}CF_2)_2$ 30 °C (630 mm)); conversion 79%; IR (C=N) 1765 cm^{-1} (C=N in $(CF_3)_2NCF{=}NCF_3$ 1760, C=C in $(CF_3)_2CFCF{=}CFCF_3$ 1750); NMR (ϕ*, area) CF_3C (74.5, 6 F), CF_3N (59.9, 3 F), CF=N (17.3, 1 F), CFC (191, 1 F). $(CF_3)_3CCF{=}NCF_3$ (12), 4,4-di(*F*-methyl)-*F*-2-aza-2-pentene: bp 51–53 °C (630 mm); yield 95%; conversion 69%; mol wt 326 (calcd for C_4F_8: $CF_3N{=}CF_2$ 333); IR (C=N) 1760 cm^{-1}; NMR CF_3C (62.1, 9 F), CF_3N (56.4, 3 F), CF=N (5.6, 1 F). $(CF_3)_2CFCF{=}C(CF_3)_2$ (13), 2,4-di(*F*-methyl)-*F*-2-pentene: bp 63–64 °C (630 mm); yield 95%; conversion 83%; IR (C=C) 1680 cm^{-1} (C=C in $(CF_3)_2C{=}CFC_2F_5$ 1690, in *cis*-$(CF_3)_2CFCF{=}CFCF_3$ 1750); NMR CF_3OC (74.4, 6 F), $CF_3C{=}$ (59.4, 3 F), CFC (55.3, 1 F), CF=C (183, 1 F).

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Registry No.—**1**, 63703-12-8; **2**, 63703-13-9; **11**, 63703-14-0; **12**, 58599-97-6; **13**, 63703-15-1; $H(CF_2)_6COONa$, 2264-25-7; $H(CF_2)_6I$, 63703-16-2; $H(CF_2)_6C(CF_3){=}ClCF_3$, 6307-17-3; $H(CF_2)_6COOH$, 1546-95-8; $H(CF_2)_6COCl$, 41405-35-0; $H(CF_2)_6COF$, 5927-65-1; $H(CF_2)_7OCF(CF_3COF$, 63703-18-4; F^-, 16984-48-8; hexafluoropropene, 116-15-4; benzoyl chloride, 98-88-4; hexafluoropropylene epoxide, 428-59-1.

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Reactivity of Benzylic Carbanions. 4. Kinetic Studies of Reactions of Alkyl Halides with 9-Alkyl-10-lithio-9,10-dihydroanthracenes and Diphenylmethyllithium. The Relationship of Reaction Rates to Product Stereochemistry

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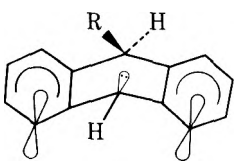
The kinetic measurements of a series of highly reactive anion reactions with primary and secondary halides were made and related to the stereochemistry of the products. There is evidence for a change of factors affecting the reactivity between the primary and secondary systems.

The stereochemistry of reactions of 9-alkyl-10-lithio-9,10-dihydroanthracene and alkylanthracene has been studied extensively with interesting and sometimes inconsistent results.[2] The crux of these apparent inconsistencies involves the stereochemistry and mechanistic implications of the anion, I, as a flattened boat conformer with preferred axial orienta-



Ia, R = H
b, R = Et
c, R = *i*-Pr
d, R = *t*-Bu

tions of the alkyl substituent in the lithio derivative.[2b,c] This conformational preference is determined by two factors. First, the anion in the axial position permits maximum interaction with the π orbitals on the neighboring rings, thus stabilizing the charge by delocalization. Most of this delocalization is unavailable when the anion is in an equatorial conformation. Second, the alkyl group in the axial position has minimum steric interaction with the peri hydrogens of the neighboring rings. That this conformer is of lower energy than the equatorial is substantiated by NMR studies, which indicate for the series 9-alkyl-9,10-dihydroanthracenes that the orientation of the 9-ethyl, 9-isopropyl, and 9-*tert*-butyl groups is essentially 100% pseudoaxial.[3] If these were the only factors, then alkylation reactions should lead to products with cis stereochemistry. Interestingly, while there are many reactions that do give mainly cis products, there are many that give predominately the trans isomer.[2a,4-6] Moreover, there does not appear to be a simple explanation based on steric factors. For example, ethyl bromide reacts with Ic to give product mixtures of 74% cis and 26% trans isomers.[2a] Similar results were obtained with methyl and isopropyl iodide.[6] The wide range of stereoselectivity appears not to be confined to alkylation reactions, as deuteration of the anion[7,5] and reduction of alkyl anthracene[8,9] can lead to widely varying ratios of cis to trans isomer by changing reaction conditions.

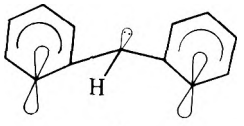
The variation in reaction parameters such as temperature, solvent, leaving group, and anion structure has in general led

Table I. Second-Order Rate Constants for Reactions of Anions with Alkyl Halides[a]

R'X	Registry no.	Anion[b]	Registry no.	k_1, M^{-1} s^{-1}[c]	% cis isomer[d]
HexCl	544-10-5	Ph_2CH	881-42-5	1.0×10^1	
		HAnth	17228-13-6	1.0×10^1	
EtCl	79-00-3	EtAnth	17228-12-5	6.0	92
		i-PrAnth	35150-61-9	4.1	75
HexCl				2.3	
		t-BuAnth	35150-62-0	1.0	
HexBr	111-25-1	Ph_2CH		2.7×10^3	
		HAnth		2.7×10^3	
		EtAnth		1.5×10^3	92
		i-PrAnth		5.9×10^2	74
		t-BuAnth		3.3×10^2	
i-PrBr	75-26-3	Ph_2CH		1.9×10^2	
		HAnth		6.2×10^1	
		EtAnth		4.3×10^1	30
		i-PrAnth		4.0×10^1	15
		t-BuAnth		4.0×10^1	2[e]
i-PrI	75-30-9	Ph_2CH		4.9×10^3	
		HAnth		3.4×10^3	
		EtAnth		1.7×10^3	30
		i-PrAnth		1.4×10^3	12

[a] In THF at 20 °C. [b] Lithium counterion. [c] The average of at least three determinations at three different concentrations. The absolute values are within 10% variation. [d] See ref 7. [e] See ref 2c.

to changes in product yields and composition.[2a,c] We have sought further and definitive mechanistic information by bringing the powerful and quantitative techniques of kinetics to this study. We have now studied the effect of reaction variables upon the absolute reaction rates. We have used rapid-mixing stopped flow techniques for a systematic kinetic study of I with alkyl halides. Further, we have included in our study reactions of diphenylmethyllithium, II, which serves



II

as a model having maximum electronic interaction but none of the steric factors present in I. Thus by comparing the absolute reaction rates of these compounds we have attempted to assess directly the structural effects that result in product mixtures of cis and trans isomers.

Whereas product studies have indicated reaction differences, kinetic studies can differentiate between the possibilities that the decrease in formation of the cis isomer is a consequence of a reaction being slowed or of another reaction being accelerated. Equally important, this study is novel in that heretofore absolute rates have not been reported for these highly reactive, air- and moisture-sensitive anions. We report the kinetic data for the substitution reactions of perhaps the most reactive nucleophiles that have been studied to date.

Results and Discussion

The kinetics were measured with a rapid-mixing stopped flow apparatus previously described[10] by monitoring the decay of the highly colored anions at 500 nm. The reactions were overall second order, with first-order dependence on both the anion and the alkyl halide. This was demonstrated by observing the first-order decay of the anions when reacted with an excess of the halide and by determining first-order behavior of the halide over a concentration range of 10^{-2} to 10^{-1} M. The second-order rate constants are summarized in Table I. Inspection of the table reveals that, for each halide reaction, there is a decrease in rate as the size of substituent increases, going from Ia to Ic. Also, there is a concomitant decrease in the amount of cis product. Of greater interest, the log of the

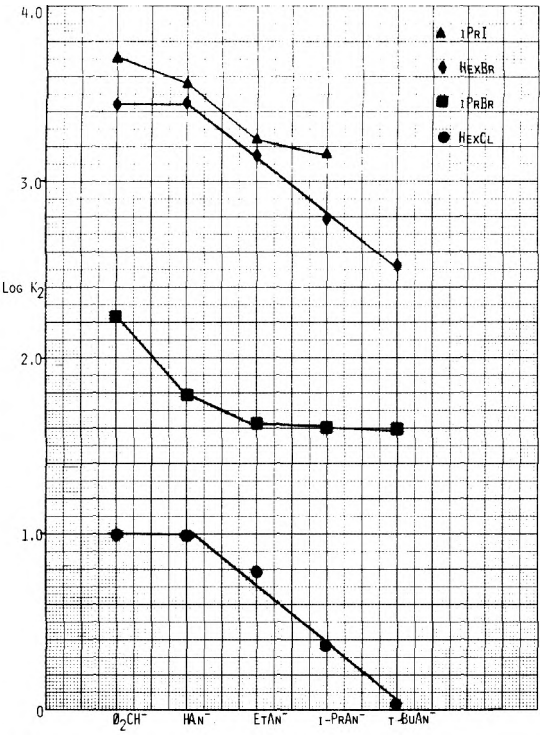


Figure 1.

absolute rate constant is related to the energy of the reaction, and therefore a plot of these values vs. the degree of substitution in the anions indicates the relationship of the alkylation reaction to the steric requirements of the anions. As seen in Figure 1, there appear to be two different relationships operating that depend on the nature of the halide. When alkylation involves a primary bromide or chloride, the rates are equal for II and Ia, and equally important there is a monotonic decrease in rate with increase in steric bulk of the anions. In contrast, when reaction involves a secondary bromide or iodide, there is a large decrease in rate of reaction of II compared to Ia. Also, significantly the decrease in rate of Ib–d is not monotonic and in fact the differences are quite small in the case of the bromide.

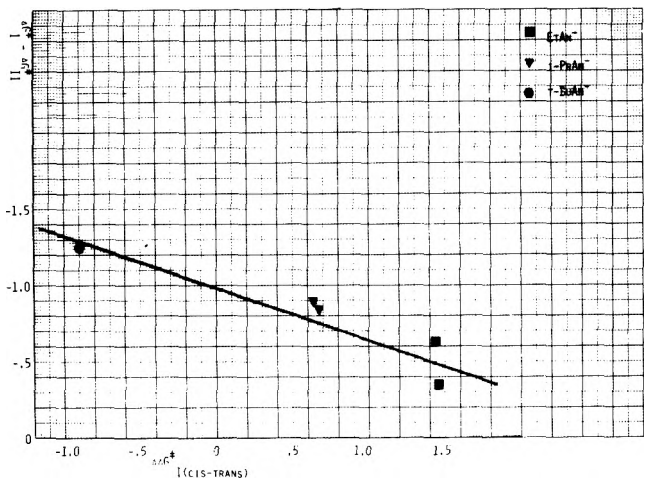


Figure 2.

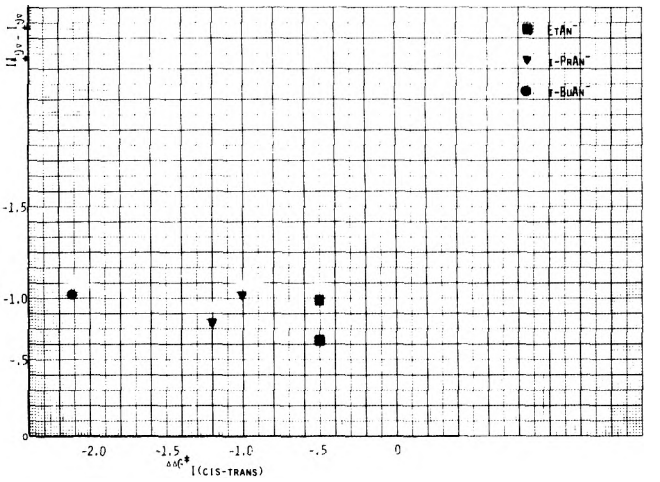


Figure 3.

Therefore it appears that there is a relationship between the rates of reaction of the anions with primary halides and the steric properties of the anion. That there is a similar and quantitative relationship between reaction rates and product stereochemistry is shown in Figure 2. The relationship of the free energies of activation relative to II to the differences in activation energies leading to cis and trans products for primary halides is plotted in Figure 2. Inspection of the plot suggests that the factors producing the overall rate retardation and the decrease in amounts of cis compound are quantitatively related over an extended range of reactivities. In contrast, for secondary halides the absence of a relationship is indicated by the comparable plot for the same anions. In this case the factors producing the decrease in cis compound and overall rates do not appear to correlate as shown by Figure 3.

The emerging pattern is that the kinetic and product studies are related and fall into two distinct sets. For the first (with primary halides), the incursion of a steric effect is seen with substitution at the 9 position and increases as the size of the group increases. Importantly, this is confirmed by the pattern of rate decrease (Et > *i*-Pr > *t*-Bu) with a greater effect in going from *i*-Pr to *t*-Bu. This pattern is characteristic of a classical steric effect and is ascribed to the spherical symmetry of the *tert*-butyl group. In this regard the similarity of the rates of Ia and II signal an absence of important steric differences between these compounds.

In the second set (with secondary halides), a significant rate difference is seen before substitution at the 9 position and increases in the size of the group have a surprisingly small effect on the reaction rate with the bromide. The rate difference of 3 to 1 between Ia and II signals an important difference between the two anions. Moreover the rate ratio of primary to secondary bromide for II is 14, typical of anion values, whereas the rate ratio for Ia is 44.

The possibility that a dominant elimination reaction with the secondary halides obscures the comparison with the primary can be shown to be unimportant by the following considerations. First, while the reported yields of alkylated products vary considerably, yields of 90% or greater have been obtained in preparations of 9-isopropyl-9,10-dihydroanthracene,[2c] 9-isopropyl-10-ethyl-9,10-dihydroanthracene,[2a] and 9-isopropyl-10-*tert*-butyl-9,10-dihydroanthracene[2c] using secondary halides. Second, in all cases comparisons are made between the rate of the dihydroanthracenyl anion and the diphenylmethyl anion with the same halide. In related systems there are data that show that the amount of elimination with the two types of anions is comparable.[11] Finally, in reactions of related "naked anions" with 2-chloro- and 2-bromooctane, the amount of elimination products was determined to be 3 and 17%, respectively.[12] Thus it is unlikely that the amount of elimination in the several systems is either substantial or that it differs significantly from that of the reference anion.[13]

Conclusion

For reaction with the primary halides, the results can be accommodated in a straightforward manner. The preponderant attack by anion is in the preferred conformer of axial–axial orientation (I). This is true whatever the exact nature of the anion in the absence of halide, whether quasiplanar, pseudoaxial, rapidly equilibrating, or a complex mixture of ion-pair equilibria.[2c] There is little difference in the steric effect of the model compound and that with a hydrogen in the 9 position. With increasing size of the substituent in the 9 position two effects are noted, the overall rate decreases and increasing amounts of the trans compound are formed. Thus the 9-alkyl group in an axial position hinders axial attack as would be expected.

Reaction with secondary halides, accompanied by both slower reaction rates and product compositions of mainly trans stereochemistry, can be explained by two different schemes. First, there is an increasing and dominant attack of anion in the conformer with the lithio derivative in the equatorial orientation. This allows the alkyl group to remain in the more favorable axial orientation but provides less charge delocalization. Or second, attack is by the conformer with increasing amounts of the alkyl group in the equatorial position, thus allowing the anion to maintain the favorable axial orientation. It is possible that both schemes contribute depending on the reactants. In the present study, the pattern of a rate difference between the model compound and the unsubstituted anion, together with a dampened steric effect, is more consistent with the scheme of quasiequatorial anion attack.[14]

Experimental Section

Materials. The alkyl halides were obtained from Eastman Organic Chemical, purified by trap-to-trap transfer through calcium hydride, and stored over calcium hydride. Chromoquality THF from Matheson Coleman and Bell was distilled from benzophenone sodium ketyl immediately before using. *n*-Butyllithium (1.6 M in hexane) was obtained from Aldrich Chemical Co., Inc. Diphenylmethane was obtained from Matheson Coleman and Bell and distilled before using (fraction bp 255–265 °C collected (lit.[15] bp 262 °C)).

Kinetic Procedures. Kinetic measurements were determined as follows. THF (50 mL) was distilled from sodium benzophenone ketyl into a side-arm flask, fitted with a septum stopper and containing I or II (0.5 mmol) under an argon atmosphere. To the stirred solution an equimolar amount of *n*-butyllithium was added dropwise by sy-

ringe through the septum to give the characteristic deep red color of the anion. THF (50 mL) was distilled into another side-arm flask containing a carefully weighed amount of halide (1.0 to 10.0 mmol) also under an argon atmosphere.

The rapid-mixing stopped flow apparatus, thermostated at 20 °C, was flushed with several aliquots of dry THF and then with the anion solution until the effluent in the stop syringe maintained the anion color. Solutions of anion and halide were transferred to the apparatus by gas-tight syringes in a manner that excluded air or moisture. After several flushes of the respective chambers by the anion and halide solutions, oscilloscope traces of multiple runs were photographed. Each photograph was analyzed by measuring the intensities at various times and obtaining the pseudo-first-order slope by computer analysis.

9,10-Dihydroanthracene. To a solution of anthracene (36 g, 20 mmol) in THF (300 mL) and an excess of sodium (20 g) was added methanol (75 mL) over a period of 3 h. The product was isolated and recrystallized twice from ethanol to give 27 g, mp 107–108 °C (lit.[10b] mp 108 °C).

Alkylation of 9-Alkyl-9,10-dihydroanthracene. All the reactions were conducted in the following way. To the 9-alkyl (5 mmol) dissolved in 100 mL of THF and maintained under an atmosphere of argon at −40 °C was added over 30 min *n*-butyl lithium (5 mmol, 2.3 M in hexane). The solution turned red immediately. After 30 min of stirring, the alkyl halide (2 mL in 40 mL of THF) was added drop by drop. After decolorization and extraction with ether, the reaction products were analyzed by gas chromatography (3 m, 10% silicon QF, on Varaport 100–120, at 130 °C). The products were separated by chromatography on an activated aluminum column. The isomers were first collected together and the purity was checked by mass spectroscopy. A second chromatography using petroleum ether eluted first the trans isomer, next the cis isomer, and finally 9-alkyl-9,10-dihydroanthracene.

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Registry No.—9,10-Dihydroanthracene, 613-31-0; anthracene, 120-12-7.

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(13) In control experiments under the conditions of the kinetic experiments we have shown that the major reaction between diphenylmethyllithium and 2-bromohexane is substitution. Additionally work in progress at Bordeaux indicates similar amounts of substitution products with the dihydroanthracenyl anions under kinetic conditions compared to product conditions with primary and secondary halides.
(14) Referees suggest the possibility of an electron transfer mechanism for the secondary halides. Our experiments and discussion centers on the preferential stereochemistry of the anion attack and cannot distinguish between one- or two-electron transfer.
(15) L. F. Fieser, "Experiments in Organic Chemistry", D. C. Heath and Co., Boston, Mass., 1975, p 157.

Oxidative Cleavage of α-Ketols and Related Ketones with Alkaline Hydrogen Peroxide[1]

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The oxidative C–C cleavage of α-ketols $R_1COC(OH)R_2R_3$ (1) has been found to proceed smoothly with alkaline hydrogen peroxide in aqueous methanol affording high yields of ketones $R_2R_3C{=}O$ and carboxylic acids R_1CO_2H. The reaction obeys second-order kinetics: $v = k_2[R'OO^-][\text{ketol}]$, where $R'OO^-$ may be t-$BuOO^-$ or $PhCO_3^-$ in place of HOO^-. The cleavage of aromatic ketones (R_1 = Ph) is much faster than that of aliphatic ketones (R_1 = Me). The relative rate with $PhCO_3^-$ (a stronger oxidant) vs. HOO^- varies from 0.14 to 2.8 with changing ketols. These results are explained by the rate-determining concerted fragmentation of the C=O adduct **6** (Scheme I). Acyloins (**1**, R_2 = H) were cleaved to carboxylic acids and aldehydes R_3CHO, which were further oxidized to acids. α-Amino ketones **3** were cleaved to ketimine or ketone. α-Methoxy-α,α-diphenylacetophenone (**2**) is also cleaved, the rate being only $^1/_{2000}$ that of the corresponding α-ketol **1a** ($R_1 = R_2 = R_3$ = Ph), to benzophenone dimethyl acetal and α-hydroperoxy-α-methoxydiphenylmethane, suggesting an intermediacy of α-alkoxy carbonium ion. Alkaline hydrogen peroxide is advantageous in the selective cleavage of α-ketols in comparison with the other ordinary oxidants.

Ordinary reagents for the oxidative cleavage of α-hydroxy ketones (α-ketols) are periodic acid in aqueous solution and lead tetraacetate in organic solvents.[2] The other known reagents are bromine,[3] peracids,[4] and nickel peroxide.[5] We wish to report here that alkaline hydrogen peroxide is a mild and effective oxidant for the cleavage of α-ketols and related ketones. This reagent is inactive to 1,2-glycols, contrary to the case with periodic acid or lead tetraacetate, and hence may cleave α-ketols selectively even in the presence of a 1,2-dihydroxy group.

Results and Discussion

Oxidative Cleavage of α-Phenylbenzoins. α-Phenylbenzoin **1a** ($R_1 = R_2 = R_3$ = Ph) can be easily oxidized by al-

Table I. Rates of Oxidative Cleavage of α-Phenylbenzoin 1a by Alkaline Hydrogen Peroxide in 80% Aqueous MeOH at 25.0 °C[a]

Initial concentrations, M [α-ketol]	[H_2O_2]	[NaOH][a]	HOO^-, %[b]	$10^2 k_{obsd}$,[c] $M^{-1} s^{-1}$
		(A) Effect of [α-ketol] and [H_2O_2]		
0.05	0.10	0.30	79	6.65
0.05	0.05	0.30	79	6.71
0.05	0.025	0.30	79	6.31
0.07	0.04	0.30	79	6.89
		(B) Effect of [NaOH]		
0.05	0.05	0.025	24	~1.53
		0.05	39	2.38
		0.10	56	4.14
		0.20	72	6.05
		0.30	79	6.71
		0.50	86	7.20
		(C) Oxidation with *t*-BuOOH in place of H_2O_2		
0.05	0.05	0.1	10[d]	0.49
		0.2	18[d]	1.03
		0.4	31[d]	2.12

[a] [NaOH] indicates total alkali concentration added as aqueous NaOH containing 0.05 mol % EDTA based on [NaOH]. Since MeOH is more acidic than water, most of the added base exists as MeO^- rather than HO^-. [b] Percent dissociation of R'OOH was obtained from the K_6 values of 12.7 and 1.13 M^{-1} for R' = H and *t*-Bu, respectively, in 80% MeOH at 25 °C. [c] Second-order plots vs. time were linear up to 80% conversion; probable error ±5%. [d] *t*-$BuOO^-$.

kaline hydrogen peroxide to give high yields of benzophenone and benzoic acid in aqueous MeOH at 25 °C (eq 1). The re-

$$\underset{\text{1}}{R_1C(=O)CR_2R_3(OH)} + H_2O_2 \xrightarrow[\text{aq MeOH}]{\text{NaOH}} R_1CO_2H + R_2R_3C{=}O \quad (1)$$

action is complete within 1 h with a 1:1 stoichiometry of 1a and H_2O_2. The rate was followed iodometrically and expressed as eq 2 as obvious from Table I(A).

$$v = k_{obsd}[H_2O_2][\text{ketol}] \quad (2)$$

The k_{obsd} value increases with increasing [NaOH] and approaches a constant at high base concentrations [Table I(B)]. All the reactions were started by adding aqueous NaOH containing 0.05 mol % EDTA to avoid a possible redox reaction, although the presence or absence of EDTA was not essential under our conditions. The oxidation with alkaline *t*-BuOOH is considerably slow at low base concentrations but has a comparable rate at high alkalinity [Table I(C)]. The reaction does not occur in neutral solution or in the presence of sodium acetate.

The cleavage reaction of substituted α-phenylbenzoins proceeds similarly to give benzophenone in 80–95% yields. The rates are faster for the ketols with electron-attracting groups, affording a Hammett's ρ value of 1.96 (vs. σ) with a correlation coefficient $r = 0.995$ (Table II). The positive ρ value is comprehensible in view of the substituent effect for a nucleophilic addition to C=O, which is of the similar magnitude with other additions to C=O (i.e., ρ = 2–3).[6]

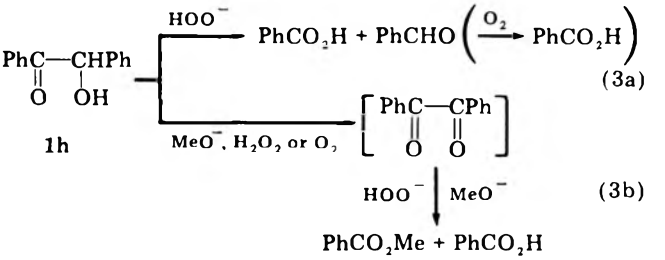
Cleavage of Other α-Ketols and Related Compounds. Various α-ketols are likewise cleaved by alkaline hydrogen peroxide to give carboxylic acids and ketones or aldehydes (Table III). When R_2 = H (**1i,j**), produced aldehydes are further oxidized to acids. The base-catalyzed oxidation or autoxidation (eq 3b) also occurs competitively for the case of benzoin **1h**, affording benzoic acid, benzaldehyde, and methyl benzoate. The formation of the ester occurs probably via

Table II. Oxidative Cleavage of Substituted α-Phenylbenzoins by Alkaline Hydrogen Peroxide[a]

Ketol	Registry no.	R_1 in $R_1C(=O)CPh_2(OH)$	$10^2 k_{obsd}$,[b] $M^{-1} s^{-1}$
1b	4338-69-6	*p*-MeOPh	1.16
1c	4625-47-2	*p*-MePh	1.43
1a	4237-46-1	Ph	4.14
1d	63704-18-7	*p*-ClPh	11.0
1e	63704-19-8	*m*-ClPh	18.2

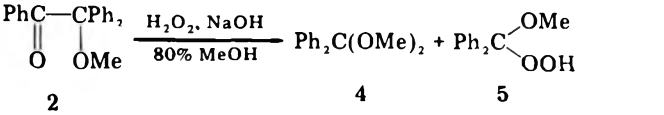
[a] Reaction with [ketol] = [H_2O_2] = 0.05 M, [NaOH] = 0.10 M, and [EDTA] = 10^{-4} M in 80% MeOH at 25.0 °C. Ph = C_6H_5 or C_6H_4. Substituted phenylbenzoins afforded benzophenone in 80–95% yields and the corresponding benzoic acids which were identified as methyl esters. [b] Average of two or three determinations. Plot of log k_{obsd} vs. σ gives ρ = 1.96 (r = 0.995).

benzil as shown in eq 3b.[7] While the autoxidation of benzoin is a slow reaction with base alone,[8] the present oxidation with alkaline H_2O_2 is complete within several minutes under N_2 and hence the oxidation may proceed also via the reaction of H_2O_2 with the enolate ion of **1h** to afford benzil.



The rates of cleavage are much faster for the ketols with R_1 = Ph than that with R_1 = Me (**1g**); when R_2 = H, the order of reactivities is **1h** > **1i** ≫ **1j**. Mandelic acid (**1k**) is also cleaved slowly with excess H_2O_2. This reaction is probably homolytic in view of the low (<30%) selectivity vs. consumed H_2O_2, the poor reproducibility of the yield, and the tendency of alkaline H_2O_2 to radical decomposition.[9a] Presumably, the reaction proceeds via the abstraction of α-hydrogen by HO· or HOO· produced from the spontaneous decomposition of alkaline H_2O_2. Similar oxidative cleavage was recently reported for ketols and α-hydroxy acids having α-hydrogen using excess superoxide ion in nonaqueous solvents.[9b]

Table IV lists the reactions of HOO^- with α-methoxy and α-amino ketones. The reaction of α-methoxy-α,α-diphenylacetophenone **2** is 2000 times slower than that of **1a**, and the major product is not benzophenone but its dimethyl acetal **4**. Excess H_2O_2 gives a significant yield of α-hydroperoxy-α-methyldiphenylmethane (**5**) (Table IV).



The cleavage of α-amino ketones is also observed; the oxidation of **3a** (X = NH_2) is fast to give high yield of benzophenonimine ($Ph_2C{=}NH$). The reaction of α-methylamino ketone **3b** (X = NHMe) is considerably slower (ca. 0.1), affording benzophenone, a hydrolysis product of imide. The reaction of α-dimethylamino ketone **3c** (X = NMe_2) is too slow probably because of the steric retardation by dimethyl group on the C=O addition.

The oxidative cleavage with alkaline H_2O_2 is thus shown to be effective for α-hydroxy, α-methoxy, α-amino, and α-methylamino ketones. Since 1,2-glycols are easily cleaved by periodate or lead tetraacetate[2] and C=C is attacked by bromine or peracid, this cleavage of α-ketols with HOO^- is an effective reagent especially when the substrates, α-ketols,

Table III. Rates and Products from the Oxidative Cleavage of Various α-Ketols by Alkaline Hydrogen Peroxide in 80% MeOH at 25 °C[a]

	Registry no.	$R_1COC(OH)R_2R_3$			$10^2 k_{obsd}$,[b] $M^{-1} s^{-1}$	Products (%)[c]	
		R_1	R_2	R_3		R_1CO_2H	$R_2R_3C{=}O$
1a	7473-98-5	Ph	Ph	Ph	6.52	86	97
1f	3155-01-9	Ph	Me	Me	2.62	89	69[d]
1g	119-53-9	Me	Me	Ph	0.338	[e]	88
1h	513-86-0	Ph	H	Ph	~22[f]	110–130[f]	30–50[f]
1i	4444-11-5	Me	H	Me	~4.47[g]	[e]	18[d,g]
1j	90-64-2	n-C_7H_{15}	H	n-C_7H_{15}	0.06	~180	Trace
1k[h]	5457-37-4	HO	H	Ph[h]	<0.01	$PhCO_2H$, 10–48%[h]	

[a] Reaction with 0.20 M NaOH, 0.05 M α-ketol, 0.06 or 0.05 M H_2O_2, and 0.1 mM EDTA. [b] Second-order rate constant with $[H_2O_2]$ = 0.05 M. [c] Reaction with 0.06 M H_2O_2 and reaction time of 2 h for **1a**, **1f**, **1h**, **1i**, and 30 h for the other substrates. Products were determined by GLC analysis, benzoic acid being down after methylation with diazomethane. [d] Determined as 2,4-dinitrophenylhydrazone. [e] Not determined. [f] Base-catalyzed autoxidation of benzoin and benzaldehyde occurred simultaneously. Hence, k_{obsd} value was not determined accurately. Approximately 20% of methyl benzoate was also produced. [g] The rate constant was obtained from the initial reaction up to 40% conversion, since the consumption of H_2O_2 increased gradually owing to the further reaction with acetaldehyde produced. [h] Mandelic acid with 0.10 M H_2O_2 and 0.20 M NaOH afforded 10–49% of benzoic acid; 90–49% of the starting material was recovered. This oxidation is probably homolytic, since the consumption of H_2O_2 was fast in the absence of EDTA and the reproducibility of the conversion was low.

Table IV. Oxidative Cleavage of α-Methoxy and α-Amino Ketones with Alkaline H_2O_2[a]

	Registry no.	$R_1COCXR_2R_3$				$10^2 k_{obsd}$,[b] $M^{-1} s^{-1}$	Products (%)[c]
		R_1	X	R_2	R_3		
1a	5457-37-4	Ph	OH	Ph	Ph	6.52 (47.1)	$Ph_2C{=}O$, 95%
2		Ph	OMe	Ph	Ph[d]	0.0035	$Ph_2C(OMe)_2$, 43%; $Ph_2C{=}O$, 8%
2		Ph	OMe	Ph	Ph[e]		$Ph_2C(OMe)_2$, 50%; $Ph_2C(OMe)OOH$, 45%; $Ph_2C{=}O$, 3%
3a	56140-60-4	Ph	NH_2	Ph	Ph	(26.2)	$Ph_2C{=}NH$, 93%
3b	63704-20-1	Ph	NHMe	Ph	Ph	0.32 (3.0)	$Ph_2C{=}O$,[g] 90%
3c	63704-21-2	Ph	NMe_2	Ph	Ph	<0.1[h] (<0.5)	$Ph_2C{=}O$, <2%[h]

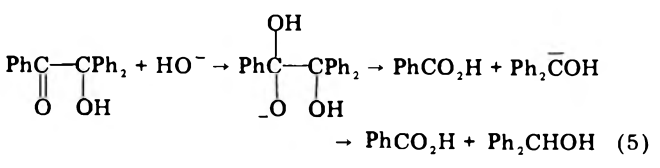
[a] Reaction with [substrate] = $[H_2O_2]$ = 0.025 M, [NaOH] = 0.20 M, and [EDTA] = 0.1 mM in 80% MeOH at 25 °C if not noted otherwise. [b] The values in parentheses are those in 30% MeOH–20% H_2O–50% DMF (vol %). [c] Reaction with 0.05 M H_2O_2. Products were determined by GLC and/or NMR analysis. Benzoic acid was not determined. [d] Reaction with 0.10 M H_2O_2 for 65 h; 45% of the starting ketone was recovered. [e] Reaction with 13 M H_2O_2 for 42 h resulted in 99% conversion. [g] Product was not an imine but benzophenone produced by its hydrolysis. [h] The reaction was very slow, while the presence of the amine accelerated considerably the base-catalyzed decomposition of H_2O_2.

contain such a group as *gem*-diol or C=C. The solvents may be water, aqueous alcohol, or aqueous DMF.

Effect of Solvent. The solvent effect was examined for α-ketol **1f** in order to distinguish (a) rate ∝ $[R'OO^-]$ from (b) rate ∝ $[R'OOH][HO^-]$. The rate in 50% MeOH is faster by a factor of 2 than that in 80% MeOH (Table V). This factor is always the same when 0.1 or 0.2 M NaOH is used or when *t*-BuOOH is used in place of H_2O_2. The same is true for the case of **1g**.

Table V also lists the molar ratio of $R'OO^-$:R'OOH together with the K_6 value determined from UV absorbance at 280 nm. Apparently, k_{obsd} values are parallel with $[R'OO^-]$ and not with $[R'OOH][HO^-]$; the change from 80% MeOH to 50% MeOH decreases both [R'OOH] and $[HO^-]$ and hence it is difficult to explain the duplicate increase in k_{obsd} by means of the relation: rate ∝ $[R'OOH][HO^-]$.

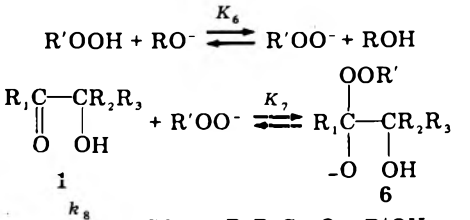
Mechanism. A similar type of reaction is the base-catalyzed α-fission of α-ketols:[10]



$$\rightarrow PhCO_2H + Ph_2CHOH \quad (5)$$

However, this reaction is only possible by heating above 60 °C. The present oxidative cleavage proceeds smoothly at room temperature and may be written as Scheme I containing a rate-determining fragmentation of C=O adduct **6** (eq 8). This scheme leads to a rate equation

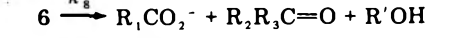
Scheme I[a]



$$R'OOH + RO^- \overset{K_6}{\rightleftharpoons} R'OO^- + ROH \quad (6)$$

$$R_1C(=O)CR_2R_3(OH) + R'OO^- \overset{K_7}{\rightleftharpoons} R_1C(OOR')(O^-)CR_2R_3(OH) \quad (7)$$

i **6**



$$6 \xrightarrow{k_8} R_1CO_2^- + R_2R_3C{=}O + R'OH \quad (8)$$

[a] R' = H, *t*-Bu, or PhCO; R = H or Me.

$$v = k_{obsd}[R'OOH][ketol] = k_2[R'OO^-][ketol] \quad (9)$$
$$= k_8K_7[R'OO^-][ketol]$$

For the case of **1a** in 80% MeOH, the relation of k_{obsd} vs. [NaOH] can well be reproduced by assuming k_2 = 0.079 $M^{-1} s^{-1}$ for HOO^- and 0.057 $M^{-1} s^{-1}$ for *t*-$BuOO^-$ (see Figure 1). The positive ρ value of 1.96 is consistent with Scheme I, reflecting the substituent effect in the nucleophilic addition to C=O.[6] The rate equation (eq 9) satisfies the solvent effect in Table V.

Rate-Determining Step. The following consideration leads to a conclusion that the rate-determining step is not the addition to C=O (eq 7) but the fragmentation of the adduct **6** (eq 8). (i) The reactivity order, **1a** > **1f** ≫ **1g** (i.e., benzoyl ≫ acetyl), is abnormal since nucleophilic additions to acetyl are generally much faster than those to benzoyl.[11] The observed order is comprehensible only if the addition is not rate

Table V. Solvent Effect on the Reaction of PhCOC(OH)Me$_2$ 1f with Alkaline H_2O_2 or *t*-BuOOH in Aqueous MeOH[a]

R'OOH	[NaOH],[b] M	Solvent,[c] % M	K_6[d]	R'OO$^-$:R'OOH[e]	$10^2 k_{obsd}$,[f] M^{-1} s^{-1}
HOOH	0.10	80	12.7	56:44	1.76
		50	30.2	75:25	3.68
	0.20	80	12.7	72:28	2.62
		50	30.2	86:14	4.47
t-BuOOH	0.20	80	1.13	18:82	0.331
		50	3.24	39:61	0.696

[a] Reaction with [1f] = [R'OOH] = 0.050 M at 25.0 °C. [b] See footnote *a* in Table I. [c] Vol % of aqueous methanol. [d] Determined from UV absorbance at 280 nm at 25 °C. [e] Molar ratio of R'OO$^-$:R'OOH was calculated from K_6 values listed. [f] Average of two to six determinations.

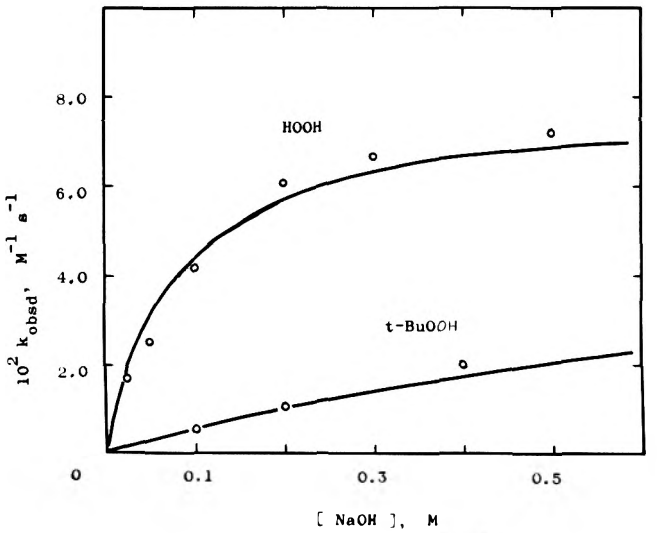


Figure 1. Plots of k_{obsd} vs. [NaOH] for the oxidative cleavage of **1a** in 80% MeOH at 25 °C (see Table I for data). Solid lines were calculated from k_2 = 0.079 M^{-1} s^{-1} and K_6 = 12.7 M^{-1} for H_2O_2 and k_2 = 0.057 M^{-1} s^{-1} and K_6 = 1.13 M^{-1} for *t*-BuOOH.

Table VI. Comparison of the Rates between HOO$^-$ and PhCO$_3^-$ in 80% MeOH at 0 °C[a]

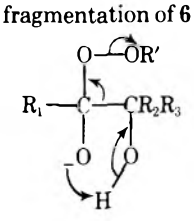
α-Ketol (R_1, R_2, R_3)	$10^2 k_2$,[b] M^{-1} s^{-1} HOO$^-$	PhCO$_3^-$
1a (Ph, Ph, Ph)	1.10	0.152
1f (Ph, Me, Me)	0.585	1.65
1g (Me, Me, Ph)	0.103	0.098
1h (Ph, H, Ph)[c]	~1.55	~1.34
PhCOC(OOH)Ph$_2$[d]	10.0[e]	

[a] Reaction with [ketol] = [oxidant] = 0.025 M, [NaOH] = 0.20 M, and [EDTA] = 0.1 mM. Perbenzoate ion afforded similar yields of the products as in the case of H_2O_2, except that methyl benzoate was formed in 10–20% yields via the reaction of the peracid with MeO$^-$. [b] Second-order rate constant calculated from $v = k_2$[R'OO$^-$][ketol]; the dissociation of H_2O_2 into HOO$^-$ is 72%. [c] Reaction in 90% MeOH gave 35–50% yields of PhCHO together with 10–40% of PhCO$_2$Me. [d] Alkaline decomposition of α-hydroperoxy ketone with 0.20 M NaOH in 80% MeOH in the absence of oxidant. [e] Second-order rate constant for the reaction with HO$^-$ from $v = k_2$[α-HOO-ketone][HO$^-$]. [HO$^-$] was estimated from the acidity difference hetween H_2O and MeOH (see ref 14 and 21).

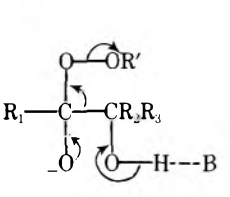
determining. (ii) The reaction of PhCO$_3^-$, an oxidant much stronger than HOO$^-$, is faster for **1f** but slower for the cases of **1a** and **1h** than that of HOO$^-$ (Table VI). If the C=O addition were slow, the order should be HOO$^-$ > PhCO$_3^-$,[12a] which is not the case. The rate-determining fragmentation of **6** may explain the observed variable order in reactivity; that is, the overall rate is governed by the product K_7k_8 and compensated with each other. This is because the relative order of K_7 is probably HOO$^-$ > PhCO$_3^-$ but k_8 for PhCO$_3^-$ is much faster than that for HOO$^-$ because the pK_a of the departing PhCO$_2^-$ is 12 units higher than that of HO$^-$ in the fragmentation step. (iii) The base-catalyzed decomposition of PhCOC(OOH)Ph$_2$ with HO$^-$ gave k_{obsd} = 0.10 M^{-1} s^{-1} in 80% MeOH at 0 °C (Table VI).[13] This value is much higher than that (0.011 M^{-1} s^{-1}) of **1a** and HOO$^-$ (Table VI). Since the α-effect for C=O addition is large, i.e., HOO$^-$ ≫ HO$^-$,[12] the rate-determining fragmentation of **6** can only explain why the reaction of HO$^-$ with the α-hydroperoxy ketone is much faster than that of HOO$^-$ with **1a**, a less hindered ketone. Thus, it is concluded that the fragmentation of the C=O adduct (eq 8) is rate determining.

Fragmentation of C=O Adduct 6. The transition state for the fragmentation of **6** may be written as **7a** or **7b** (B = base or solvent).[15] Apparently, the hydroxyl group plays an important role in the transition state, since the reaction of α-methoxy ketone **2** is quite slow. The choice of **7a** or **7b** is not straightforward, but the following examinations suggest **7a** is more probable. The addition of 50% DMF, an aprotic basic solvent, accelerated the reaction by factors of 4–10 (Table IV), while the effect of 10–20% DMF is rather small (within a factor of 1.5);[16a] this nonlinearity between k_{obsd} and [DMF] seems to deny the reaction via **7b** of general base catalysis by DMF. No observation of a general base catalysis by HO$^-$ at a high concentration (0.5 M) is also consistent with **7a** rather than **7b**. The nonlinear acceleration by DMF is explicable by solvation of DMF by the hydroxylic solvent, resulting in a decrease of intermolecular hydrogen bonding by MeOH or H_2O to the adduct anion **7** and then in an increase of naked [**7a**].[16b]

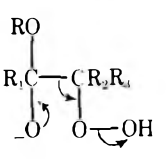
The facile fragmentation of **6** is probably caused by the concerted C–C and O–O fission, which is contrary to the α-fission of α-ketol with HO$^-$ (eq 5). A preference of Ph ≫ Me in the substituent effect of R_1 suggests a conjugation of phenyl with the developing carbonyl group in **7a**. The effect of an R_2 or R_3 group is much smaller, which indicates a less important resonance with the developing C=O of the right-hand carbon in **7a**. A related transition state **8** was reported for the base-catalyzed decomposition of α-hydroperoxy ketones,[14] where



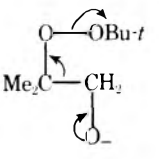
7a



7b

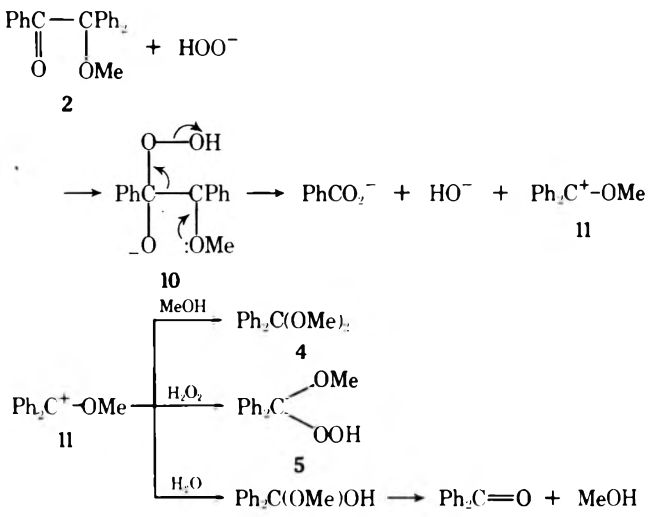


8



9

Scheme II



a phenyl group always accelerated the fragmentation by any substitution in R_1, R_2, and R_3. The cause of this difference is not obvious at present. A related case of peroxide reaction is the fragmentation of **9** to acetone, formaldehyde, and t-BuO^-, the rate of which was assumed to be 0.5 s^{-1} (40% MeOH, 30 °C).[17] The common driving force for the facile decomposition of **7**, **8**, and **9** is surely the concerted carbonyl-forming fragmentation together with the pushing effect by the α-oxy anion. The latter effect is well known in other peroxide reactions[18] and in benzilic acid rearrangement.[19]

Mechanism of Cleavage of α-Methoxy Ketone (2). The reaction of HOO^- with α-methoxy ketone **2** gave acetal **4** and in the presence of excess H_2O_2 hydroperoxide **5** (eq 4). The results are explicable by Scheme II. One of the driving forces for the concerted fragmentation of **10** is the high stability of the α-alkoxy carbonium ion **11**. Cation **11** is then trapped by neutral solvents but not by anions. This is based on the following examination between reactions of **2** with 0.1 and 13 M H_2O_2 in the presence of 0.20 M NaOH. There is no large difference between the concentrations of anions; i.e., $[HOO^-]$ = 0.085 and 0.108 M, $[MeO^-]$ = 0.094 and 0.075 M, and $[HO^-]$ = 0.021 and 0.017 M for the reactions with 0.1 and 13 M H_2O_2, respectively.[20] Thus, the only one large difference between the two conditions is the concentration of neutral H_2O_2, i.e., $[H_2O_2]$ = 0.15 and 12.9 M, which should be reflected on the product distribution (see Table IV).

An analogous mechanism as Scheme II will be written for the reaction of α-amino ketone **3**, since amines are much less weak acids[22] and have lower ionization potentials than alcohols or ethers.[23] The large difference of the acidity between NH_2 and OH makes it difficult to explain the observed comparable rates between **1a** and **3a** by the same mechanism as Scheme I.

Experimental Section

Melting and boiling points were not corrected. IR and NMR spectra were recorded on a Perkin-Elmer 337 spectrophotometer and a Hitachi R-24B NMR spectrometer using Me_4Si as an internal standard. The GLC analysis was performed with a Yanagimoto 550-F gas chromatograph.

Materials. α-Phenylbenzoin **1a** was obtained by the reaction of benzil with PhMgBr,[24] mp 87–88 °C (lit.[24] 87–88 °C). Substituted phenylbenzoins **1b–e** were synthesized via the α-bromination of the corresponding α,α-diphenylacetophenones[14] followed by its hydrolysis. Thus, α,α-diphenyl-p-methoxyacetophenone (2.0 g, 6.6 mmol) in 20 mL of dioxane was brominated with 0.5 mL (10 mmol) of bromine at 40 °C for 2 h. After the addition of 10 mL of water, the mixture was refluxed for 30 min, poured into water, and extracted with benzene (30 mL). After drying (Na_2SO_4) and condensation, n-hexane was added to precipitate the crude α-ketol **1b**. Recrystallization from benzene–n-hexane gave 1.5 g (71%) of α-phenyl-p-methoxybenzoin **1b**: mp 132–133.5 °C; IR (Nujol) 3340 (OH), 1650 cm^{-1} (C=O). Anal. Calcd for $C_{21}H_{18}O_3$: C, 79.22; H, 5.70. Found: C, 79.02; H, 5.79.

Other α-phenylbenzoins **1c–e** were obtained by a similar method, as in the case of **1b**, and crystallized from n-hexane. α-Phenyl-p-methylbenzoin (**1c**) was synthesized in 76% yield; mp 57–59 °C (lit.[25] 57–59.5 °C). α-Phenyl-p-chlorobenzoin (**1d**) (92% yield): mp 87–88 °C; IR (nujol) 3400 (OOH), 1650 cm^{-1} (C=O). Anal. Calcd for $C_{20}H_{15}O_2Cl$; C, 74.42; H, 4.99. Found: C, 73.96; H, 4.85. α-Phenyl-m-chlorobenzoin (**1e**): mp 58–60 °C; IR (nujol) 3450 (OH), 1670 cm^{-1} (C=O). Anal. Calcd for $C_{20}H_{15}O_2Cl$: C, 74.42; H, 4.99. Found: C, 73.88; H, 4.90.

α-Hydroxyisobutyrophenone (**1f**) was prepared similarly from ketone. Thus, bromine (19.2 g, 0.12 mol) was added dropwise to isobutyrophenone (14.8 g, 0.1 mol) in 40 mL of dioxane and stirred for 1 h at room temperature. Ethanol (10 mL), water (50 mL), and NaOH (8 g, 0.2 mol) were then added and refluxed for 3 h. Extraction and distillation gave the ketol **1f** (80% yield): bp 118–120 °C (10 mmHg) [lit.[26] bp 125 °C (12 mmHg)]; IR (film) 3450 (OH), 1670 cm^{-1} (C=O); NMR (CCl_4) δ 1.52 (s, 6 H, CH_3), 3.80 (s, 1 H, OH), 7.2–7.5 (m, 3 H, m- and p-H), 7.8–8.0 (m, 2 H, o-H).

2-Phenylacetoin (**1g**),[27] capryloin (**1j**),[28] and α-methoxy-α,α-diphenylacetophenone (**2**)[29] were prepared by the literature methods. **1g**: bp 108–110 °C (3 mmHg); IR (film) 3450 (OH), 1710 cm^{-1} (C=O); NMR (CCl_4) δ 1.66 (s, 3 H, α-CH_3), 2.00 (s, 3 H, CH_3C=O), 4.12 (s, 1 H, OH), 7.1–7.4 (m, 5 H, ArH). **2**: mp 91–92 °C (benzene–n-hexane); NMR (CCl_4) δ 3.03 (s, 3 H, OCH_3), 7.0–7.5 (m, 13 H, ArH), 7.8–8.0 (m, 2 H, o-H). Acetoin (**1i**) was commercial grade.

α-Amino-α,α-diphenylacetophenone (**3a**) was easily obtained by refluxing α-bromo ketone in dioxane–28% aqueous ammonia (2:1) for 1 h. The reaction mixture was poured into water to precipitate the amino ketone; recrystallization from MeOH gave 53% of **3a**: mp 133–134 °C (lit.[30] 132 °C).

The same method with aqueous methylamine gave crude α-methylamino-α,α-diphenylacetophenone (**3b**); the crude amino ketone was extracted with 1 N aqueous HCl and then, after addition of excess NaOH, with CH_2Cl_2. Evaporation of the solvent and 3 days' standing led to crystallization of **3b**, which was recrystallized from MeOH to give 40% yield of **3b**: mp 90–92 °C; IR (film) 3350 (NH), 1675 cm^{-1} (C=O); NMR (CCl_4) δ ~2.0 (br s, 1 H, NH), 2.05 (s, 3 H, NCH_3), 7.0–7.6 (m, 15 H, ArH). Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 82.94; H, 6.50; N, 4.76.

α-Dimethylamino-α,α-diphenylacetophenone (**3c**) was obtained by the same method using aqueous dimethylamine. Prolonged standing of the neat sample led to crystallization of **3c**: mp 82–84 °C; IR (film) 1670 cm^{-1} (C=O); NMR (CCl_4) δ 2.08 [s, 6 H, $N(CH_3)_2$], 7.0–7.3 (m, 13 H, ArH), 8.1–8.3 (m, 2 H, o-H). Anal. Calcd for $C_{22}H_{21}NO$: C, 83.77; H, 6.71; N, 4.44. Found: C, 80.86; H, 6,78; N, 4.67.

Rates. To a mixture of α-ketol **1** (5 mL of a 0.10 M solution in MeOH), H_2O_2 (1 mL of a 0.5 M solution in water), and MeOH (3 mL) was added 1 mL of 2.0 M aqueous MeOH containing 1 mL of EDTA at 25.0 °C. Aliquots (1 mL) were taken out at appropriate time intervals, and the remaining hydrogen peroxide was titrated iodometrically using sodium molybdate catalyst in MeOH–H_2O–AcOH (2:1:1). The second-order rate constant, k_{obsd}, was calculated according to eq 2, and the reproducibility was within ± 5% for most runs.

Products. Products were identified and determined by GLC analysis, and by IR, NMR, and UV spectra in comparison with an authentic samples. GLC analyses were conducted at 80–250 °C using three different columns (1 m): PEG 20M, 2% on Chamelite CK; Silicone SE30, 10% on Chromosorb; Apiezone grease L, 15% on Celite 545. Carboxylic acids were determined after methylation with diazomethane.

For the case of ketols **1a–e**, a simple extraction with CH_2Cl_2 from water afforded benzophenone (over 90% yield). In the oxidative cleavage of benzoin **1h**, yields of PhCHO ranged from 30 to 50%, which were not altered by the reaction under N_2 or at 0 °C. The formation of methyl benzoate (~20%) indicates a competitive oxidation via benzil (eq 3b).

The oxidation of mandelic acid (**1k**) did not occur with equimolar H_2O_2 and the results in Table III are those with 4 equiv of H_2O_2.

Reaction of α-Methoxy Ketone 2 with Excess H_2O_2. The reaction of **2** with 0.1 M H_2O_2 in the presence of 0.2 M NaOH gave predominantly benzophenone dimethyl acetal **4**, but the reaction with a large excess of (13 M) H_2O_2 resulted in a new hydroperoxide **5**. Thus, **2** (88 mg) in 9 mL of MeOH was oxidized with 1 mL of 50% H_2O_2 and 2 M NaOH at 25 °C for 25 h. The reaction mixture was poured into cold 5% aqueous NaOH and neutral products were extracted with CH_2Cl_2 (10, 5, and 5 mL). Evaporation of the solvent yielded 25 mg (35%) of **4**; GLC retention time and IR and NMR spectra were iden-

tical with those of an authentic sample. The aqueous alkaline solution was neutralized with acetic acid, extracted with CH_2Cl_2, washed with aqueous Na_2HPO_4, and dried with Na_2SO_4. Evaporation of the solvent yielded a crude product, mp 58–60 °C; recrystallization from CCl_4–petroleum ether gave pure α-hydroperoxy-α-methoxydiphenylmethane (**5**) in 30% yield: mp 62–64 °C; IR (film) 3400 (OOH), 1205, 1085 cm^{-1} (C–O); NMR (CCl_4) δ 3.22 (s, 3 H, OCH_3), 7.0–7.5 (m, 11 H, ArH + OOH). The hydroperoxidic proton in NMR spectra is probably overlapped in the aromatic region, since the treatment with D_2O decreased the peak area at 7.0–7.5 by 1 H. The reduction of **5** with KI gave solely henzophenone. The pyrolysis GLC (injection temperature 250 °C) yielded benzophenone and methyl benzoate (2:3 ratio); the formation of the ester suggests the thermal 1,2 shift of the phenyl group in the hydroperoxide.

Reaction of α-Amino Ketone. The reaction of α-amino ketone **3a** with alkaline H_2O_2 was conducted in aqueous MeOH–50% DMF; DMF was added because of the low solubility of **3a**. The reaction mixture was diluted with water and extracted with CH_2Cl_2 to give pure benzophenonimine, $Ph_2C{=}NH$: IR (film) 3430, 3240 (NH), 1670 cm^{-1} (C=N); UV λ_{max} 242 nm in MeOH, 274 nm in 1 N HCl (lit.[31] 275.5 nm). The imine was converted to benzophenone by hot aqueous HCl.

The corresponding methylimine was not ohtained for the case of **3b**, but solely benzophenone, a hydrolysis product, resulted. α-Dimethylamino ketone **3c** gave only a trace amount of benzophenone after 3 days of reaction.

Registry No.—**5**, 63704-22-3; $MeOC_6H_4$-*p*-C(=O)$CHPh_2$, 1889-74-3; MeC_6H_4-*p*-$COCHPh_2$, 41993-27-5; ClC_6H_4-*p*-$COCHPh_2$, 63704-23-4; ClC_6H_4-*m*-$COCHPh_2$, 63704-24-5; $Ph_2C{=}NH$, 1013-88-3; HOOH, 7722-84-1; *t*-BuOOH, 75-91-2; HOO^-, 14691-59-9; $PhCO_3^-$, 33451-32-0; isobutyrophenone, 611-70-1; α-bromo-α,α-diphenylacetophenone, 6905-43-7; ammonia, 7664-41-7; methylamine, 74-89-5; dimethylamine, 124-40-3.

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$$\mathbf{7} \xrightarrow{-R'O^-} R_1CO_2C(OH)R_2R_3 \rightarrow R_1CO_2H + R_2R_3C{=}O$$

We feel that the transition states **7a** and **7b** are the same for the fragmentation or the Baeyer–Villiger reaction. The difference lies only in whether the hemiacetal intermediate $R_1CO_2C(OH)R_2R_3$ is involved or not. Since the base-catalyzed decomposition of hemiacetals is very fast, the choice is difficult. But the relatively smaller difference in the rate between $R'OO^-$ and $PhCO_3^-$ (Table VI) seems to favor the fragmentation mechanism, since the Baeyer–Villiger reaction depends on the nature of peroxides (i.e., stretching of the O–O bond is important in the transition state);[15b] (b) Y. Ogata and Y. Sawaki, *J. Am. Chem. Soc.*, **94**, 4189 (1972).
(16) (a) The 10^2 k_{obsd} values for the cleavage of **1f** with HOO^- in 20% H_2O–80 − *a*% MeOH–*a*% DMF at 25 °C are 2.62, 3.05, 3.80, 6.05, and 13.4 M^{-1} s^{-1} for *a* = 0, 10, 20, 30, and 50% DMF. (b) In fact, the reaction in the presence of over 30% DMF resulted in the precipitation of sodium benzoate. This indicates that the protic solvent (H_2O and MeOH) available to solvate the ion **7a** is significantly decreased by the interaction with DMF. Presumably, the conversion (i.e., desolvation) to naked **7a** occurs dramatically by adding 50% DMF, resulting in the four- to tenfold increase in the rate.
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Marked Normal Salt Effects on the Stereoselectivity of the Ring Opening of an Aryloxirane in Acid Media

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The salt effect on the stereoselectivity of the ring opening of 1-phenyl- (**1a**) and 1-(*m*-chlorophenyl)cyclohexene oxide (**1b**) in acid media has been examined. The syn stereoselectivity of the reactions increases markedly with increasing amounts of added salt. The salt parameters b_c and b_t for the two parallel reactions leading to the cis and to the trans adduct have been calculated. The results show in all cases positive values both for b_c and for b_t, b_c being always much higher than the corresponding b_t. The b_c values are strongly dependent on the solvent, but they appear to be independent of the substituent on the phenyl group of **1**. The relatively large b_c and the corresponding small b_t parameters observed are in accordance with the previously proposed mechanistic scheme.

A detailed knowledge of the mechanisms of the ring opening of aryloxiranes can be of some importance[1] in understanding the chemical behavior of K-region arene oxides,[2] which have been often proposed as the reactive metabolic intermediates responsible for the carcinogenic and mutagenic activity shown by some polycyclic arenes.[3]

Previous work carried out in these laboratories[4-6] has shown that the stereoselectivity observed in the ring opening of aryloxiranes depends to a large extent on several factors, such as the structure, configuration, and conformation of the epoxides, the nature of the aryl group, the solvent, the acid catalyst, the temperature, etc.,[4-6] with the reaction stereochemistry ranging from complete retention to complete inversion of configuration. The results obtained were rationalized through mechanisms[4-6] involving species with a high degree of positive charge on the benzylic carbon. A recent reformulation of these mechanisms[7] (schematized for 1-arylcyclohexene oxides (**1**), see Scheme I) has been proposed, which can be strictly related to the "ion–dipole pair" mechanisms,[8] a close analogue of the classical Winstein ion pair formulation of nucleophilic substitutions and eliminations.[9a,10,11] According to this interpretation the trans products (**5, 7**) arise by attack of a nucleophile (ROH) on the back side[9a,11] of an intramolecular intimate ion–dipole pair **3**, originating from the protonated oxirane (**2**), in which there is "an extended benzylic C–O bond with considerable ionic character".[12] The cis adducts (**6, 8**), on the other hand, can be formed by the collapse of a solvent-separated ion–dipole pair **4**. This collapse should take place with retention of configuration.[12,13]

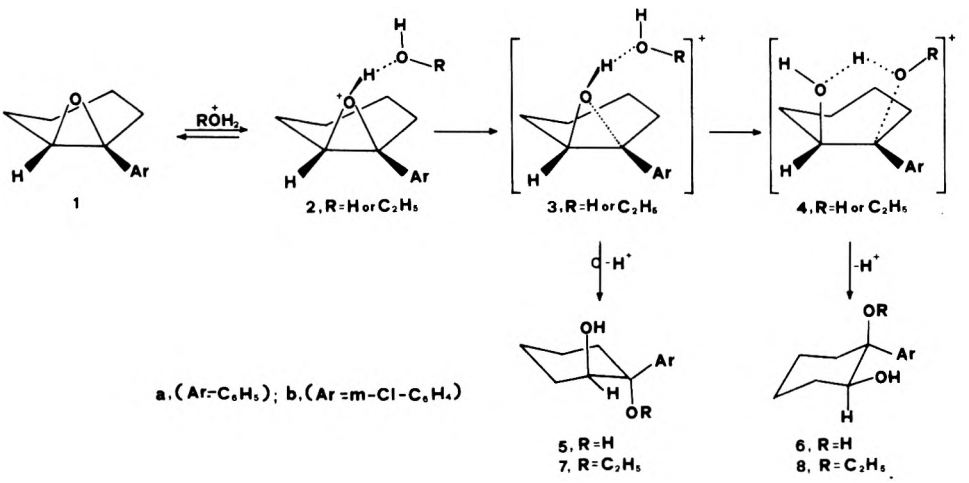
In such a mechanistic scheme, any factor which increases the stability of the benzylic carbocationic center should significantly favor intermediate **4**, and thus increase the syn/anti ratio.[4-7] The addition of inert salts produces a rate acceleration and this result has been quantitatively explained on the basis of an increase in polarity of the medium;[9,14] the addition of a salt should stabilize ionic transition states more than the reactants, and therefore result in an increase of the rate constant.[9,14] Several semiquantitative interpretations of such salt effects have been given,[9,15] but most of the theoretical treatments predict a linear relationship between log k and the concentration of the uni-univalent added salt.[9] This relation has been, however, inadequately tested[9,16] and the dependence of the rate constant on the salt concentration [S] can be better described by the empirical relationship:[9,16]

$$k = k^0(1 + b[S]) \quad (1)$$

where k and k^0 are the rate constants in the presence and absence of salt, and b is the salt parameter representing the magnitude of the normal salt effect. The b value varies with the nature and the polarity of solvent, substrate, added salt, and temperature.[9,16] Deviations from linearity occur at relatively high concentration of salt when the observed rates increase more rapidly than predicted.[9,16] In some cases, however, the addition of small amounts of salt can induce an initial sharp acceleration followed by a normal linear acceleration (special salt effect).[9]

The present paper deals with the study of the salt effect on the course and stereoselectivity of the acid-catalyzed ring opening of aryloxiranes **1a** and **1b**. As a text of our mechanistic hypothesis it would be of significance to determine the salt parameters b_c and b_t for the two parallel reactions leading to the cis (**6, 8**) and the trans compounds (**5, 7**) from the epoxides **1**. This information can be obtained from a determination of

Scheme I



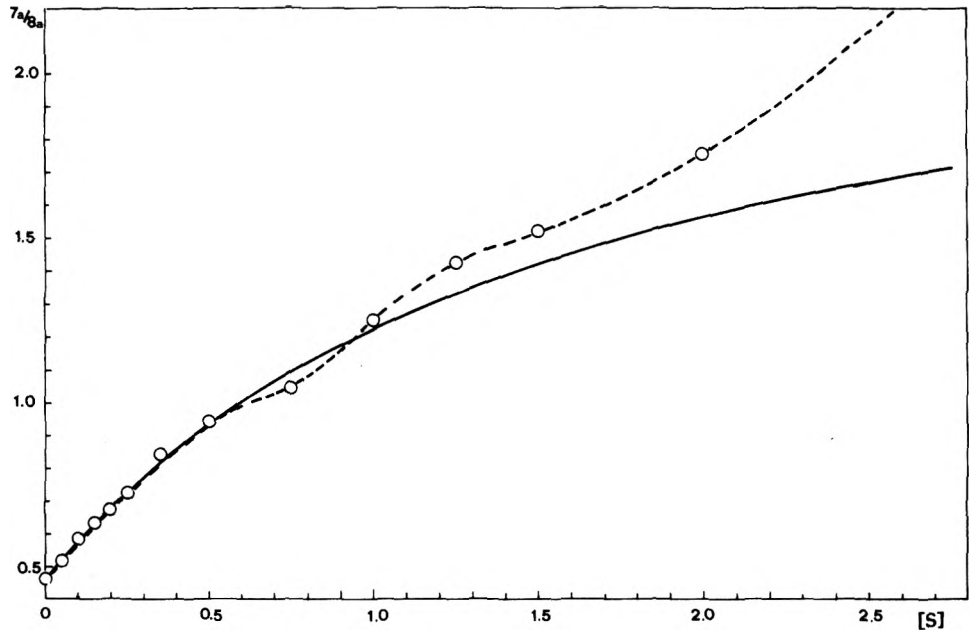


Figure 1. Dependence of the [C]/[T] ratio for the acid-catalyzed ethanolysis of **1a** on the salt concentration [S]. Experimental points and curve (O, broken line); curve calculated on the basis of eq 3 (solid line).

Table I. $LiClO_4$ Salt Effects upon the Acid-Catalyzed Solvolysis of Epoxides 1

	1a in EtOH			1b in EtOH		1a in H_2O		1b in CH_3COOH	
$[LiClO_4]$	8a	7a	Carbonyl products, %[a]	8b	7b	6a	5a	6b	5b[b]
0	31.6	68.4	4.1	10.3	89.7	62.6	37.4	64.0	36.0
0.05	34.2	65.8	5.6	11.7	88.3	63.7	36.3	72.2	27.8
0.10	37.1	62.9	5.7	12.5	87.5	64.0	36.0	77.9	22.1
0.15	38.7	61.3	7.0	13.5	86.5	65.2	34.8	82.1	17.9
0.20	40.3	59.7	7.7	14.0	86.0	66.0	34.0	84.9	15.1
0.25	42.1	57.9	5.9	14.9	85.1	66.0	34.0	87.4	12.6
0.35	45.8	54.2	7.7	16.9	83.1	67.5	32.5	88.0	12.0
0.50	48.5	51.5	6.7	18.4	81.6	69.7	30.3	90.8	9.2
0.75	51.2	48.8	6.9	20.3	79.7	71.3	28.7	92.4	7.6
1.00	55.6	44.4	9.1						
1.25	58.7	41.3	7.4						
1.50	60.3	39.7	13.9						
2.00	63.7	36.3	15.3						
3.00	73.5	26.5	27.0						

[a] 2-Phenylcyclohexanone and 1-phenylcyclopentane-1-carboxaldehyde in a ratio of about 9:1; yields are expressed in moles. [b] After saponification of the monoacetates.

Table II. Correlation Coefficients r for Equation 4 and Salt Parameters b_c and b_t for Acid-Catalyzed Solvolysis of Epoxides 1

	1a in EtOH	1b in EtOH	1a in H_2O	1b in CH_3COOH
b_c	3.29	3.27	1.32	12.57
b_t	0.62	0.72	0.49	0.63
r	0.9968	0.9924	0.9819	0.9886

the ratios of these products in the reaction mixtures. Thus, division of eq 1 for the cis products (subscript c) by the corresponding equation for the trans products (subscript t) affords eq 2. Furthermore, k_c/k_t can be equated to the concentration ratios [C]/[T] on the very likely assumption that the two parallel reactions follow the same kinetic equation,[5,6,17] yielding eq 3. Equation 3 can be further transformed into a linear relationship (eq 4) with respect to 1/[S], which allows one to obtain the $1/(b_c - b_t)$ and the $b_t/(b_c - b_t)$ values, and from these the parameters b_c and b_t.

$$\frac{k_c}{k_t} = \frac{k_c^0}{k_t^0}\left\{1 + \frac{(b_c - b_t)[S]}{1 + b_t[S]}\right\} \quad (2)$$

$$\frac{[C]}{[T]} = \frac{[C^0]}{[T^0]}\left\{1 + \frac{(b_c - b_t)[S]}{1 + b_t[S]}\right\} \quad (3)$$

$$\frac{1}{([C][T^0]/[T][C^0]) - 1} = \frac{1}{(b_c - b_t)}\frac{1}{[S]} + \frac{b_t}{b_c - b_t} \quad (4)$$

The effect of lithium perchlorate on the acid-catalyzed ethanolysis of epoxide **1a** was investigated over a wide range of salt concentrations (up to 3 M) (see Figure 1). In all cases the reaction yielded exclusively mixtures of the two hydroxy ethers *cis*-**8a** and *trans*-**7a**[17] together with minor amounts of carbonylic products (2-phenylcyclohexanone and 1-phenylcyclopentane-1-carboxaldehyde).[17] The syn stereoselectivity of the reaction rises on increasing the amount of salt added, whereas the increase in rearrangement products becomes marked only at very high salt concentration (see Table I). The [C]/[T] variation could be described nicely by equations of type 3, but at salt concentration higher than 0.75 M the ratios observed increase much more rapidly than predicted. Strong

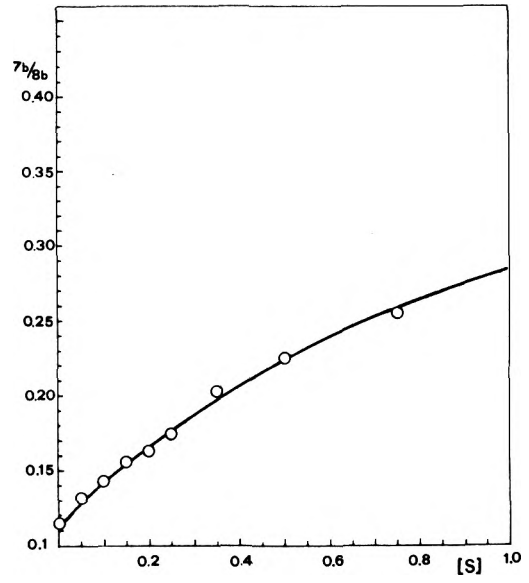


Figure 2. Dependence of the [C]/[T] ratio for the acid-catalyzed ethanolysis of **1b** on the salt concentration [S]. Experimental points (O); curve calculated on the basis of eq 3 (solid line).

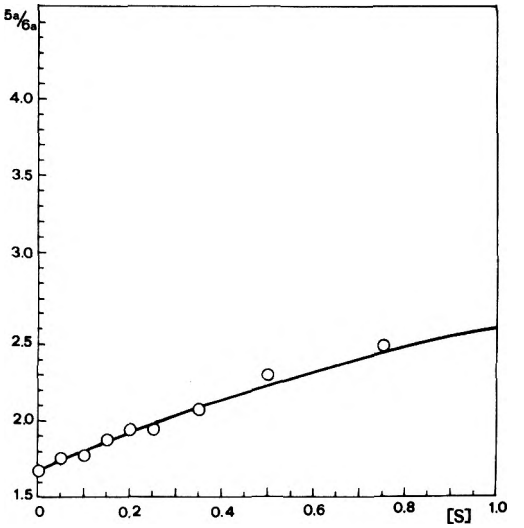


Figure 3. Dependence of the [C]/[T] ratio for the acid-catalyzed hydrolysis of **1a** on the salt concentration [S]. Experimental points (O); curve calculated on the basis of eq 3 (solid line).

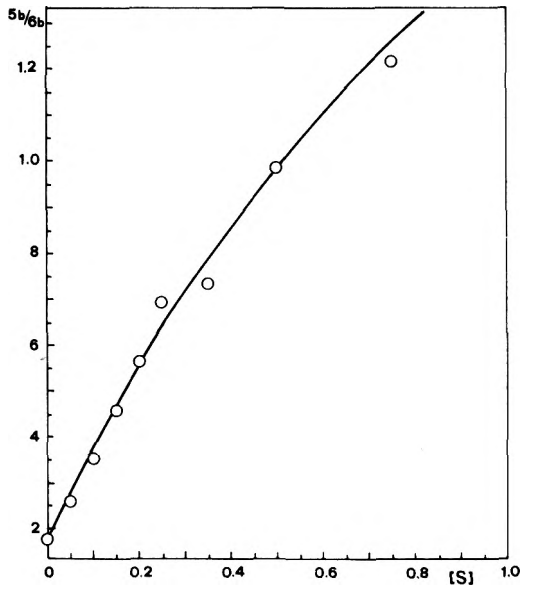


Figure 4. Dependence of the [C]/[T] ratio for the acetolysis of **1b** on the salt concentration [S]. Experimental points (O); curve calculated on the basis of eq 3 (solid line).

deviations from the linear relationship (eq 1) have been previously observed for high salt concentrations.[16a] By making use of eq 4 a fairly good linear correlation is obtained between $1/([C][T^0]/[T][C^0] - 1)$ and $1/[S]$ for lithium perchlorate concentrations up to 0.75 M (the correlation coeficient was $r = 0.9968$). The points for 0.05 and 0.10 M lithium perchlorate concentrations have been excluded in the calculations due to the large relative error in the ratios $1/([C][T^0]/[T][C^0] - 1)$ at such low salt ratios. The b values obtained are reported in Table II. As anticipated the [C]/[T] ratio can be described by eq 3 using the b parameters obtained, and the calculated curve superimposes satisfactorily on the experimental one up to 0.75 M lithium perchlorate concentrations (see Figure 1).

Similarly good results (see Tables I and II and Figures 2–4) have been obtained for the acid-catalyzed hydrolysis of **1a**, for the acid-catalyzed ethanolysis of **1b**, and for the acetolysis of **1b** in the presence of *p*-toluenesulfonic acid. These reactions have been carried out for salt concentrations up to 0.75 M. The reaction mixtures consisted mainly of the known diols **5a** and **6a** for the hydrolysis reactions of **1a**, and of the hydroxy ethers **7b** and **8b** for the ethanolysis of **1b** (see Table I). Within the salt concentration range used only small amounts (~5%) of side products (2-arylcyclohexanone and 1-arylcyclopentane-1-carboxaldehyde) were present in the crude reaction mixtures, and their variation with the salt added was practically negligible. The structure and the configurations of **7b** and **8b** were shown by their oxidation to 2-(*m*-chlorophenyl)-2-ethoxycyclohexanone (**9b**), and by their ^1H NMR and IR spectra in the 3-μm range in dilute solution of CCl_4, which are in agreement with those of the corresponding hydroxy ethers unsubstituted on the phenyl **7a** and **8a**.[17] In the case of the acetolysis of **1b** the reaction mixtures were analyzed after hydrolysis of the monoacetates to the corresponding diols (**5b** and **6b**). Also in these cases the points for 0.05 and 0.10 M lithium perchlorate concentrations have been excluded in the calculations of the parameters of eq 4 (see Table II and Figures 2–4). The consistency of the results obtained argues for the validity of the approach.

The results show in all cases positive b values for the formation of both the cis and the trans products, the b_c values being always much higher than the corresponding b_t ones. Furthermore the b_c values are strongly dependent on the solvent, but they appear to be independent of the substituent on the phenyl group of the epoxide. The relatively large salt effects observed for the paths leading to the cis products (**6** and **8**) and the corresponding small effects on the reaction leading to the trans compounds (**5** and **7**) are in good agreement with the mechanistic scheme suggested above; the addition of the salt, leading to an increase in the polarity of the medium, should greatly stabilize the separated ion–dipole pair **4**, which is much more polar than the starting compound, as expected for an A-1 type reaction.[9,18] On the contrary, the salt added should have little effect on the intimate ion–dipole pair **3**, which resembles more an A-2 or borderline A-1 type of structure in which the positive charge on the benzylic carbon is more distributed between carbon and oxygen.[9,18] However, it may be pointed out that a certain degree of breaking must have occurred between the benzylic carbon and the epoxidic oxygen in structure **3**; this can be shown on the basis of the same regiospecificity of the ring opening of **1** for both the cis (**6**, **8**) and the trans products (**5**, **7**),[17,19] and of a previous study on the dependence of the stereoselectivity of these reactions on the substituents on the phenyl.[5] Furthermore, as required

by the theory,[9,18] the magnitude of the salt effect (expressed by the salt parameter b) for the reaction proceeding through the highly polar structure 4, markedly increases in the series of solvents (water, ethanol, acetic acid), i.e., when the polarity of the solvent is decreased.[9,18] The salt effect for the formation of the trans adducts remains almost constant in the three solvents.

The marked increase in the yield of carbonyl products as the salt concentration becomes very high (this has been checked only in the ethanolysis of **1a**) could be due either to the increase in the polarity of the medium, thus favoring paths leading to the rearranged products, and/or to a "drying" of the solvent by the salt. Large amounts of electrolyte will compete with the carbocationic structures of type 3 and 4 by attracting solvent molecules, thus making them less available as nucleophiles and making the rearrangement paths more competitive.[1b,20]

Experimental Section

Melting points were determined on a Kofler apparatus. IR spectra were taken on a Perkin–Elmer Model 257 double beam grating spectrometer in dried (P_2O_5) CCl_4, using the indene band at 3110 cm^{-1} as a calibration standard; a quartz cell of 2 cm optical length was employed. The NMR spectrum of **7b** has been determined with a Jeol C-60 HL spectrometer and that of **8b** has been measured on a Bruker HXS 360 NMR spectrometer on ~10% $CDCl_3$ solutions using Me_4Si as an internal standard. Preparative TLC was performed on 2-mm silica gel plates (Merck 254) containing a fluorescent indicator; spots were detected under UV light (245 nm). The relative percentages of compounds **5a** and **6a**, and **7** and **8a,b** were determined on a Fractovap GV apparatus with a flame ionization detector, using a dual column system with glass columns. **5a** and **6a** (columns packed with 10% Carbowax 20M on 80–100 mesh silanized Chromosorb W, 2.5 mm × 1 m): temperature of columns 185 °C, evaporator and detector 200 °C; nitrogen flow 35 mL/min; order of increasing retention times, **6a** < **5a**. **7a** and **8a** (columns packed with 10% ethylene glycol succinate on 80–100 mesh silanized Chromosorb W, 2.5 mm × 1 m): temperature of columns 135 °C, evaporator and detector 200 °C; nitrogen flow 35 mL/min; order of increasing retention times, 1-phenylcyclopentane-1-carbaldehyde < 2-phenylcyclohexanone < **7a** < **8a**. **7b** and **8b** (columns packed with 10% Carbowax 20M on 80–100 mesh silanized Chromosorb W, 2.5 mm × 1 m); temperature of columns 175 °C, evaporator and detector 220 °C; nitrogen flow 35 mL/min; order of increasing retention times, **7b** < **8b**. The relative percentages of **5b** and **6b** were determined on a Perkin-Elmer Model F-11 apparatus using a glass column (2.5 mm × 1 m) packed with 10% ethylene glycol succinate on 80–100 mesh silanized Chromosorb W, temperature of column 215 °C evaporator and detector 250 °C, nitrogen flow 45 mL/min; order of increasing retention times, **6b** < **5b**.

The values given in Table I were the average of at least three measurements done on at least two different runs for each point. The accuracy is ±1%.

1-Phenylcyclohexene oxide (**1a**),[21] 1-(*m*-chlorophenyl)cyclohexene oxide (**1b**),[22] 1-phenyl-*r*-1-*cis*-2-cyclohexanediol (**6a**),[21] 1-phenyl-*r*-1-*trans*-2-cyclohexanediol (**5a**),[23] 1-(*m*-chlorophenyl)-*r*-1-*cis*-2-cyclohexanediol (**6b**),[22] 1-(*m*-chlorophenyl)-*r*-1-*trans*-2-cyclohexanediol (**5b**),[22] 2-phenyl-*cis*-2-ethoxy-*r*-1-cyclohexanol (**8a**),[17] 2-phenyl-*trans*-2-ethoxy-*r*-1-cyclohexanol (**7a**),[17] 2-phenylcyclohexanone,[24] and 1-phenylcyclopentane-1-carboxaldehyde[24] were prepared as previously described.

2-(*m*-Chlorophenyl)-*trans*-2-ethoxy-*r*-1-cyclohexanol (7b). A solution of **1b** (2.0 g) in 0.2 N H_2SO_4 in anhydrous ethanol was left at −25 °C for 4 days, then quenched with solid $NaHCO_3$ and saturated $NaHCO_3$, diluted with water, and extracted with ether. Evaporation of the washed (H_2O) and dried ($MgSO_4$) ether extracts yielded an oily residue (2.05 g) consisting mostly of **7b**, which was subjected to preparative TLC (eluent: 75/25 petroleum ether and ether mixture). Extraction of the main band yielded pure **7b** (1.70 g), which crystallyzed from petroleum ether at −25 °C: mp 33–34 °C; IR ν_{OH} (CCl_4) 3608 cm^{-1} (OH···π); NMR δ 3.76 (m, 1, $W_{1/2}$ = 7.0 Hz, CHO). Anal. Calcd for $C_{14}H_{19}ClO_2$: C, 66.01; H, 7.52. Found: C, 66.21; H, 7.59.

2-(*m*-Chlorphenyl)-*cis*-2-ethoxy-*r*-1-cyclohexanol (8b). A solution of **1b** (2.0 g, 9.6 mmol) in anhydrous CH_2Cl_2 (200 mL) and anhydrous ethanol (3.35 mL, 57.4 mmol) was treated with *p*-toluenesulfonic acid (0.182 g, 0.9 mmol). The resulting solution was stirred for 24 h at room temperature, then treated with solid $NaHCO_3$ and saturated aqueous $NaHCO_3$. Evaporation of the washed (H_2O) organic solvent yielded an oily residue (1.96 g) consisting of a mixture of **7a** and **8a** together with carbonylic compounds [mainly 2-(*m*-chlorophenyl)cyclohexanone and 1-(*m*-chlorophenyl)cyclopentane-1-carboxaldehyde], which was subjected to preparative TLC (a 75/25 mixture of petroleum ether and ether was used as the eluent). Extraction of the band corresponding to the *cis*-hydroxy ether **8b** (the trans isomer **7b** has higher R_f) yielded **8b**, impure with carbonylic compounds (0.95 g), as an oil from which pure **8b** has been obtained by crystallization from petroleum ether at −25 °C: mp 47.5–48 °C; IR ν_{OH}(CCl_4) 3591 cm^{-1} (OH···O); NMR δ 3.46 (dd, 1, J = 9.4, 4.4 Hz, CHO). Anal. Calcd for $C_{14}H_{19}ClO_2$: C, 66.01; H, 7.52. Found: C, 66.24; H, 7.72.

2-(*m*-Chlorophenyl)-2-ethoxycyclohexanone (9b). (A) A solution of **7b** (0.050 g, 0.196 mmol) in acetone (4 mL) was treated with Jones reagent[25] (0.15 mL). After 15 min at room temperature the mixture was diluted with water and extracted with ether. Evaporation of the washed (H_2O, saturated aqueous $NaHCO_3$, and H_2O) and dried ether extracts gave an oily residue of **9b** (0.045 g): IR λ 5.80 μm (C=O); 2,4-dinitrophenylhydrazone,[26] mp 51.5–52 °C (from ethanol). Anal. Calcd for $C_{20}H_{21}ClN_4O_5$: C, 55.50; H, 4.89; N, 12.94. Found: C, 55.80; H, 4.89; N, 12.66.

(B) **8b** (0.050 g) was oxidized under the conditions used above to give **9b** (0.044 g): 2,4-dinitrophenylhydrazone,[26] mp 51.5–52 °C.

Acid-Catalyzed Solvolyses of 1-Arylcyclohexene Oxides (1) in the Presence of $LiClO_4$. The reactions were carried out in the following way. A suspension (water) or a solution (other solvents) of **1** (100 mg) in a 0.2 N solution of the acid (H_2SO_4 for the reactions in water and monohydrate *p*-toluenesulfonic acid for the reactions in the other solvents) in the solvent (see Table I) containing anhydrous $LiClO_4$ in the concentrations shown in Table I (10 mL) was stirred at 25 °C for 0.5 h (2 h in the case of the reactions in water), then quenched with solid $NaHCO_3$ and saturated acqueous $NaHCO_3$ (in the case of the reactions in acetic acid the mixtures were diluted with water) and thoroughly extracted with ether. Evaporation of the washed (H_2O, saturated aqueous $NaHCO_3$, and H_2O) and dried ($MgSO_4$) ether extracts yielded crudes consisting of the diols **5** and **6** (reactions in water), or the hydroxy ethers **7** and **8** (reactions in ethanol), or monoacetates (reactions in acetic acid) accompained by minor amounts of 2-arylcyclohexanone and 1-phenylcyclopentane-1-carboxaldehyde, which were directly analyzed by GLC, except for the reactions carried out in acetic acid. The crudes obtained from the reactions in acetic acid were analyzed by GLC after hydrolysis of the monoacetates formed to the corresponding diols **5** and **6**: the crude residues were dissolved in THF (5 mL), treated with 1 M KOH in ethanol (2 mL), and left for 5 h at room temperature. Dilution with water, extraction with ether and evaporation of the washed (H_2O) and dried ($MgSO_4$) ether extracts yielded residues consisting practically of **5** and **6**.

The solvolysis addition products of epoxides **1** were completely stable under the reaction conditions used, and rearrangement products (2-arylcyclohexanones and 1-arylcyclopentane-1-carboxaldehyde) were shown to be not derived from a further transformation of the addition products of epoxides **1**.

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Registry No.—**1a**, 4829-01-0; **1b**, 54637-84-2; **7b**, 63641-45-2; **8b**, 63641-46-3; **9b**, 63641-47-4; **9b** DNP, 63641-48-5; $LiClO_4$, 7791-03-9.

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Synthesis and Interconversion by Hydrogen Exchange of Isomeric Quinhydrones[1,2]

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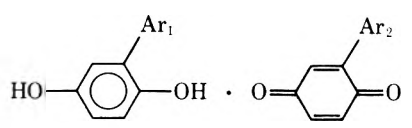
Isomeric quinhydrones, 2-phenylquinone/2-(4′-chlorophenyl)hydroquinone (1:1) (**1a**) and 2-(4′-chlorophenyl)-quinone/2-phenylhydroquinone (1:1) (**1b**), have been prepared as crystalline solids and shown to resist interconversion by a redox (hydrogen exchange) process even at temperatures as high as 140 °C when kept in the solid state. It is suggested that these unsymmetrically substituted complexes are inert to oxidation–reduction interconversions because of a stabilizing combination of hydrogen bonding and charge-transfer forces. A semiquantitative survey of the rates in solution of the redox equilibration of a number of quinone–hydroquinone pairs has been studied by NMR spectroscopy as the basis for the rational selection of the pair of quinhydrones described above.

Molecular complexes (1:1) (quinhydrones) of benzoquinones and hydroquinones have long been known as stable solids which, however, in solution separate into their components.[3] The possibility of preparing isomeric quinhydrones by virtue of the presence of different substituents on the quinone and hydroquinone ring has been recognized, and investigations of deuterium- and carbon-14-labeled compounds have been carried out as a method of studying the redox interconversions in solution of such compounds.[4] In other cases where preparation of isomeric pairs of substituted quinhydrones has been attempted, the rapid redox interconversion in solution coupled with a lack of adequate methods of characterization has led to confusing results.[5] Nevertheless crystals of unsymmetrically substituted complexes of this type as, for example, **1a** and **1b**, could be of great interest, because of their possible optical and electrical properties coupled with the fact that their interconversion requires only the transfer between oxygen atoms of hydrogen atoms (or hydride ions plus protons). Furthermore, determinations of the crystal structures of the monoclinic[6a] and triclinic[6b] forms of the parent symmetrical quinhydrone (**1** with $Ar_1 = Ar_2 = H$) have shown that in each case the structures are composed of chains of alternating, well-defined, quinone and hydroquinone molecules hydrogen bonded in such a way that it might be hoped that hydrogen switching could be induced without seriously disrupting the structure.[7] With the proper choice of substituents, spectral or other properties should differ sufficiently for the isomers analogous to **1a** and **1b** to permit ready recognition of whether a crystal is in state **1a** or state **1b**.



1a, Ar_1 = 4-ClC_6H_4; Ar_2 = C_6H_5
b, Ar_1 = C_6H_5; Ar_2 = 4-ClC_6H_4
c, $Ar_1 = Ar_2 = C_6H_5$
d, $Ar_1 = Ar_2$ = 4-ClC_6H_4

This paper describes a study of the factors affecting the redox interconversion of hydroquinone–quinone pairs in solution and the synthesis of the crystalline redox isomers **1a** and **1b**.

Experimental Section

Spectra and other supplementary experimental data are available in ref 1.

Synthesis of Quinones and Hydroquinones. Hydroquinone-*2,3,5,6-d*$_4$. To 40 mL of acetyl chloride was added, over 30–45 min, 20 mL of D_2O (90% D, Columbia Organic Chemicals) with regular stirring and such that the evolution of gas was not too vigorous. The hydrolyzed mixture was added to 2.1 g of hydroquinone (Mallinckrodt, twice sublimed, mp 171 °C) and 4.0 g of amalgamated zinc and the resulting mixture was heated under reflux for 24 h.[8] The reaction was arrested with about 150 mL of water and the reaction mixture was repeatedly extracted with ether. The combined ethereal extracts were washed with $NaHCO_3$ solution until the washings remained alkaline. The organic layer was dried and the ether was removed to leave the crude deuterated hydroquinone which was sublimed at 70 °C and at 0.04 Torr to give 1.75 g (82%) of product that showed approximately 88% deuterium incorporation (by NMR and mass spectrometry). A final recrystallization from ethanol–benzene yielded 1.42 g (68%) of solid: mp 171–173 °C (lit. mp 175 °C);[9] IR (KBr) 3270, 2234, and 1210 cm^{-1}; mass spectrum (CH-5, 10 eV) M^+ (base peak) (*m/e*) 114, 113 (39%), 112 (22%).

Anal. Calcd for $C_6D_4(OH)_2$ with 88% D: C, 63.44; H, 5.29. Found: C, 63.08; H, 5.53.

2,5-Dichlorohydroquinone-*3,6-d*$_2$. 2,5-Dichloro-1,4-benzoquinone was reduced to the hydroquinone with $SnCl_2$ in virtually quantitative yield.[10,11] This hydroquinone (250 mg) was deuterated

in the manner described above. After two exchanges the partially deuterated compound (185 mg) was sublimed at 70 °C and 0.04 Torr to yield 161 mg (64%) of 2,5-dichlorohydroquinone containing 80% D in the aromatic positions as shown by NMR (82% by mass spectrometry): mp 171–172 °C (lit. mp 172 °C);[12] IR (KBr) 3390, 2286, 1205, and 1190 cm^{-1}; mass spectrum (CH-5, 10 eV) M^+ (*m/e*) 180, 184, base peak 180, 179 (29%), 181 (29%), 182 (64%), 183 (7%), 184 (11%).

Anal. Calcd for $C_6D_2Cl_2(OH)_2$ with 82% D: C, 39.95; H, 1.34; Cl, 39.33. Found: C, 39.78, H, 1.56; Cl, 39.27.

2,5-Di-*tert*-Butylhydroquinone-3,6-d_2. The unlabeled hydroquinone (0.5 g) was deuterated as above. Recrystallization from 1:1 ethanol–water and sublimation at 100 °C and 0.04 Torr gave 0.30 g (60%) of the deuterated compound. The IR spectrum showed no O–D stretching vibrations and the intensity of the hydroxylic proton singlet was used as an internal reference in the ^1H NMR experiments to obtain the percent D in the aromatic positions since the methyl groups were also deuterated extensively: mp 213 °C (lit. mp 213 °C);[13] IR (KBr) 3420, 2940, 2220, and 2140 cm^{-1}; NMR (acetone-d_6) δ 7.3 (s, 2 H, hydroxyl), 6.7 (s, 2 H, aromatic shows 82% deuterium), 1.35 (s, 18 H, aliphatic shows 73% D); mass spectrum (CH-5, 10 eV) M^+ at *m/e* 242, base peak 240, 238 (71%), 239 (84%), 241 (91%), 244 (21%).

Methylhydroquinone-3,5,6-d_3. The unlabeled methylhydroquinone (0.5 g) was deuterated as above. The crude material was sublimed at 60 °C and 0.04 Torr to yield 0.47 g (94%) of solid: mp 124–127 °C (lit. mp 127 °C);[14] IR (KBr) 3350, 1400, 1160, and 1040 cm^{-1}; ^1H NMR shows that deuterium incorporation is almost 100%.

Anal. Calcd for $C_7D_3H_5O_2$: C, 66.14; H, 6.30. Found: C, 66.13; H, 6.50.

Purification of 1,4-Naphthoquinone. The crude black powder purchased from the Aldrich Chemical Co. was recrystallized from AcOH–water to yield a brown solid. Recrystallization from an ethanolic solution containing animal charcoal followed by sublimation at 50 °C and 0.04 Torr gave light yellow crystals, mp 126 °C.

2-Phenyl-1,4-benzoquinone was prepared by the method of Brassard and L'Écuyer.[15] The diazonium salt of aniline was allowed to react with quinone (Eastman, twice sublimed). The reaction time was, however, increased to 36 h since insufficient product was obtained in the prescribed time.[15] The crude solid was recrystallized from high boiling petroleum ether and sublimed at 90 °C and 0.05 Torr to give the pure compound in 51% total yield: mp 110–112 °C (lit. mp 112 °C);[16] NMR ($CDCl_3$) δ 7.6 (s, 5 H), 6.9 (s, 3 H).

2-(4′-Chlorophenyl)-1,4-benzoquinone was obtained from the diazonium salt of *p*-chloroaniline by an analogous method.[15] Recrystallization from 2:1 EtOH–acetone followed by sublimation at 100 °C and 0.05 Torr gave the compound in 71% total yield: mp 129–130 °C (lit. mp 129 °C);[16] NMR (acetone-d_6) δ 7.5 (m, 4 H), 6.9 (s, 3 H).

2-Phenyl-1,4-dihydroxybenzene (2-Phenylhydroquinone). Although the other quinones used in this study were readily reduced, even when crude, to hydroquinones which were easily isolated as crystalline solids, on treatment with acidic $SnCl_2$,[10,11] phenylquinone did not readily give a solid product on reduction. Reduction itself seemed to occur easily as the color of the solution changed from yellow to colorless. Yet no solid could be induced to crystallize from solution. When the reduction was repeated on a large quantity (20 g) of analytically pure quinone, the reaction mixture separated into two layers. On cooling the mixture to 0 °C and scratching the sides of the vessel the hydroquinone crystallized slowly. Phenylhydroquinone was obtained from phenylquinone in essentially quantitative yield: mp 100 °C (lit. mp 97 °C);[17] ^1H NMR (DMSO-d_6) δ 8.6 (d, 2 H), 7.2–7.7 (m, 5 H), 6.5–7.1 (m, 3 H).

2-(4′-Chlorophenyl)-1,4-dihydroxybenzene (2-(4′-Chlorophenyl)hydroquinone). Reduction of the 4-chlorophenylquinone (20 g) with $SnCl_2$ in acidic EtOH–water gave 20.1 g (99.6%) of hydroquinone.[18] In this and the previous reduction, quinone of a high purity seems to be required if the hydroquinone is to crystallize easily. Sublimation at 110 °C and 0.05 Torr gave a white solid: mp 118–120 °C; NMR (DMSO-d_6) δ 8.8 (s, 2 H), 7.5 (q, 4 H), 6.7 (m, 3 H).

Anal. Calcd for $C_{12}H_9O_2Cl$: C, 65.31; H, 4.08; Cl, 16.10. Found: C, 65.60; H, 4.17; Cl, 15.99.

Equilibration Experiments. The NMR studies were carried out by weighing out equivalent amounts of the analytically pure quinone and hydroquinone under study, adding a previously calculated volume of solvent (deuterated when necessary), and recording the NMR spectra immediately. Additional spectra were recorded at suitable time intervals, depending on the reaction rate. Spectra were measured at a probe temperature of 44 °C. Integration of the NMR peaks was performed with a Keuffel and Esser planimeter. Details of the procedure and calculations employed are illustrated for one set of compounds.

Oxidation–Reduction Reaction between 1,4-Naphthoquinone and Tetramethyl-1,4-dihydroxybenzene. Naphthoquinone (19.8 mg) and the tetramethylhydroquinone (20.8 mg) were dissolved in 0.5 mL of DMSO-d_6. The methyl resonance of the tetramethylhydroquinone (124 Hz) decreases in intensity and the methyl resonance of tetramethylquinone (116 Hz) increases in intensity as the reaction goes toward equilibrium. Integration of the relative intensities of these peaks gives a measure of the extent of equilibration.

The initial concentrations of the species are A_0, B_0, C_0, and D_0 and the concentrations of the species at time t are A_t, B_t, C_t, and D_t. If $C_0 = D_0 = 0$ and $A_0 = B_0$, then $A_t = A_0 - x$ and $B_t = A_0 - x$, and $C_t = D_t = x$, where x is the number of moles/liter the starting materials lost or products gained at time t. Now for the above reaction

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C + D, \quad \text{where } K = \frac{k_1}{k_{-1}} \neq 1$$

$$\frac{dx}{dt} = k_1(A_0 - x)(A_0 - x) - k_{-1}x^2$$

On integration we obtain:

$$\ln \frac{A_0(K^{1/2}+1) - x(1 - [1/K])K^{1/2}}{A_0(K^{1/2}-1) - x(1 - [1/K])K^{1/2}} = \frac{2ak_1t}{K^{1/2}} + \ln \frac{K^{1/2}+1}{K^{1/2}-1}$$

$$\log \frac{A_0(K^{1/2}+1) - x(1 - [1/K])K^{1/2}}{A_0(K^{1/2}-1) - x(1 - [1/K])K^{1/2}} = \frac{2ak_1t}{2.303K^{1/2}} + \log \frac{K^{1/2}+1}{K^{1/2}-1}$$

i.e., $\log Z = \alpha t + c$, where α and c are constants. In this example A_0 = 0.25 and K = 5.44. The value of K was calculated from the position of equilibrium. A plot of $\log Z$ vs. t gave a straight line with a positive slope and intercept. Eighteen points were included and the standard deviation in the slope was about 3%. Simple substitution in the rate equation gave a value for the time required for a 90% (or any other desired percentage) exchange.

Equilibration of Quinones and Their Hydroquinones Obtained by Reduction. Three quinones, *p*-benzoquinone, 2,5-dichloro-1,4-benzoquinone, and 2,5-di-*tert*-butyl-1,4-benzoquinone, were studied. In each case the hydroquinone obtained from the quinone by reduction was deuterated as described and equivalent amounts of the quinone and deuterated hydroquinones were used. In these cases K = 1 and the second-order rate expression simplifies to

$$(1/p) \ln [p(A_0 - x) + q] = kt + c$$

where

$$p = -(A_0 + B_0), \quad q = A_0B_0$$

and k and c are constants.

A_0, B_0, and t have the same meaning as before. Thirteen points were included for benzoquinone, fifteen for 2,5-dichlorobenzoquinone, and twenty for 2,5-di-*tert*-butylbenzoquinone. See Table I for the results.

Equilibration of Quinones and Hydroquinones Bearing Different Substitution Patterns. The data were handled as in the case of the tetramethylhydroquinone–naphthoquinone equilibrium experiment. Benzoquinone and methylhydroquinone exchange too rapidly for the equilibrium to be followed by NMR. Chloranil and hydroquinone equilibrate at a convenient rate. Twenty spectra were included. It was possible to follow the equilibration of 2,5-diphenylquinone and 2,5-di-*tert*-butylhydroquinone in DMSO, but rapid precipitation of the 2,5-diphenylquinone–2,5-diphenylhydroquinone 1:1 complex occurred in benzene (see Table I).

Unsymmetrical 2-Phenylquinone/2-(4′-Chlorophenyl)-hydroquinone 1:1 Complex, 1a. The quinone (0.5 g) and hydroquinone (0.6 g) were saturated separately in 3:1 benzene/AcOH and the two solutions were mixed. There was an immediate black precipitate which was filtered off within 15 s of precipitation: mp 162–165 °C; IR (KBr) 1633, 1495, and 1455 cm^{-1}.

Anal. Calcd for $C_{24}H_{17}O_4Cl$: C, 71.20; H, 4.20; Cl, 8.78. Found: C, 71.26; H, 4.20; Cl, 8.50.

Unsymmetrical 2-(4′-Chlorophenyl)quinone/2-phenylhydroquinone 1:1 Complex, 1b. This was prepared from 0.6 g of the quinone and 0.5 g of the hydroquinone as described in the preparation of **1a**. The blue-black precipitate was quickly filtered: mp 162–164 °C; IR (KBr) 1629, 1490, 1455, and 1432 cm^{-1}.

Anal. Calcd for $C_{24}H_{17}O_4Cl$: C, 71.20; H, 4.20; Cl, 8.78. Found: C, 70.98; H, 4.20; Cl, 9.02.

Characterization of the Unsymmetrical Complexes 1a and 1b by NMR. The complexes were dissolved separately in DMSO-d_6 (30 mg in 0.5 mL). NMR spectra were recorded after about 5 min. Addi-

Table I. NMR Studies on the Equilibration of Quinone/Hydroquinone Pairs[a,j]

$$Q_1 + HQ_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Q_2 + HQ_2 \qquad K = k_1/k_{-1}$$

	Starting quinone Q_1	Starting hydroquinone HQ_1	Registry no.	Initial concn of each, mol/L	Solvent	^{1}H NMR feature obsd[b] Reactants signal (decreases)	Product signal (increases)	% of Q_1 (= HQ_1) at equil (value of K)	Time required for 90% reaction, min[c,d]	Formation of complex (ref)
(1)	*p*-Benzoquinone	Hydroquinone-*2,3,5,6-d*$_4$	63715-58-2	0.25	Acetone or DMSO	Q (4 H)	HQ (4 H)	50 (1)	12	Yes (*e*)
(2)	2,5-Dichloro-*p*-benzoquinone	2,5-Dichlorohydroquinone-*3,6-d*$_2$	63715-60-6	0.25	DMSO	Q (2 H)	HQ (2 H)	50 (1)	65	Yes (*f*)
(3)	2,5-Di-*tert*-butyl-*p*-benzoquinone	2,5-Di-*tert*-butylhydroquinone-*3,6-d*$_2$	63743-82-8	0.41	Acetone	Q (2 H)	HQ (2 H)	50 (1)	35	Yes (*g*)
(4)	*p*-Benzoquinone	Methylhydroquinone-*3,5,6-d*$_3$	63715-62-8	0.25	Acetone	Q (4 H)	HQ (4 H)	19 (18.2)	0	?
(5)	1,4-Naphthoquinone	Tetramethylhydroquinone	63715-63-9	0.25	DMSO	HQ (12 H)	Q (12 H)	30 (5.4)	3060	No (*g*)
(6)	Tetrachloro-*p*-benzoquinone	Hydroquinone	63715-64-0	0.25	DMSO	HQ (4 H)	Q (4 H)	62 (0.38)	77	No (*g*)
(7)	2,5-Diphenyl-*p*-benzoquinone	2,5-Di-*tert*-butylhydroquinone	63715-65-1	0.03	DMSO Benzene	HQ (18 H) HQ (18 H)	Q (18 H) Q (18 H)	5 (361) *i*	12[h] 3	No (*g*)
(8)	2-Phenyl-*p*-benzoquinone	2-(4′-Chlorophenyl)hydroquinone	63715-66-2	0.10	DMSO	m, δ 7.25–7.50 Hz (9 H)	s, 7.55 Hz (4 H)	71 (.17)	ca. 100	Yes (*g*)
(9)	2-(4′-Chlorophenyl)-*p*-benzoquinone	2-Phenylhydroquinone	63715-67-3	0.13	DMSO	s, δ 7.55 Hz (4 H)	m, δ 7.25–7.50	40 (2.25)	ca. 100	Yes (*g*)

[a] For details of a representative calculation, see Experimental Section. [b] Q = quinone, HQ = hydroquinone. [c] The maximum error in this value is ±18%. [d] This is the time required to reach 90% equilibrium concentration of products. [e] F. Wöhler, *Justus Liebigs Ann. Chem.*, **51**, 145 (1844). [f] A. R. Ling and J. L. Baker, *J. Chem. Soc.*, **63**, 1314 (1893). [g] This study. [h] When the equilibration was carried out in benzene, a precipitate of 2,5-diphenylquinhydrone was formed almost at once. The amount of precipitate obtained in 3 min showed that at least 36% exchange had occurred in that time; in comparison 36% exchange occurs in DMSO in 12 min and 90% exchange in DMSO in 40 min. Precipitation of the complex from DMSO does not occur under these conditions. [i] Precipitation of the complex occurs prior to equilibration. [j] NMR spectra of quinone/hydroquinone mixtures in solution were recorded at a probe temperature of 44 °C. Acetone and DMSO used for the spectra were fully deuterated.

tional spectra after various intervals of time were observed to change. After about 8 to 10 h the spectra showed no further change. Application of the second-order rate equation permits a calculation of extent of exchange at the time the "initial" NMR spectra (Figure 1) was run. The "final" spectra from complexes **1a** and **1b** give values of 71 and 60% of phenylquinone and chlorophenylhydroquinone at equilibrium. An average value of 65.5% leads to a value of K equal to 3.40. The kinetic parameters may be estimated from the observation that 90% equilibration is achieved in 100 min when **1b** is dissolved in DMSO-d_6. These parameters were used to calculate the amount of equilibration in 5 min.

1:1 Complex of 2-Phenylquinone and 2-Phenylhydroquinone, 1c. Solutions of the components saturated at 0 °C in 3:1 benzene/AcOH were mixed to give an immediate black precipitate which was filtered rapidly and dried: mp 178–180 °C (lit. mp 176 °C);[17-19] IR (KBr) 1629, 1490, 1455, and 1437 cm^{-1}. Single crystals were prepared by reaction of the components in a nonaqueous gel.[20] Optical goniometry showed the prominent face to be (001), interfacial angles observed (calcd): (001):(012) 55° (52.8°), (001):(012) 52° (52.8°), (001):(100) 77.7° (77.5°), (001):($\bar{1}$00) 103.5° (102.5°), (012):(100) 82.7° (82.5°), (0$\bar{1}$2):(100) 82.8° (82.5°).

Anal. Calcd for $C_{24}H_{18}O_4$: C, 77.84; H, 4.86. Found: C, 78.04; H, 5.00.

1:1 Complex of 2-(4′-Chlorophenyl)quinone and 2-(4′-Chlorophenyl)hydroquinone, 1d. This complex was prepared by mixing saturated solutions of the components. It is a black solid: mp 168 °C; IR (KBr) 1640, 1495, and 1458 cm^{-1}.

Single crystals grown in a nonaqueous gel[20] were shown by optical goniometry to have as the prominent face (001), interfacial angles observed (calcd): (001):(100) 79.3° (79.7°), (001):($\bar{1}$00) 100.5° (100.3°), (001):(012) 57° (56.2°), (001):(02$\bar{1}$) 105° (99.4°), (001):(02$\bar{1}$) 103.8° (99.4°), (100):(012) 85.8° (84.3°), (100):(02$\bar{1}$) 89.9° (91.7), ($\bar{1}$00):(012) 93.4° (95.7°), ($\bar{1}$00):(02$\bar{1}$) 90.3° (88.3°).

Anal. Calcd for $C_{24}H_{16}O_4Cl_2$: C, 65.60; H, 3.64; Cl, 16.17. Found: C, 65.66; H, 3.59; Cl, 16.20.

Attempts to Prepare Single Crystals of the Unsymmetrical Complexes 1a and 1b. Experiments using the constituent quinones and hydroquinones of these complexes in nonaqueous gels yielded only quinhydrone **1c** which was presumably formed after an initial redox reaction.[20]

Powder X-Ray Crystallographic Studies. Powder photographs were taken of samples of **1a**, **1b**, **1c**, and **1d** (Cu Kα radiation, Debye-Sherrer camera made by Charles Supper Co.) and powder diffractometer traces of all four samples were recorded by Dr. Ralph Pfeiffer and associates, Eli Lilly Co., Indianapolis, Ind. The values for the d spacings on the pictures from the symmetrical quinhydrones, **1c** and **1d**, could be correlated[21] with the known cell dimensions[22] for these complexes.[1] The positions of the powder lines on the photographs from **1a** and **1b** were identical, although the diffractometer traces did indicate some differences in intensities. Attempts to correlate the values for the observed d spacings for **1a** and **1b** with those obtained from the cell dimensions (a = 5.98, b = 7.52, c = 20.30 Å, β = 102.5°) for the symmetrical complex **1c** did not result in a good fit. A much better fit was found when the cell dimensions for **1d** (a = 5.98, b = 7.45, c = 22.92 Å, β = 100.34°) or those obtained (a = 5.98, b = 7.48, c = 21.61 Å, β = 101.42°) by averaging the cell dimensions for the symmetrical quinhydrones **1c** and **1d** were used in the comparison.

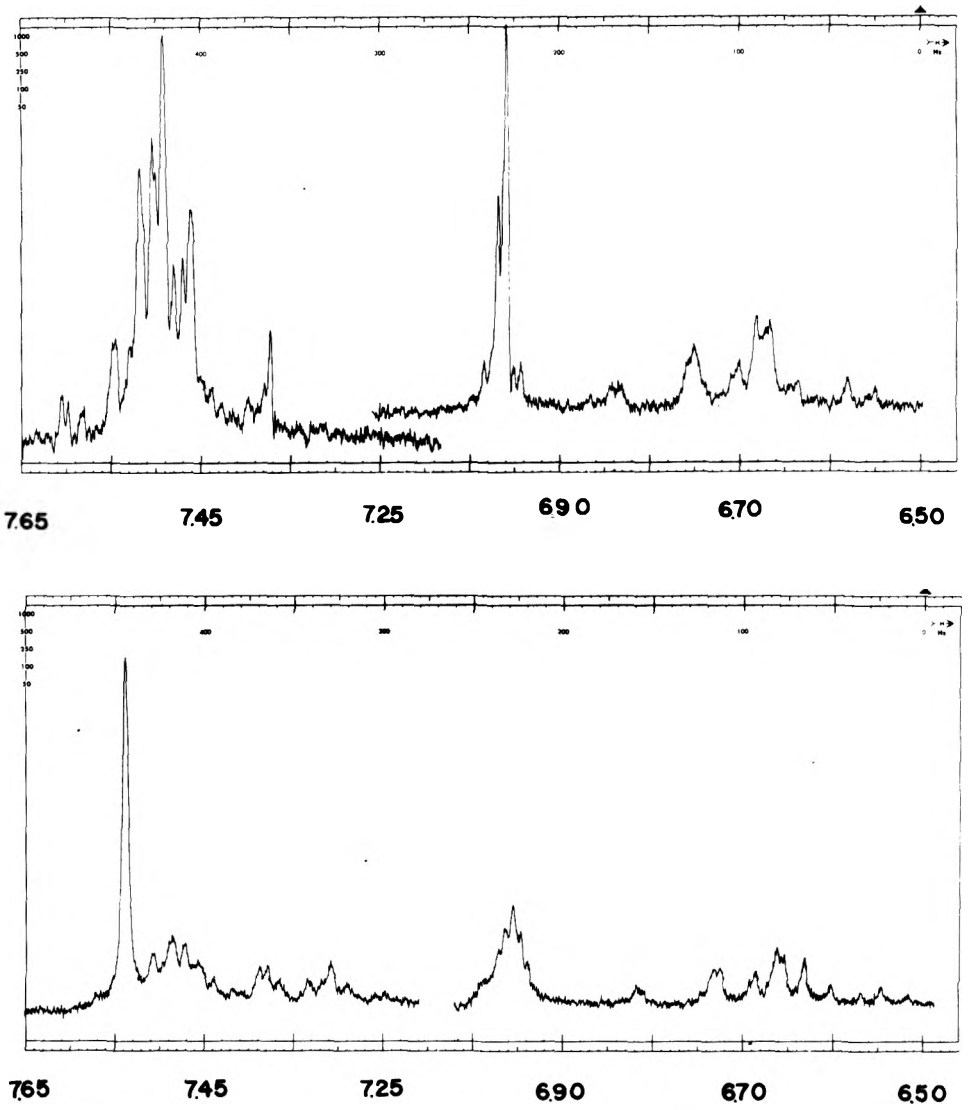


Figure 1. Upper: NMR spectrum of complex **1b** about 5 min after it was dissolved in DMSO. Shifts in ppm downfield from Me_4Si are shown at the bottom of the spectrum. Lower: NMR spectrum of complex **1a** about 5 min after it was dissolved in DMSO. Shifts in ppm downfield from Me_4Si are shown at the bottom of the spectrum.

Results and Discussion

The formation of a quinhydrone complex from a quinone and a hydroquinone bearing different substituents is complicated by the reversible redox reaction that the two components undergo in solution. If the composition of such a complex is to be unambiguous, the complementary hydroquinone and quinone should be prevented from forming in appreciable amounts prior to complex precipitation; this condition is obtained when the rate of the redox reaction is relatively slow.

In Table I are summarized results of an NMR study of the exchange reactions of a number of quinone/hydroquinone pairs. Although no attempt was made to carry out detailed quantitative studies of the effect of substituents on this hydrogen exchange, there may be inferred certain tentative generalizations which served as a guide in the search for an appropriate set of compounds for study. An earlier study[4e] had suggested that an increase in acidity of the hydroquinone component of the starting mixture leads to faster exchange. A number of other factors seem to be of equal importance. Comparison of the exchanges (2) and (3) with (1) in Table I suggests that substitution of both the starting materials leads to retardation of the exchange rate. On the other hand examples (5)–(7) show that too much substitution prevents the formation of the desired complex. In this connection it is instructive to note some of the factors governing the formation of symmetrically substituted quinhydrones. The donor capability of the hydroquinone, the acceptor strength of the quinone, and steric factors all seem to be of some importance. For example, it may be noted that tetrachlorohydroquinone and chloranil do not form a quinhydrone partly because the former is not a sufficiently strong donor. Recently, the importance of the above factors in quinhydrone formation has been discussed[23] and these factors would appear to be of obvious importance in the formation of unsymmetrically substituted quinhydrones also. The comparison of DMSO with benzene as solvent suggests that the strong hydrogen-bond acceptor, DMSO, leads to slower exchange. Comparison of examples (4) and (1) suggests that a slow exchange rate is favored by a close balance of redox potentials of the two component pairs.

These considerations based on exchanges (1)–(7) in Table I led to the synthesis of the components of the exchanges in lines (8) and (9). As is seen in Table I this is a compromise between an adequately slow exchange rate on the one hand and sufficient reactivity for complex formation on the other.

Complexes **1a** and **1b** were formed rapidly (filtration in 30

s) when saturated solutions of the components in DMSO were mixed. The quinone/hydroquinone stoichiometry was 1:1 even when the relative concentrations of the components were varied widely. The infrared spectra (KBr disk) showed marked differences between 1400 and 1500 cm^{-1} but do not differ sufficiently to make it easy to set upper limits for possible small amounts of contamination of **1a** by **1b** and vice versa. The NMR spectrum of **1a** in DMSO (Figure 1) (measured after the complex had been dissolved for about 5 min) approximated the sum of the spectra of phenylquinone and 4′-chlorophenylhydroquinone. Similarly the spectrum of **1b** (Figure 1) was approximately the sum of the spectra of 4′-chlorophenylquinone and phenylhydroquinone. However, integration of spectral peaks indicated that the solution of **1a** measured after 5 min contained 17% of **1b** and that the solution of **1b** contained 15% of the components of **1a**. Since when the complex was prepared quinone and hydroquinone were in solution together for only about 30 s before the complex precipitated as compared with a time of 5 min (300 s) after dissolution for the spectral measurement, it seems clear that most of the equilibration occurred in each case when the complex was redissolved for spectral determination.[24]

The unsymmetrically substituted quinhydrones **1a** and **1b** in the crystalline state are stable indefinitely at ambient temperature; even when heated to 140 °C they do not undergo sufficient equilibration to be detected by infrared spectroscopy. The basis of this stability is suggested by the crystal structures of the monoclinic and triclinic forms of quinhydrone,[6] as well as the structure of the complex between 1,4-hydroquinone and 1,4-naphthoquinone,[25] and also the results[1] on the structures of the symmetrical compounds **1c** and **1d**. A common theme runs through all of these structures. Chains of alternating quinone and hydroquinine molecules held together by hydrogen bonding are formed. In turn, the chains associate by overlap of the π-electron systems of the hydroquinone and quinone rings in adjacent chains thus generating a two-dimensional layer of molecules. Any molecule in the layer is thus related to its neighbors by hydrogen bonding and by charge-transfer forces. Were the redox hydrogen exchange to occur, a whole layer would have to undergo the exchange simultaneously if the stabilizing effect of these highly specific interactions is not to be lost.

Experiments designed to obtain single crystals of the unsymmetrically substituted complexes **1a** and **1b** by gel diffusion[20] produced only single crystals of the unchlorinated quinhydrone **1c** by a process which must have involved redox interaction of the reactants before crystallization occurred. Even attempts to bias the situation by allowing the phenylquinone to diffuse into a gel containing an excess of chlorophenylhydroquinone produced only crystals of the unchlorinated complex **1c**.

It is to be hoped that the foundation laid in the present paper will lead to control of the rates of the hydrogen exchange and crystallization processes so as to make possible the preparation of single crystals of isomeric substituent-labeled quinhydrones.

Registry No.—**1c**, 41758-38-7; **1d**, 63715-68-4; hydroquinone-*2,3,5,6-d*$_4$, 25294-85-3; hydroquinone, 123-31-9; 2,5-dichlorohydroquinone-*3,6-d*$_2$, 63715-59-3; 2,5-dichloro-1,4-benzoquinone, 615-93-0; 2,5-di-*tert*-butylhydroquinone-*3,6-d*$_2$, 63715-69-5; 2,5-di-*tert*-butylhydroquinone, 86-58-4; methylhydroquinone-*3,5,6-d*$_3$, 63715-61-7; methylhydroquinone, 95-71-6; 1,4-naphthoquinone, 130-15-4; 2-phenyl-1,4-benzoquinone, 363-03-1; 2-(4′-chlorophenyl)-1,4-benzoquinone, 20307-43-1; 2-phenylhydroquinone, 1079-21-6; 2-(4′-chlorophenyl)-1,4-dihydroxybenzene, 10551-37-8; 2,5-di-*tert*-butylhydroquinone, 88-58-4; *p*-benzoquinone, 106-51-4; tetrachloro-*p*-benzoquinone, 118-75-2; 2,5-diphenyl-*p*-benzoquinone, 844-51-9; tetramethylhydroquinone, 527-18-4.

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Catalysis of Keto-Enol Tautomerism of Oxaloacetic Acid and Its Ions Studied by Proton Nuclear Magnetic Resonance[1]

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The proton nuclear magnetic resonance spectra of solutions of oxaloacetic acid (OA) have been measured at a number of pH values between 1 and 7 at 4 °C, and the line widths of the signals due to the enol, hydrate (*gem*-diol), and keto forms determined. The line width of the CH proton of the enol of OA is pH dependent, passing through a maximum at about pH 3. The pH dependence parallels that for the fraction of OA existing in the monoanion form. In contrast, the width of the signal due to the enol of 4-ethyl oxaloacetate exhibits only a monotonic change in the same pH region. The line broadening is attributed to keto–enol equilibration involving monofunctional general acid catalysis by the diacid of OA acting on the enol dianion. Involvement of one of the carboxyl groups of the enol in this catalytic process is possible.

Proton NMR spectra of solutions of oxaloacetic acid (OA) at pH 1–7 and 4 °C contain peaks assignable to enol, keto, and hydrate (gem-diol) forms. In the pH region 2 to 5, the line width for the signal due to the CH proton of the enol form passes through a maximum. Because of the small size of the enol peak and rapid decarboxylation, line width measurements are very difficult, but the enol line width is found to be proportional to the square of the monoanion concentration. This dependence along with the fact that the signal due to the enol of 4-ethyl oxaloocetate (the monoethyl ester group is β to the ketone carbonyl group) exhibits only a monotonic change between pH 2 and 5 is interpreted in terms of a catalytic mechanism in which the diacid of OA acts as a monofunctional general acid catalyst for the ketonization of the dianion of the enol of OA. The evidence does not appear to support a mechanism in which the monoanion of OA acts as a bifunctional catalyst for the ketonization of the enol monoanion in a manner analogous to the mechanisms suggested for the termolecular terms found for the enolization of acetone[2] and cyclohexanone[3] and as suggested[4] but disproven[5] for OA ketonization. But the results are consistent with intramolecular participation of a carboxylate group of the enol as in the case of catalysis of the enolization of 2-oxobicyclo[2.2.2]octane-1-carboxylic acid[6] and as might be possible in the enzyme-catalyzed tautomerization.[7]

Experimental Section

Chemicals. Oxaloacetic acid was obtained from several sources: British Drug House (BDH), Nutritional Biochemicals, and Sigma Chemical Co. The material obtained from BDH was found to be 98.5% pure by means of equivalent weight determinations. 4-Ethyl oxaloacetate was obtained from Nutritional Biochemicals and was recrystallized from benzene and/or chloroform, mp 96–97 °C. This compound was also prepared by two different procedures from sodium diethyl oxaloacetate, which was obtained from Eastman. The first method involved direct saponification of the diester[8] and the second involved hydrolysis of a copper complex of the diester.[10] In each case the material was recrystallized from chloroform to yield products with melting points of 98–104 and 89–94 °C, respectively. Formic acid (Baker Chemical Co.), acetic acid (Baker Chemical Co.), malic acid (Eastman Chemical), succinic acid (Sigma), ethylenediaminetetraacetic acid EDTA (Sigma) and *tert*-butyl alcohol (Baker Chemical Co.) were used without further purification.

Solutions and NMR Spectra. To minimize the extent of decarboxylation, which is especially rapid with the monoanion form of OA, samples were prepared at 4 °C immediately before NMR measurements. The pH, which was measured using a Radiometer PHM or PH 26 meter, was adjusted by addition of either NaOH (for values above 1.2) or HCl. The ionic strength varied from 0.1 at pH 1.5 to 1.56 at pH 5.0 when only OA is present. When other carboxylic acids are also present the ionic strength is substantially higher.

All proton NMR spectra were measured at 4 ± 1 °C (determined using a thermometer and the chemical shift between the OH and the CH_3 proton resonance of methanol) to reduce bubbling, which results from the decarboxylation of OA. Most spectra were measured at 60 MHz using a Varian A-60A spectrometer; however, a Varian HA-100 spectrometer was used for the OA concentration study because of its better sensitivity. The A-60A, which uses an external lock, was more convenient to use than the HA 100 whose internal lock was affected by the build-up of bubbles. For each sample the line width at half-height of each signal was measured at least four times using a 100-Hz sweepwidth, and each measurement was alternated with the line width measurement for the CH_3 proton resonance of *tert*-butyl alcohol. When the width of the *tert*-butyl alcohol signal varied by more than 0.1 Hz from one measurement to the next, the data were rejected. This procedure avoided occasional spurious line width values caused by bubbles on the wall of the sample tube. To minimize the accumulation of bubbles on the wall, the tubes were washed several times with Decon 75 detergent (Decon Laboratories Ltd.). All solutions were prepared with distilled water, but to assure that the line width effects were not due to traces of paramagnetic metal ions several runs were made with 0.04 M EDTA present and with doubly distilled water.

Results

Line width data for the keto, hydrate, and enol CH proton resonances at 4 °C are reported in Table I as $\Delta = \Delta\nu_{OA} - \Delta\nu_{t\text{-BuOH}}$ in which $\Delta\nu$ is the line width at half-height in hertz. $\Delta\nu_{t\text{-BuOH}}$, which refers to the line width of *tert*-butyl alcohol CH_3 protons, is used to eliminate line width fluctuations caused by changes in the homogeneity of the magnetic field from one measurement to the next. In the pH range 2.0 to 4.0 the evolution of CO_2 due to decarboxylation of OA can cause additional line broadening, and $\Delta\nu_{t\text{-BuOH}}$ takes this effect into account also (see Experimental Section). The number of samples used at each pH is designated as n. For each sample, the line width for each signal is an average of four measurements, and the value given in the table along with its standard deviation is an average of all the samples. The signal intensities were measured at the beginning and completion of the line width measurements, and it was found that the concentration of OA decreased about 20% during the time of the measurements (about 30 min) in this pH region. Below pH 4, the pH increases about 0.1 to 0.2 of a unit during the time of the measurement and the final value is listed in the table. For 4-ethyl oxaloacetate, Δ values were also measured under the same pH and temperature conditions, and the value for its enol CH proton resonance increases in a monotonic manner as the pH decreases (see Figure 1). We did not attempt measurements on 1-ethyl oxaloacetate because the anion decarboxylates even more rapidly than the monoanion of oxaloacetic acid.[9] In addition Δ values for the CH proton of the enol of 4-ethyl oxaloacetate were measured for a number of solutions containing 1 M concentrations of acids having pK_a values close to pK_{a2} of OA, which is 4.37 at 25 °C,[11,12] i.e., formic ($pK_a = 3.76$)[13] at pH 3.70, acetic ($pK_a = 4.75$)[13] at pH

Table I. NMR Line Width Data for Oxaloacetic Acid in Aqueous Solution as a Function of pH at 4 °C[a]

pH	Δ_{enol},[b] Hz	Δ_{keto},[b] Hz	Δ_{Hyd},[b] Hz	n[c]
1.1 ± 0.1	0.76 ± 0.24	0.24 ± 0.07	0.48 ± 0.06	3
1.3 ± 0.1	0.41 ± 0.05	0.16 ± 0.02	0.49 ± 0.02	2
1.9 ± 0.1	0.27 ± 0.1	0.1 ± 0.1	0.27 ± 0.05	3
2.7	0.81	0.02	0.22	1
3.0	0.91 ± 0.15	0.16 ± 0.01	0.30 ± 0.1	3
3.7 ± 0.1	0.68 ± 0.25[d]	0.15	0.30	1
3.7 ± 0.1	0.37 ± 0.01[e]			2
3.8 ± 0.1	0.63 ± 0.15[f]			4
4.3 ± 0.1	0.19 ± 0.16	0.28 ± 0.23	0.21 ± 0.05	3
5.0	−0.02	0.04	0.27	1
6.0	−0.11	−0.08	0.11	1
7.1	−0.11	−0.04	0.17	1

[a] Concentration of OA is 0.85 M unless otherwise specified. [b] Enol CH, keto CH_2, and hydrate CH_2 proton resonances. Relative to the line width of the CH_3 proton resonance of *tert*-butyl alcohol; see text. [c] Number of samples. At least four measurements of each line width were made on each sample. [d] n = 4, measured using an A-60A and an HA-100 spectrometer. [e] [OA] = 0.40, measured using an HA-100 spectrometer. [f] [OA] = 1.0, measured using an HA-100 spectrometer.

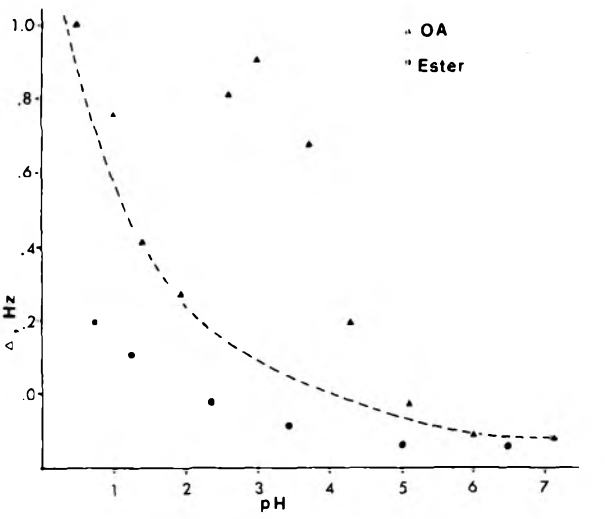
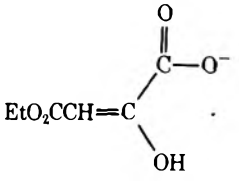


Figure 1. pH dependence for the NMR signal width due to the CH proton of the enol of OA and the monoethyl ester of OA in H_2O at 4 °C. $\Delta = \Delta\nu_{OA} - \Delta\nu_{t\text{-BuOH}}$, in which $\Delta\nu$ is the line width at half-height and $\Delta\nu_{t\text{-BuOH}}$ refers to the line width of the CH_3 proton of *tert*-butyl alcohol.

3.2, and malic acid (pK_{a_1} = 3.40 and pK_{a_2} = 5.11)[13] at pH 2.80 and 3.65. In the pH range employed the 4-ethyl oxaloacetate (pK_a = 2.74)[14] is mainly in the anionic form,



and the added acids are mainly in their acidic forms. The Δ values obtained under these conditions are within experimental error of those found for the monoester in the absence of added acid (see Figure 1), ranging from −0.03 Hz for malic to −0.10 Hz for acetic and formic acids.

Discussion

For the enol CH proton resonance of OA, Δ is pH dependent, and the form of this dependence is illustrated in Figure 1. As the pH is decreased from 7.1 to about 1.1, Δ passes through a maximum and a minimum, and this behavior is in contrast to that of the monotonic increase observed for the enol CH proton resonance of 4-ethyl oxaloacetate, which is illustrated in Figure 1, also, and was measured under identical conditions. Since effects due to fluctuation in field homogeneity have been removed, the variation in Δ is due to a variation in the proton exchange rate of a process involving the enol CH proton. We suggest that this process involves exchange between the enol CH proton and the keto and/or hydrate CH_2 protons. Proof for this exchange process involves detection of commensurate broadening of the CH_2 proton resonance of the keto and/or hydrate. The enol makes up only about 6% of the total OA concentration, while in the pH region at which Δ passes through a maximum, the keto and hydrate have comparable concentrations. Therefore, the broadening of the keto and hydrate signals is expected to be too small to be detected because the ratio of the line widths is inversely proportional to the ratio of the proton fractions when the signals are resolved.[15] That this is the case is indicated in Table I, which illustrates that the variation in Δ with pH is within the standard deviation for the keto and hydrate signal widths at pH values of 1.9 and above. Thus, while the broadening effects in this pH region are consistent with proton exchange between enol and keto and/or hydrate forms of OA (and similarly for the monoester), more accurate measurement would be needed to distinguish between these two processes. But the exchange process can be tentatively identified as an enol ⇌ keto tautomerization on the basis of experiments at 38 °C. At this temperature the enol signal for OA monoanion is too broad to be observed,[16,17] and although the keto/hydrate ratio ≃ 2.4, the width at half-height for the keto peak is twice that for the hydrate (1.8 vs. 0.9 Hz).[16]

The variation in Δ in the pH region 2 to 5 parallels that for the fraction of OA present as monoanion. To treat the data quantitatively, we have drawn a smooth curve through the points at low and high pH's and have calculated the difference (Δ_{dif}) between the experimental points and the dashed curve.[18] Values of Δ_{dif} along with the ionic strength are tabulated in Table II for various pH values. Also listed in Table II is the fraction of OA that exists as the monoanion calculated for each pH using the expression,[19]

$$f = ([H^+]/K_{a_1} + 1 + K_{a_2}/[H^+])^{-1}$$

in which $[H^+]$ = antilog [−pH]. The values for the macroscopic acid dissociation constants K_{a_1} and K_{a_2} for OA at 4 °C at zero ionic strength were obtained by extrapolation of values given at 25 and 37 °C[11] and differ only slightly from those at 25 °C. Since the ionic strength is not zero and varies with pH, values for K_{a_1} and K_{a_2} that are listed in Table II were calculated using the empirical expressions determined previously[11,12] at 25 °C, assuming that the ionic strength dependence at 4 °C is identical with that at 25 °C. The only modification of these equations involved substitution of the 4 °C values of K_{a_1} and K_{a_2} at zero ionic strength for the 25 °C values. This approach must be considered approximate for two reasons: (1) the empirical equations were developed from potentiometric data for solutions having ionic strengths up to 0.3 (NaCl)[11] whereas our solutions have substantially larger ionic strengths (see Table II); (2) the coefficients in these equations appear to be temperature dependent.[12] Consequently the analysis given below must be considered semiquantitative at best.

As indicated in Table II, the pH dependence of f parallels that for Δ_{dif} when the concentration of OA is constant. With these two parameters, it is possible to deduce a rate expression for exchange involving the enol proton in the following manner. Since the CH proton resonances of the keto, hydrate, and enol forms of OA are resolved, the average lifetime τ and rate for the enol CH proton can be calculated[15] using the expres-

Table II. Kinetic and Equilibrium Parameters for OA at 4 °C

pH	u[a]	$[OA]_t$,[b] M	pK_{a_1}	pK_{a_2}	f	Δ_{dif}, Hz	k_2', $M^{-1}s^{-1}$	k_2, $M^{-1}s^{-1}$
2.7	0.5	0.85	2.41	3.72	0.62	0.64	3.8[c]	6.2[d]
3.0	0.6		2.42	3.75	0.69	0.80	4.3	6.2
3.7	0.9		2.48	3.89	0.59	0.64	4.0	6.8
3.7	0.56	0.40	2.48	3.89	0.59	0.33	4.4	7.4
3.8	1.0	1.0	2.49	4.01	0.55	0.59	3.4	6.1
4.3	1.2	0.85	2.55	4.06	0.36	0.22	2.3	6.3
5.0	1.6		2.65	4.29	0.15	0.05	1.2	7.4

[a] Ionic strength, calculated assuming that OA^{2-} is equivalent to two monoanions. [b] Total concentration including all tautomeric forms and all degrees of protonation. [c] $k_2' = (\Delta_{dif}\pi)/(f[OA]_t)$. [d] $k_2 = (\Delta_{dif}\pi)/(f^2[OA]_t)$.

sions $1/\tau = \pi\Delta_{diff}$ and $1/\tau$ = rate/[enol]. Thus, rate = $\pi\Delta_{diff}$[enol], and the concentration dependence of the rate may be deduced from the pH and concentration data in Table II. A good fit is obtained using,

$$\text{rate} = k_2 f^2[\text{enol}]_t[\text{OA}]_t \quad (1)$$

in which $[OA]_t$ is the total concentration of OA, including all tautomeric forms and degrees of protonation, and $[enol]_t$ is the total enol concentration, including all degrees of protonation. The values of k_2 calculated according to eq 1 are listed in Table II. For comparison, the data also were fitted to the expression,

$$\text{rate} = k_2' f[\text{enol}]_t[\text{OA}]_t \quad (2)$$

and values of k_2' are listed in Table II. The data appear to fit eq 1 better than eq 2, although the very good fit obtained with eq 1 may be somewhat fortuitous in view of the precision of the line width measurements (see Table I) and the semiquantitative manner in which Δ_{dif} and the acid dissociation constants are determined. But eq 2 is unlikely to be correct. Let us consider eq 2 rewritten in two forms: rate = k_2'-$[EH^-][OA]_t$ and rate = $k_2'[enol]_t[OAH^-]$, in which EH^- is the monoanion of the enol and OAH^- is the monoanion of all tautomers of OA. The first form suggests that the catalytic power of an OA molecule is independent of its state of protonation, and the second suggests that the reactivity of an enol molecule is independent of its state of protonotion. Neither of these possibilities seems reasonable.

Furthermore, the magnitude of the broadening is too large to be explained on the basis of uncatalyzed or proton-catalyzed pathways.[20] The contribution from these pathways may be estimated from data of Banks[4] at 1.5 °C that indicate that the enol monoanion is more reactive than the dianion and from data of Leussing[21] at 25 °C which indicate that the enol monoanion is also more reactive than the diacid. Consequently, the pH rate profile for the enol would be bell shaped. However, the maximum contribution to the line width from this process is calculated to be only 0.35 Hz at 25 °C or 0.04 Hz to 1.5 °C. Thus this process cannot account for the maximum observed for Δ, which is 1.0 Hz larger at pH 3 than at pH 7, the pH at which the exchange has a negligible effect on the line width.

Therefore, to account for the additional line broadening, we have considered possible mechanisms of keto–enol tautomerisim that are consistent with eq 1. Equation 1 can be rewritten in at least three kinetically equivalent forms: (a) rate = $k_2[EH^-][OAH^-]$, (b) rate = $k_2(K_{a_1}/K_{a_2})[E^{2-}][OAH_2]$, and (c) rate = $k_2(K_{a_1}/K_{a_2})[EH_2][OA^{2-}]$. Form b can be interpreted mechanistically in terms of general acid catalysis and form c in terms of general base catalysis. Form a is consistent with either type of catalysis and with concerted general acid plus general base catalysis. We would like to identify the form that is kinetically most significant and to determine if there are any special bifunctional catalytic effects operating.

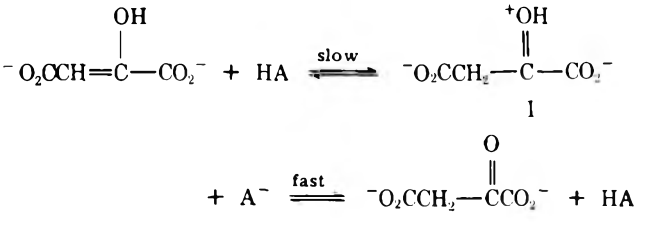
One approach to the detection of bifunctional catalysis is the comparison of the catalytic activities of monofunctional and bifunctional molecules using the Brönsted relationship. Unfortunately, experimentally determined Brönsted coefficients are not available, and it is necessary to estimate values for two of the possible five reaction pathways as discussed below.[22]

For a monofunctional acid such as acetic acid for which data are available, general acid catalysis of the reaction of the enol dianion (form b) and general base catalysis of the reaction of the enol monoanion (form a) are kinetically equivalent, and, therefore, if the Brönsted relations are obeyed, the coefficients are related by $\alpha + \beta = 1.0$. Scheme I shows the usual mechanisms for general acid and base catalysis of keto–enol tautomerization. Because of the kinetic equivalence it is impossible to know a priori which of the two slow steps is actually the rate-determining step. That is, in the absence of experimental Brönsted coefficients, any extrapolation from the observed catalytic coefficient of one catalyst to a predicted coefficient for some other catalyst must be done using the probable Brönsted coefficients for each of the pathways in Scheme I.

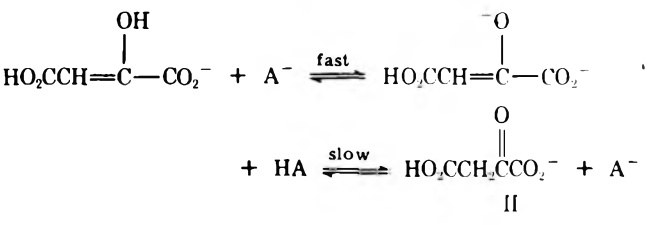
Our estimates of Brönsted coefficients are based on an observation by Bell[23] that the β for carboxylate ion catalyzed ionization of ketones is a function of the acidity of the ketone. Thus, for a general base-catalyzed reaction (involving the slow step of the lower pathway of Scheme I) we estimate $\beta = 0.52$, the value for the carboxylate-ion-catalyzed enolization of benzoylacetone, which has nearly the same pK_a as 4-ethyl oxaloacetate ion.[24] To estimate the Brönsted coefficient for a general acid-catalyzed reaction (involving the upper pathway of Scheme I) we make use of the fact that $\alpha' = 1 - \beta'$, in

Scheme I

General acid catalysis



General base catalysis



which β' is the Brönsted coefficient for the single step $^{-}O_2C-CH_2C(OH^+)CO_2^- + A^- \rightarrow {}^{-}O_2CCH{=}C(OH)CO_2^- + HA$. β' is expected to be smaller than β because the CH protons of the carbonyl-protonated oxaloacetate are much more acidic than those of carboxyl-protonated oxaloacetate. The difference, $\beta - \beta'$, for the oxaloacetate system is estimated to be 0.43, which is obtained from the values (0.88 and 0.45)[23,25] for the corresponding reactions for acetone. This approximation that $\beta - \beta'$ is the same for both acetone and oxaloacetate systems seems justified because the difference in acidity between the CH_2 protons in I and II is about the same as the corresponding difference between protonated acetone and acetone ($\Delta pK_a = -11$ and -14, respectively).[26] Thus, β' for oxaloacetate is the difference between 0.52 and 0.43, and α' is $1 - \beta'$ or 0.91.

With these values for α' and β, data for the catalysis of keto–enol tautomerization by acetic acid[4] can be used to estimate the effectiveness of other monofunctional catalysts. First consider kinetic form b, according to which OAH_2 acts as a general acid toward E^{2-}. For this form, a value of $k_2K_{a_1}/K_{a_2} = 150\ M^{-1}\ s^{-1}$ can be calculated using the average of the values of k_2 given in Table II and the values of K_{a_1} and K_{a_2} at pH 3.7. This can be compared to a value of 140 $M^{-1}\ s^{-1}$ obtained by extrapolation of Banks'[4] value of 1.2 $M^{-1}\ s^{-1}$ for acetic acid catalysis at 1.5 °C using the Brönsted relation and $\alpha' = 0.91$. According to this comparison, the observed catalysis is no greater than expected for *monofunctional* general acid catalysis by OAH_2.[30,31]

It is also possible to make the comparison in terms of the kinetically equivalent action of OAH^- or acetate ion on the (carboxyl protonated) enol monoanion. For form a, the average of the values of k_2 given in Table II is 6 $M^{-1}\ s^{-1}$, which can be compared to a value of 0.8 $M^{-1}\ s^{-1}$. The latter value was obtained by a Brönsted extrapolation of the corresponding rate constant (12 M^{-1}) that was calculated from the data of Banks[4] for acetate catalysis on the enol monoanion using $\beta = 0.52$. Thus, *monofunctional* general base catalysis according to form a cannot account for the observed exchange rate. Allowing that 4-ethyl oxaloacetate anion is a good model for the principal protonated form of OAH^-, the line width for the ester in the presence of formic acid provides information that also appears to preclude this mechanism. Assuming that the exchange rate makes a negligible contribution to the line width for the ester enol CH proton resonance at pH 6.5, the excess line width at pH 3.72 in the presence of 1 M formic acid is 0.14 rad/s. Thus, the upper limit for the rate constant is calculated to be 0.28 $M^{-1}\ s^{-1}$ for formate ion catalysis of the ketonization of enol of the ester monoanion. Since the formate ion is a stronger base than OAH^-, this value is an upper limit for monofunctional general base catalysis by OAH^-. This limit is about 20 times smaller than k_2 (Table II), indicating that monofunctional general base catalysis cannot account for the exchange broadening.

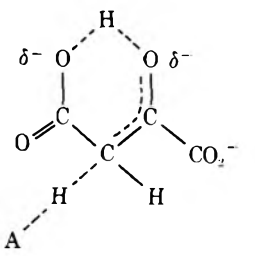
The ester results appear to rule out some of the other possible mechanisms also. Acid catalysis by formic acid for ketonization of the enol of the ester anion should be similar to monofunctional general acid catalysis according to form a. Based on the data in the preceding paragraph, the upper limit for the rate constant for formic acid catalysis of ketonization of the ester monoanion is 0.28 $M^{-1}\ s^{-1}$. Since the pK_a of formic acid is lower than pK_{a_2} for OA, this value would be an upper limit for general acid catalysis by OAH^- according to form a. This value is more than a factor of 20 smaller than k_2 in Table II; therefore, the contribution due general acid catalysis by OAH^- on EH^- appears to be negligible.

The relative importance of form c may also be ascertained by reference to the formic acid catalysis for the ester. Since the expression $k[E^-][HA]$ is kinetically equivalent to $k'\cdot[EH][A^-]$, in which HA is formic acid, an upper limit to k' can be obtained as $kK_{a(EH)}/K_{a(HA)}$, which has a value 2.8 $M^{-1}\ s^{-1}$. Assuming that the Brönsted relation applies, this value may be converted to one for the rate constant for general base catalysis by OA^{2-} according to form c. For this purpose, the difference between the pK_a for formic acid and that for OAH^- is assumed to be independent of ionic strength. Even if β were 1.0, the extrapolated value of the rate constant would be only 11 $M^{-1}\ s^{-1}$, which is over a factor of 10 smaller than the value for the experimental rate constant in terms of form c, 150 $M^{-1}\ s^{-1}$. Thus, the contribution to ketonization rate by form c appears small.

According to the discussion above then, general acid catalysis by OAH_2 of the ketonization of enol dianion (upper path of Scheme I) is the only *monofunctional* process that would be expected to be fast enough to explain the bell-shaped dependence observed for Δ for the enol in the pH range 2 to 5. However, none of the discussion presented above precludes the possibility of bifunctional catalysis by OAH^- in a general acid–general base fashion using the carboxyl and carboxylate groups on the OAH^- molecules.[32] If the monoanion of malic acid is used as a model for OAH^- then the line width data for the ester in the presence of 1 M malic acid indicate that this path is probably unimportant. At pH 3.65, the line width for the enol CH proton of the ester has the same value in the presence of either malic or formic acid. If the monoanion of malic acid were an effective bifunctional catalyst, its presence should result in a larger line width compared to formic acid. Thus general acid catalysis by OAH_2 appears to be the predominant pathway for the ketonization of the enol.

It is possible that this pathway is more complex than the process illustrated in Scheme I. The results for OA do not preclude the possibility of intramolecular assistance by one of the carboxylate groups. Bell suggests an intramolecular contribution in the enolization of 2-oxobicyclo[2.2.2]octane-1-carboxylic acid catalyzed by acetate ions (or its kinetic equivalent, enolization of the carboxylate ion catalyzed by acetic acid)[6] in the enolization of 2-oxocyclopentanecarboxylic acid[6] and in the enolization of acetoacetic acid.[33] These suggestions are based on comparison of the reactivity of a keto acid with its corresponding ester, and the intramolecular contribution is pictured as an H-bonding or electrostatic stabilization of the transition state by the carboxyl group. The case for such participation may be stronger than previously suggested. The formulation of general acid catalysis in a mechanism like that in Scheme I is based on the observation that the general acid catalysis of ketonization of an enol and hydrolysis of its enol ether proceed with similar rates.[34] On the other hand, if protonation of the vinyl carbon is facilitated by intramolecular interaction between the OH of the enol and a carboxylate group, the enol should react considerably faster than the corresponding enol ether. In at least one case such a comparison is possible. Thus the "uncatalyzed" ketonization of the enol of cyclopentanone-2-carboxylic acid[6] is at least ten thousand times faster than the uncatalyzed hydrolysis of the corresponding enol ether.[35] For the purposes of this comparison, the rate constant for ketonization, k_{keto}, of the enol of 2-oxocyclopentanecarboxylic acid can be calculated using $k_{keto} = k_{enol}/K_{enol}$, in which k_{enol} is the experimental value of the enolization rate constant[6] and $K_{enol} = [enol]/[keto]$. Since the value of K_{enol} seems to be unreported, we have used $K_{enol} = 0.064$, which is the value for ethyl 2-oxocyclopentanecarboxylate in ethanol.[36] The ketonization rate constant obtained in this manner is probably too small, since we have probably overestimated K_{enol}, i.e., for ethyl acetoacetate, K_{enol} is reduced by a factor of about 30 when the solvent is changed from ethanol to water.[37] When the mechanism of OA enolization includes intramolecular participation of one of the carboxyl groups the distinction between general acid and base catalysis may vanish.[38] For example, if participation of the β-carboxyl

group is involved, then the mechanisms in Scheme I merge to one involving the transition state species III.



III

Registry No.—Oxaloacetic acid, 328-42-7; oxaloacetic acid enol, 7619-04-7; oxaloacetic acid hydrate (gem-diol), 60047-52-1; 4-ethyl oxaloacetate, 2401-96-9; 4-ethyl oxaloacetate enol, 63797-61-5.

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Nucleophilic Aromatic Substitution Promoted by Cobalt(III) Trifluoroacetate[1]

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A series of aromatics was subjected to oxidation by cobalt(III) trifluoroacetate in the presence of a variety of nucleophiles. In this manner benzene was successfully halogenated with chloride, bromide, and iodide, and toluene, chlorobenzene, and benzotrifluoride were also chlorinated. Attempts to substitute fluoride, cyanide, and nitrate onto benzene were thwarted by solvent interference. Nitrite ion was oxidized to nitrogen dioxide and no substitution products were formed. A mechanism involving aromatic radical cations is most consistent for the aromatic–chloride–cobalt(III) reactions. However, with many of the other nucleophiles an alternate reaction pathway involving ligand oxidation by metal ion appears more likely.

An interesting type of nucleophilic aromatic substitution can be accomplished by reacting nucleophiles with aromatic radical cations produced by an appropriate oxidant (eq 1). Both electrochemical oxidation[2] and chemical oxidizing agents such as xenon difluoride,[3,4] peroxydisulfate,[5,6] manganese(III) acetate,[7,8] and cobalt(III) acetate[9] have been effectively used in this manner. One of the limitations of these reactions, however, is the need to use aromatics of somewhat lower ionization potential (i.e., more electron rich).[8] Substitution of trifluoroacetate for acetate ligands on the cobalt complex was found to enhance its oxidative powers,[9-11] thus allowing radical cations to be formed from benzene and deactivated

Table I. Chlorination of Benzene

Reactant ratio C_6H_6–Co(TFA)$_3$–LiCl	Products % C_6H_5Cl[a]	% C_6H_5OTF[a]
12:0:3	0	0
12:1:0	0	39
12:1:1	37	30
12:1:2	67	6
12:1:3	66	0
12:1:5	70	0
12:1[b]:3	<1	0

[a] Yield based on 0.5 mol of product produced per 1.0 mol of cobalt(III) consumed; OTF = O_2CCF_3. [b] Cobalt(III) acetate in acetic acid solvent.

aromatics such as chlorobenzene and benzotrifluoride. The radical cations of benzene and chlorobenzene underwent trifluoroacetoxylation with cobalt(III) trifluoroacetate.[10]

$$ArH \xrightarrow{[O]} ArH^+ \cdot \xrightarrow{X^-} Ar\overset{H}{\underset{X}{\cdot}} \xrightarrow[-H^+]{[O]} ArX \qquad (1)$$

The purpose of this study was to utilize the potent oxidant cobalt(III) trifluoroacetate with a series of aromatics (anisole, toluene, benzene, chlorobenzene, and benzotrifluoride) in the presence of a variety of nucleophiles (halides, cyanide, nitrate, and nitrite) in an effort to determine whether the corresponding nucleophilic substitution products could be obtained.

Results

Aromatic–Cobalt(III) Trifluoroacetate–Lithium Chloride. Initially, a control reaction in which benzene was treated with a solution of cobalt(III) trifluoroacetate[10,11] was performed. Phenyl trifluoroacetate was the only product observed (Table I), consistent with an earlier report.[10] The less than quantitative yield in the presence of excess benzene has been suggested to be due to polyphenylated materials arising from side reaction with excess aromatic.[10]

Inclusion of chloride ion (1:1 molar ratio with the cobalt(III) salt) led to a 37% yield of chlorobenzene and a somewhat reduced amount of phenyl trifluoroacetate. Increasing the ratio of chloride ion to cobalt(III) led predominantly or exclusively to chlorobenzene (Table I). Since the optimum reaction condition for chlorination was a 3:1 ratio of nucleophile-containing salt to cobalt(III), these conditions were adopted for most other reactions in the study.

A number of control reactions demonstrated the importance of this particular cobalt(III) salt. Treatment of benzene with chloride or with chloride and cobalt(III) acetate in acetic acid gave no substitution products (Table I).

Reaction of chlorobenzene using the same conditions as with benzene also resulted in chlorination (Table II). The dichlorobenzenes consisted of 19% ortho and 81% para isomers. Treatment of chlorobenzene with chlorine in this same solvent system both with and without cobalt(III) trifluoroacetate gave dichlorobenzenes with an isomer distribution of ortho/meta/para = 28/0.3/72.

Though little substitution was observed with benzotrifluoride under usual conditions, refluxing the mixture (65 °C) led to reduction of the cobalt(III) complex and nuclear chlorination products. The isomeric distribution was not determined.

The reaction with toluene resulted in a complex mixture of products including chlorinated toluenes, dimers, and trimers. With air present, the major chlorotoluene found was the nuclear substitution product (ortho/para = 41/59), while a small amount of the side-chain product, benzyl chloride, was observed. Under nitrogen, the major chlorinated product was benzyl chloride; chlorotoluenes were formed only in small quantities. Control reactions showed that in this solvent mixture chlorine reacted with toluene to give an ortho/para mixture of 65/35.

Unlike the other aromatics, the reaction of anisole with chloride ion and cobalt(III) trifluoroacetate gave rise to no chlorination products. Instead, *p*-methoxyacetophenone was formed in a very high yield and *p,p'*-dimethoxybiphenyl in yields of 46% (no other isomers found). All the cobalt(III) species was reduced in the reaction. A control reaction in which the cobalt(III) complex was omitted and lithium acetate added instead led to the acetophenone product. This suggested that the acetate ligands present in the cobalt salt solution were responsible for the major product observed.[12]

Control reactions showed that molecular chlorine, if present, would chlorinate anisole (ortho/para = 37/63). However, when equimolar amounts of chlorine and cobalt(III) trifluoroacetate were allowed to compete for a limited amount of anisole, no chlorination was observed (Table II).

Benzene–Cobalt(III) Trifluoroacetate–Other Nucleophiles. When benzene was reacted with lithium bromide in the presence of cobalt(III) trifluoroacetate, a good yield (60%) of bromobenzene was obtained, and no phenyl trifluoroacetate was noted (Table III). Molecular bromine itself in

Table II. Other Aromatics–Co(TFA)$_3$–Chloride[a]

Aromatic	Registry no.	Reagent	Products (% yield)[b]
PhCl	108-90-7	Co(TFA)$_3$–LiCl[c]	$C_6H_4Cl_2$ (43%, *o/p* = 19/81)
PhCl		Co(TFA)$_3$–Cl_2[d]	$C_6H_4Cl_2$[e] (*o/m/p* = 27/0.3/73)
PhCl		Cl_2	$C_6H_4Cl_2$[e] (*o/m/p* = 29/0.2/71)
$PhCF_3$	98-08-8	Co(TFA)$_3$–LiCl[c]	$ClC_6H_4CF_3$ (39%)[f]
$PhCH_3$	108-88-3	Co(TFA)$_3$–LiCl[c]	$ClC_6H_4CH_3$ (≃5%, *o/p* = 41/59)
			$C_6H_5CH_2Cl$ (<1%)
			$C_{14}H_{14}$[g] (≃5%) + $C_{21}H_{21}$[g] (≃7%)
$PhCH_3$		Cl_2	$ClC_6H_4CH_3$[b] (*o/p* = 65/35)
$PhOCH_3$	100-66-3	Co(TFA)$_3$–LiCl[c]	$(p\text{-}CH_3OC_6H_4)_2$ (46%)
			$CH_3COC_6H_4OCH_3$ (≃220%[h])
$PhOCH_3$[i]		Co(TFA)$_3$–Cl_2[d]	$(p\text{-}CH_3OC_6H_4)_2$[e] + $CH_3COC_6H_4OCH_3$[e]
$PhOCH_3$[j]		Co(TFA)$_3$–Cl_2[d]	$(p\text{-}CH_3OC_6H_2)_2$[e] + $CH_3COC_6H_4OCH_3$[e]
			$ClC_6H_4OCH_3$[e] (*o/p* = 21/79)
$PhOCH_3$		Cl_2	$ClC_6H_4OCH_3$[e] (*o/p* = 37/63)

[a] Reactions carried out in trifluoroacetic acid–trifluoroacetic anhydride (90/10) solvent with excess aromatic at 25 °C. [b] Based on 0.5 mol of product produced per mol of cobalt(III) consumed. [c] In 1:3 molar ratio. [d] In 1:1 molar ratio. [e] Yield not determined. [f] Isomers not determined. [g] Isomer mixtures; tentative identification based on similarity of GC retention times to authentics. [h] Yield based on available acetate is 73%. [i] Aromatic/Co(TFA)$_3$ molar ratio = 1:2. [j] Aromatic/Co(TFA)$_3$ molar ratio = 1:1.

Table III. Reaction of Other Nucleophiles with Benzene–Co(TFA)$_3$[a]

$C_6H_6 + Co(TFA)_3 \xrightarrow{X^-}$, X =	% C_6H_5X[b]	% $C_6H_5O_2CCF_3$[b]
Br^-	60	0
I^-	38	0
F^-	0	20
F^-[c]	0	30
CN^-	0	56
NO_2^-[d]	0	0
NO_3^-	0	20[e]
I_2	83[g]	0
I_2[f]	0	0
I^-[f]	0	0
Br_2[f]	251[g]	0

[a] Mole ratio of benzene/cobalt(III)/nucleophile = 12:1:3. [b] Yield based on 0.5 mol of product formed per mol of cobalt(III) consumed. [c] With added 15-crown-5. [d] Nitrogen dioxide fumes were observed. [e] In addition, nitrobenzene (>200%) was obtained; the limiting reagent in this process is the nitrate anion accounting for the high yield based on cobalt(III). [f] No $Co(TFA)_3$ used. [g] These yields are based on cobalt(III) in comparable runs; based on the halogens, they are 14% for I_2 and 42% for Br_2.

the same solvent system but without the cobalt(III) salt effectively produced bromobenzene (Table III).

The reaction of benzene with sodium iodide and cobalt(III) trifluoroacetate gave a moderate yield of iodobenzene (Table III). Three control reactions were performed in this solvent mixture with various potential iodinating species. Without cobalt(III) trifluoroacetate neither sodium iodide nor molecular iodine was able to cause iodination. However, iodobenzene was formed when molecular iodine was used in conjunction with cobalt(III) trifluoroacetate.

An attempt to fluorinate benzene by employing lithium fluoride along with the cobalt(III) salt was made. Fluorobenzene was not obtained; phenyl trifluoroacetate was the only substitution product observed (Table III). Even the use of the crown ether, 15-crown-5, with lithium fluoride in an effort to enhance the nucleophilic properties of the fluoride[13] did not promote fluorination.

None of the anticipated substitution product, benzonitrile, was detected when benzene was reacted with cyanide and the cobalt(III) salt. Instead, a 56% yield of phenyl trifluoroacetate was obtained (Table III).

Upon introduction of sodium nitrite into the cobalt(III) system, no substitution products of any type were formed. Instead, a brown gas (NO_2) was observed above the reaction mixture immediately after mixing.

An attempt was made to substitute nitrate onto benzene to form an aryl nitrate. Instead phenyl trifluoroacetate and a large yield of nitrobenzene were the only aromatic products (Table III). Nitrobenzene was also obtained in a control experiment involving all reactants with the exception of the cobalt(III) salt. This suggested the formation of an active migrating agent such as trifluoroacetyl nitrate,[14] **1**, from nitrate and solvent (eq 2).

$$(CF_3CO)_2O + NO_3^- \rightarrow \underset{\mathbf{1}}{CF_3CONO_3} + CF_3CO_2^- \quad (2)$$

Discussion

A number of possible mechanisms exist for systems in which an aromatic and a nucleophile are subjected to a strong oxidant. Equation 1 shows one possibility, a radical cation mechanism, where the oxidant is cobalt(III) trifluoroacetate. A second pathway would involve the preferential oxidation of nucleophile by the cobalt(III) salt (eq 3) followed by substitution (electrophilic or radical) of the resultant species onto the aromatic (eq 4).[15] Some controversy over which scheme is operative has appeared in the literature for a number of chlorination reactions.[6,16]

$$2X^- \xrightarrow[-2Co(II)]{2Co(III)} X_2 \quad (3)$$

$$X_2 + ArH \rightarrow ArX + HX \quad (4)$$

The mechanism felt to be most consistent with the results in the cobalt(III)–LiCl–aromatic reactions is the radical cation scheme (eq 1, [O] = Co(III), X^- = Cl^-). The net stoichiometry is shown in eq 5.

$$ArH + 2Co(O_2CCF_3)_3 + LiX \rightarrow ArX + 2Co(O_2CCF_3)_2 + CF_3CO_2H + LiO_2CCF_3 \quad (5)$$

Few reaction pathways are open to the radical cations formed from deactivated (electron poor) aromatics; thus chlorination by way of chloride ion attack (eq 1) was the major reaction with benzene, chlorobenzene, and benzotrifluoride. Chloride ion, being a better nucleophile than trifluoroacetate, effectively competed at lower concentrations and dominated trapping of the radical cation at higher concentrations (Table I). The need to react benzotrifluoride at elevated temperatures was consistent with its hesitancy towards radical cation production as measured by its higher ionization potential.[10]

Toluene is even more readily oxidized to a radical cation than is benzene, yet poorer substitution yields were noted. This is due primarily to the tendency of toluene radical cation, **2**, to lose a proton-forming benzyl radical (eq 6). Evidence for this competing process was the identification of benzyl chloride (eq 7a) and oligomeric toluenes (eq 7b) among the products.[10]

$$\underset{\mathbf{2}}{C_6H_5CH_3^+\cdot} \rightarrow C_6H_5CH_2\cdot \quad (6)$$

$$C_6H_5CH_2\cdot \xrightarrow[-Co(II)]{Co(III)} \begin{cases} \xrightarrow{Cl^-} C_6H_5CH_2Cl & (7a) \\ \xrightarrow[-H^+]{C_6H_5CH_3} C_{14}H_{14} & (7b) \end{cases}$$

The isomer distributions of the chlorotoluenes and dichlorobenzenes obtained from toluene and chlorobenzene, respectively, were different from those obtained from molecular chlorine in the same solvent system (Table II). This would be expected if a radical cation mechanism were involved.

The failure to observe chloroanisoles from anisole–lithium chloride–cobalt(III) trifluoroacetate was somewhat perplexing. Apparently the anisole radical cation undergoes reaction with another anisole molecule leading to the observed dimer (eq 8) more readily than it undergoes attack by the chloride

$$C_6H_5OCH_3^{+\cdot} + C_6H_5OCH_3 \rightarrow CH_3OC_6H_4\overset{H}{\underset{H}{\overset{|}{\underset{|}{C}}}}C_6H_4OCH_3 \xrightarrow[-Co(II)]{Co(III)} \xrightarrow{-2H^+} CH_3OC_6H_4C_6H_4OCH_3 \quad (8)$$

nucleophile (eq 1). Kochi has reported such a reaction for radical cations of electron-rich aromatics[10] and others have also noted the occurrence of dimerization for methoxy-substituted rings in radical cation systems.[17] Eberhardt[18] has observed the failure of the anisole radical cation to react with water as the nucleophile to yield the corresponding phenol, whereas with the radical cations of fluorobenzene and toluene this process proceeded smoothly.

An additional probe for the involvement of molecular chlorine was an experiment in which cyclohexene, which reacts

readily with molecular chlorine,[19] was added to lithium chloride–cobalt(III) trifluoroacetate both with and without added benzene. In the former case no chlorinated cyclohexane products were found while in the latter cyclohexyl chloride was pinpointed among a complex product mixture. Apparently simple aromatics are oxidized in preference to chloride ion in this system.

With more readily oxidized ligands, the evidence for radical cation participation diminishes. Although bromination and iodination of benzene might involve the radical cation process (eq 1), the alternate scheme (eq 3 and 4) becomes more likely. In fact electrochemical iodinations occur by the latter mechanism.[20]

Molecular iodine itself and also the iodide ion were shown to be ineffective iodinating agents in the trifluoroacetic acid–anhydride media (Table III). However, when molecular iodine was added directly to the cobalt(III)–benzene system in the same solvent, iodination did in fact occur. Other studies have shown that aromatic iodinations require relatively reactive iodinating agents.[19] The bromination control also demonstrates that either process (eq 1 or eq 3 and 4) could account for the observed bromobenzenes.

A definitive example of preferential interaction of the cobalt(III) complex with the nucleophile rather than with the aromatic occurred when nitrite was incorporated into the system. Oxidation to nitrogen dioxide (eq 9) took place as evidenced by the brown gas above the reaction mixture. No aromatic substitution products were formed, implying that all the cobalt(III) was reduced by nitrite.

$$NO_2^- \xrightarrow[-Co(II)]{Co(III)} NO_2 \qquad (9)$$

The rationale for failure to substitute fluoride or cyanide ions under the influence of cobalt(III) trifluoroacetate is probably due to their protonation by the strongly acid solvent, thus greatly reducing their nucleophilicity. Solvent interference also prevented nitrate substitution by formation of trifluoroacetyl nitrate (eq 2), an eventual nitrating agent (vide supra). In all three cases only the trifluoroacetate ligand was left to react with the radical cation.

Experimental Section

The organic reagents, shown to be greater than 99% pure by GC, were used directly as were the reagent grade inorganic salts. Cobalt(III) acetate was prepared from the corresponding cobalt(II) salt by ozonolysis[11] and was shown to be 84% pure by iodometric titration.

Authentic aryl trifluoroacetates were prepared from the appropriate phenol (0.05 mol) and trifluoroacetic anhydride (0.071 mol) and purified by direct distillation. In this manner, phenyl trifluoroacetate (bp 145–146 °C), o-methoxyphenyl trifluoroacetate (bp 191–193 °C), *m*-methoxyphenyl trifluoroacetate (bp 195–196 °C), and *p*-methoxyphenyl trifluoroacetate (bp 196–199 °C) were prepared. *p*-Methoxyacetophenone was prepared from *p*-hydroxyacetophenone and dimethyl sulfate.[21] Most other compounds needed as authentics in this study were commercially available.

For all reactions run in this study, the cobalt(III) trifluoroacetate salt was formed "in situ" by dissolving cobalt(III) acetate in a mixture of trifluoroacetic acid and trifluoroacetic anhydride.[10,11] Verification of ligand exchange to produce the desired species was obtained from visible spectra.

Reaction of Aromatics with Cobalt(III) Trifluoroacetate and a Nucleophile. General Procedure. The aromatic to be reacted (0.047–0.065 mol) was dissolved in a portion of trifluoroacetic acid (15–40 mL). Whenever a nucleophile was also to be reacted, it was added as the sodium or lithium salt (0.005–0.015 mol) to this same portion of solvent. The cobalt(III) acetate (0.005 mol) was dissolved in a second portion of solution (10–15 mL) consisting of a mixture of trifluoroacetic acid and trifluoroacetic anhydride (50% by volume). When dissolution of solids was complete, the two solutions were rapidly mixed and allowed to react to completion at a temperature of 25 °C. In general, the presence of oxygen did not affect the reaction. The only exception was the case with toluene as the reactant.

The completeness of reaction was judged by color change (the cobalt(II) complex is violet whereas the cobalt(III) complex is green) as well as by iodometric titration to determine cobalt(III) remaining.

The reaction vessel was heated to 65–70 °C whenever the reaction did not proceed readily at 25 °C.

In reactions in which crown ethers were used, the appropriate crown ether (15-crown-5) was added to the reaction in small amounts, while all other reaction conditions remained constant.

Control reactions involving only cobalt(III) trifluoroacetate, halogen, or the nucleophile with the aromatic were run under analogous conditions.

Identification of Organic Products. Comparison of GC retention times of products from the reaction mixtures directly or from base-washed ether extracts to those of the appropriate authentics constituted one method of product analysis. A Hewlett-Packard Model 5830A GC equipped with dual columns (1.67 ft × 0.125 in. stainless steel UCW-982/Chromosorb W and 6 ft × 0.125 in. stainless steel OV-225/Chromosorb W), hydrogen flame ionization detectors, and programmable console was used for this purpose.

In addition the ether extracts of most reaction mixtures (after base extraction) were subjected to GC–MS analysis (Finnegan Model 3000 with quadrupole mass filter operated at 70 eV and coupled with a 3% OV-1/Chromosorb W GC column).

Where authentics were available, consistency between product mass spectra and authentic mass spectra confirmed identity. In this manner phenyl trifluoroacetate (molecular ion at *m/e* 190, base peak at *m/e* 69), chlorobenzene (molecular ions at *m/e* 113–115, base peak at *m/e* 51), bromobenzene (molecular ions at *m/e* 156–158, base peak at *m/e* 77), iodobenzene (molecular ion at *m/e* 204, base peak at *m/e* 51), *p*-methoxyacetophenone (molecular ion at *m/e* 150, base peak at *m/e* 65), and nitrobenzene (molecular ion at *m/e* 123, base peak at *m/e* 77) were identified. Due to relatively low yields of clorotoluenes and benzyl chloride from toluene and *o*- and *p*-dichlorobenzene from chlorobenzene no mass spectra were obtained. In these cases, identification of these products was based only on comparison of retention times with authentics on two dissimilar GC columns.

No chlorobenzotrifluoride or *p,p'*-dimethoxybiphenyl authentics were available; thus mass spectra data alone were used to determine product identity. The chlorinated benzotrifluoride mass spectra (molecular ion at *m/e* 180–182, base peak at *m/e* 59, others in decreasing intensity at *m/e* 77, 69, and 146) and the *p,p'*-dimethoxybiphenyl mass spectra (molecular ion at *m/e* 214, base peak also at 214, others in decreasing order at *m/e* 198, 169, 126, 137, 154) were a basis for identification. The melting point for the biphenyl product (173 °C) matched that of the literature value.[22]

Whenever these two techniques left some doubt as to the identity of a product, a larger scale reaction was run and products were isolated by vacuum distillation. IR and NMR spectra of the products were taken and found to be consistent with the structures proposed.

Quantitative product analysis was performed on a measured aliquot of the original reaction mixtures by GC after adding an appropriate internal standard (chlorobenzene, bromobenzene, iodobenzene, or methyl benzoate). Yields were obtained by comparing the relative peak areas of the products to those of the internal standard and correcting by means of response factors, calculated from mixtures containing known concentrations of authentic products (where available) plus the marker. Each reaction mixture was marked twice and the average value was taken as the product yield. Percent yield was based on the stoichiometry of 0.5 mol of product per mol of cobalt(III), the limiting reagent (eq 5).

Registry No.—C_6H_6, 71-43-2; $Co(TFA)_3$, 50517-80-1; phenol, 108-95-2; *o*-methoxyphenol, 90-05-1; *m*-methoxyphenol, 150-19-6; *p*-methoxyphenol, 150-76-5; trifluoroacetic anhydride, 407-25-0; phenyltrifluoroacetate, 500-73-2; o-methoxyphenyl trifluoroacetate, 31083-15-5; *m*-methoxyphenyl trifluoroacetate, 31083-16-6; *p*-methoxyphenyl trifluoroacetate, 5672-87-7; bromobenzene, 108-86-1; iodobenzene, 591-50-4; *p*-methoxyacetophenone, 100-06-1; nitrobenzene, 98-95-3; chlorobenzotrifluoride, 52181-51-8; *p,p'*-dimethoxybiphenyl, 2132-80-1.

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Generation and Reactivity of an Unstabilized Carbohydrate Phosphorane

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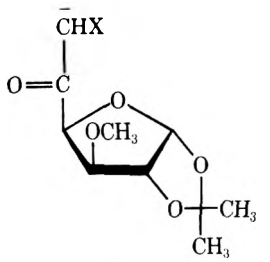
Generation of the ylide of methyl 5-deoxy-2,3-*O*-isopropylidene-5-(triphenylphosphonio)-β-D-ribofuranoside iodide (**2a**) is described. Treatment of the ylide with aldehydes affords good yields of olefinic products of the α-L-*lyxo* configuration, resulting from epimerization of the ylide prior to reaction. Ketones do not react cleanly with the ylide. Addition of a proton source to the ylide under appropriate conditions allows the formation of good yields of a self-condensation product **14**.

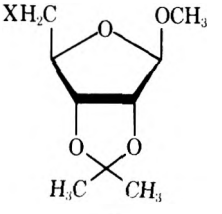
The Wittig reaction has been extensively utilized as a method of chain extension in the carbohydrate field.[1] Both aldehydo and keto sugars have proven amenable to the action of stabilized as well as unstabilized phosphorus ylides, and many unique and interesting chain-extended and branched-chain carbohydrates have been synthesized in this manner. The concept of reversing the roles of the two partners in the Wittig reaction, that is, the combination of a carbohydrate ylide and an aliphatic or aromatic carbonyl compound, has received only scant attention. Zhdanov[2,3] has generated the stabilized carbohydrate-containing phosphorane **1a** as well



1a, X = $\overset{+}{P}Ph_3$
1b, X = $\overset{+}{S}(CH_3)CH_2Ph$

as one other carbonyl-stabilized example. Both phosphoranes have very low reactivity, as would be expected, and only condense with a few activated aromatic aldehydes (*p*-nitro- and *o*-hydroxybenzaldehyde). Recently, an analogous stabilized carbohydrate sulfur ylide **1b** has been prepared and found to react with acrolein and acrylonitrile.[4] To further explore the potential of unstabilized carbohydrate ylides, we have examined the generation and reactivity of the ylide derived from methyl 5-deoxy-2,3-*O*-isopropylidene-5-(triphenylphosphonio)-β-D-ribofuranoside iodide (**2a**). Though phosphorus-containing carbohydrates have been well studied,[5] the only examples of triphenylphosphonium salts appear to be those employed as leaving groups in studies on the synthesis of α-glycosides.[6,7]

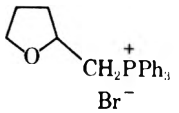
The major obstacle in the use of an unstabilized carbohydrate phosphorane is the presence of a leaving group β to the phosphorus in the vast majority of carbohydrates. Generation of the phosphorane might then be rapidly followed by elimination to form a vinylphosphonium salt. In principle, this problem can be approached through experimental manipulations (solvents, temperature) as well as by decreasing the ability of the β substituent to leave. The selection of **2a**, with



2a, X = $\overset{+}{P}Ph_3I^-$
2b, X = I
2c, X = OH
2d, X = OTs

the β substituent additionally attached through the carbon chain, should provide a particularly favorable case, since intramolecular closure to regenerate the ylide should be possible.

Precedent for this reversible β elimination is found in the ylide generated from tetrahydrofurfuryltriphenylphosphonium bromide (**3**), which will condense with carbonyl compounds to produce alkenyltetrahydrofurans.[8]



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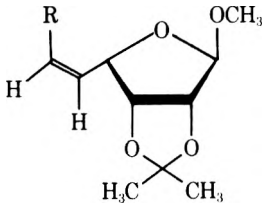
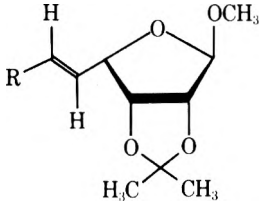
The synthesis of **2a** was accomplished in over 80% yield by treatment of methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranoside (**2b**)[9,10] with triphenylphosphine in sulfolane at 110 °C for several days. A number of other conditions were examined for this unexpectedly difficult transformation,[11] with only the above conditions providing **2a** of acceptable yield and purity. The NMR spectrum is somewhat unusual in that H-3 (or H-2), a doublet, is shifted downfield to δ 5.56, presumably residing in the deshielding region of an aromatic ring. Additionally, the chemical-shift difference between the isopropylidene methyls is only 0.10 ppm, quite narrow, and much different from any other compounds in this study. Phosphorus decoupling combined with proton decoupling at 100 MHz allowed assignment of the resonances of **2a.**

Generation of the red-brown ylide of **2a** was carried out in 2:1 THF–HMPA at −50 °C under nitrogen by the addition of 1 equiv of *n*-butyllithium. As an initial look at the reactivity of the ylide, condensation with benzaldehyde at −50 °C provided a 79% yield of two isomeric, olefinic products, readily separable by preparative TLC.[12] These compounds proved to be not of the anticipated β-D-ribo configuration, but were rather the cis and trans isomers **4a** and **5a** of the α-L-*lyxo*

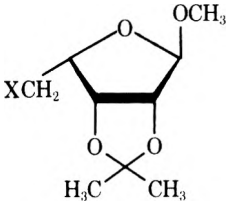


4a, R = Ph–
4b, R = pClPh–
4c, R = pCH$_3$OPh–



5a, R = Ph–
5b, R = pClPh–
5c, R = pCH$_3$OPh–

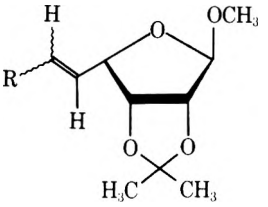
configuration. Since in principle four configurational variants are possible (β-D-*ribo*, α-D-*ribo*, β-L-*lyxo*, α-L-*lyxo*), the assignments were confirmed in several ways. The trans nature of H-1 and H-2 was clear from the sharp H-1 singlet for both **4a** and **5a.** It was not possible to clearly distinguish β-D-*ribo* and α-L-*lyxo* spectroscopically, so we resorted to chemical methods to clarify the configuration at C-4. Catalytic reduction (H_2,Pd/C) of **4a** and **5a** both afforded the same compound, indicating that they both had the same configuration at C-4. Ozonolysis followed by reductive workup ($LiAlH_4$)[13] also gave the same alcohol **6a** from both **4a** and **5a.** Compari-



6a, X = OH
6b, X = OTs
6c, X = $\overset{+}{P}Ph_3I^-$

son of this alcohol with methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**2c**) by TLC, ^{1}H NMR, and ^{13}C NMR clearly showed it to be a different compound. Methyl 2,3-*O*-isopropylidene-α-L-lyxofuranoside (**6a**) was independently synthesized by a recent method[14] and shown to be identical to the product of ozonolysis–reduction by spectral and TLC comparison. As a final check, the mixture melting point of the *p*-toluenesulfonate derivative **6b** from both routes was undepressed (a mixture melting point of **2d** with **6b** derived from **2a** showed a marked depression). Compounds of other configurations were not detected in the Wittig reaction. The cis isomer **4a** ($J_{5,6}$ = 11 Hz) was isolated in 48% yield, with the trans isomer **5a** ($J_{5,6}$ = 16 Hz) making up the other 31%. *p*-Chlorobenzaldehyde and *p*-methoxybenzaldehyde were found to react similarly to afford 79% yields, in both cases, of a mixture of the cis (**4b, c**) and trans (**5b, c**) isomers of the α-L-*lyxo* configuration.[15]

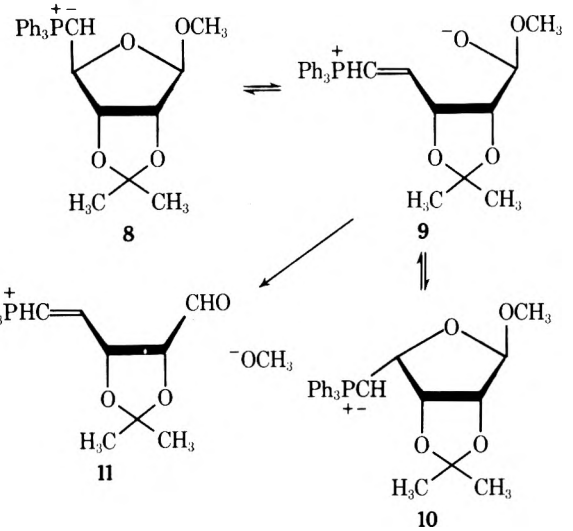
Examination of several representative aliphatic aldehydes also demonstrated their ability to react with the ylide of **2a.** Treatment of the ylide at −50 °C with 3-phenylpropionaldehyde, butanal, and pentanal, afforded the products **7a–c**



7a, R = PhCH$_2$CH$_2$–
7b, R = CH$_3$CH$_2$CH$_2$
7c, R = CH$_3$(CH$_2$)$_3$–

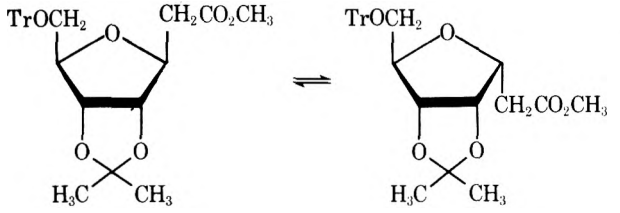
in yields of 85, 66, and 65%, respectively. In all three cases only a single isomer of the α-L-*lyxo* configuration was produced.[15] The cis or trans nature of the double bond in these cases could not be unequivocally established.

That the α-L-*lyxo* products are formed in all instances of condensation with aldehydes indicates that equilibration of the β-D-*ribo* ylide to the α-L-*lyxo* ylide through an open-chain structure (**8** ⇄ **9** ⇄ **10**) must be occurring. This equilibration



must occur very rapidly, since the aldehyde is added shortly (within several minutes) after the *n*-BuLi is added. Interestingly, under the standard conditions of the reaction the open-chain compound **9** closes back to an ylide rather than lose methoxide to form the open-chain aldehyde **11.** Isolation of the epimerized phosphonium salt **6c** proved to be possible if the ylide was generated in pure THF and then quenched with an excess of Dowex 50 (H^+) ion-exchange resin. After 1 min or so, TLC studies showed no **2a,** but only **6c.** If the ylide is generated at −78 °C and a TLC taken immediately, some **2a** is still present, though epimerization is still very rapid at

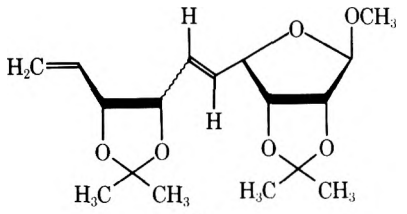
this temperature. A somewhat analogous epimerization through an open-chain structure also takes place between compounds **12** and **13**.[16] In this case, the equilibrium lies



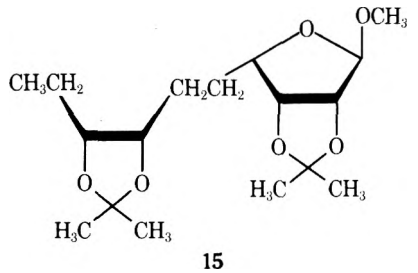
12 Tr = trityl **13**

unexpectedly far on the side of **13**. That **10**, with the configurations at C-2, C-3, and C-4 all *cis*, is the major epimer upon equilibration is also somewhat surprising.

The behavior of the ylide of **2a** also was examined with respect to ketones. Employing conditions similar to those of the aldehyde cases, it was found for all compounds examined (acetone, 2-butanone, 2-pentanone, ethylvinyl ketone, cyclohexanone, and acetophenone) that a complex mixture of products was formed. The major product (20–25%) in all of these reactions was identified as **14**, with the disubstituted double-bond configuration still in doubt. The proton NMR of **14** shows four distinct isopropylidene methyl resonances



14

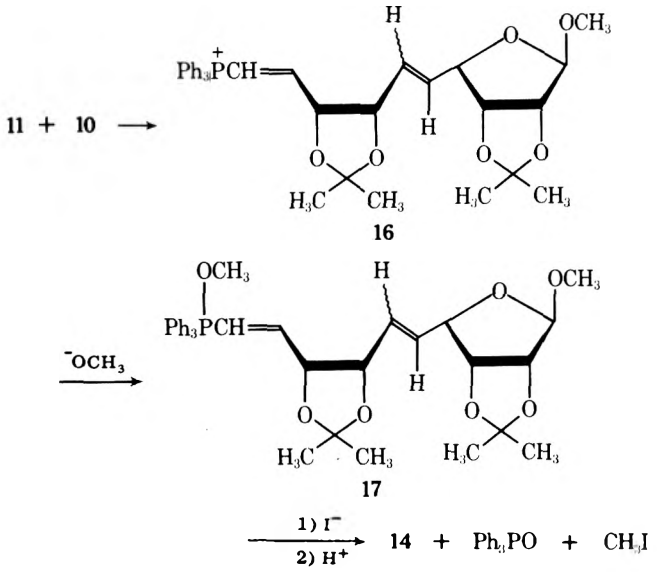


15

as well as only one methoxyl resonance. Catalytic hydrogenation produced a compound with all the expected resonances for **15**, including a newly formed methyl triplet at δ 0.98. In addition, ozonolysis–reduction of **14** afforded the α-L-*lyxo* alcohol **6a**, confirming the configuration at C-4. Formation of **14** must be the result of condensation of the vinyl phosphonium aldehyde **11** with the ylide **10** followed by loss of the phosphorus moiety. This self-condensation product can be formed in 64% yield if the ylide generated in 2:1 THF–HMPA is simply quenched with an excess of Dowex 50 (H^+). The other isolated product (94%) is triphenylphosphine oxide. One possible mechanism is shown in Scheme I. After condensation to afford the salt **16**, both methoxide (0.5 equiv) and iodide (1.0 equiv) are present. Attack by methoxide at phosphorus would give the pentavalent phosphorus intermediate **17**. Iodide attack on the methoxyl carbon would result in the formation, after protonation, of **14**, triphenylphosphine oxide, and methyl iodide. Gas chromatographic analysis of the crude reaction mixture indicates the presence of methyl iodide.[17] Ample literature precedent exists for this type of attack on phosphorus in other systems,[18] and a related cleavage of a vinyltriphenylphosphonium salt with methoxide has also been carried out.[19]

To summarize, it is possible to generate the ylide **10** and carry out high-yield condensations with aldehydes, but not

Scheme I



with ketones. The reactivity of the ylide is apparently lessened by steric constraints about C-5, seen not only in the difficulty of formation of **2a**, but also in the scope of reactivity of the ylide. The intramolecular attachment of the β-leaving group of **2a** enables the opening and reclosure to the furanoside to occur readily, keeping the general structural features intact. Our results indicate that the generation of anionic centers on other carbohydrates may be feasible with appropriate design of the molecule.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting-point apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer 467 grating infrared spectrophotometer. ^{1}H NMR spectra were measured with Varian A-60A or EM-360 instruments, and ^{13}C NMR spectra with a Bruker WP 80; chemical shifts in $CDCl_3$ are expressed in parts per million downfield from internal tetramethylsilane. Decoupling experiments on phosphonium salts **2a** and **6c** were carried out on a Varian HA-100 spectrometer. Ozone was generated with a Welsbach Ozonator T-408. Microanalysis was done by Galbraith Laboratories, Inc. The mass spectrum was recorded with an AEI-MS9 spectrometer at 70 eV.

Tetrahydrofuran (THF) was dried by distillation from sodium and benzophenone. Hexamethylphosphoric triamide (HMPA) was dried by distillation from calcium hydride. Tetramethylene sulfone was dried by distillation from KOH.

Methyl 5-Deoxy-2,3-*O*-isopropylidene-5-(triphenylphosphonio)-β-D-ribofuranoside Iodide (2a). A solution of 4.0 g (13 mmol) of methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranoside (**2b**)[9,10] and 3.67 g (14 mmol) of triphenylphosphine in 4.5 mL of tetramethylene sulfone was heated at 110 °C for 64 h. The yellow solution was diluted with 80 mL of chloroform followed by ~700 mL of ether. The mixture was cooled to −78 °C to ensure complete precipitation of the salt, which was then filtered and washed with ether, affording 6.16 g (84%) of colorless crystals. Recrystallization from ethyl acetate–methanol provided analytically pure material: mp 177.5–179 °C; IR (KBr) 3050, 2990, 2930, 2830, 2775, 1589, 1487, 1441, 1385, 1108 cm^{-1}; NMR (100 MHz) δ 7.61–8.09 (m, 15, ArH), 5.56 and 4.78 (2 d, 2, J = 6 Hz, H_2, H_3), 4.83 (s, 1, H_1), 4.45–5.0 (m, 2, H_5, H_5'), 3.47–3.85 (m, 1, H_4), 2.87 (s, 3, OCH_3), 1.27 and 1.37 [2 s, 6, $C(CH_3)_2$]. Phosphorus decoupling simplified H_4 (dd, $J_{4,5}$ = 10 Hz, $J_{4,5'}$ = 12 Hz), H_5, and $H_{5'}$. Irradiation of H_2 collapsed H_3 to a singlet, and vice versa.

Anal. Calcd for $C_{27}H_{30}IO_4P$: C, 56.25; H, 5.24. Found: C, 56.48; H, 4.99.

General Procedure for Generation of the Ylide and its Condensation with Aldehydes. A solution of 360 mg (0.625 mmol) of phosphonium salt **2a** in 3 mL of 2:1 THF–HMPA was cooled to −50 °C, and *n*-BuLi (0.625 mmol) was added via syringe. After several minutes, a solution of the aldehyde (0.75 mmol) in 0.5 mL of THF was added to the red-brown ylide via syringe, and the solution was allowed to warm up to −10 °C over 45 min. Petroleum ether (38–56 °C) was

added, followed by extraction with H_2O, aqueous $NaHSO_3$, and H_2O. Isolation of the products was accomplished by preparative TLC with an ether–petroleum ether eluant. These same relative amounts were used for larger scale runs as well.

Methyl (*E*)- and (*Z*)-5,6-Dideoxy-2,3-*O*-isopropylidene-6-phenyl-α-L-*lyxo*-hex-5-enofuranoside (4a and 5a). Condensation of **2a** (2.16 g, 3.75 mmol) with benzaldehyde afforded 818 mg (79%) of a mixture of **4a** and **5a**, after separation by preparative TLC.

4a (48%): mp 58.5–60 °C; IR (KBr) 3085, 3045, 2995, 2945, 2925, 2845, 1645, 1600, 1577, 1497, 1455, 1380, 1218, 1105 cm^{-1}; NMR δ 7.33 (s, 5, ArH), 6.84 (d, 1, J = 11.5 Hz, H_6, A of ABX), 5.79–6.17 (m, 1, H_5, B of ABX), 4.95 (s, 1, H_1), 4.53–4.90 (m, 3, H_2, H_3, H_4), 3.35 (s, 1, OCH_3), 1.35 and 1.53 [2 s, 6, $C(CH_3)_2$].

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.29. Found: C, 69.60; H, 7.16.

5a (31%): mp 65.5–67 °C; IR (KBr) 3028, 2988, 2925, 2892, 2836, 1655, 1598, 1578, 1494, 1453, 1382, 1214, 1105 cm^{-1}; NMR δ 7.37 (m, 5, ArH), 6.77 (d, 1, J = 15.5 Hz, H_6, A of ABX), 6.13–6.50 (m, 1, H_5, B of ABX), 4.95 (s, 1, H_1), 4.47–4.82 (m, 3, H_2, H_3, H_4), 3.38 (s, 1, OCH_3), 1.33 and 1.51 [2 s, 6, $C(CH_3)_2$].

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.29. Found: C, 69.88, H, 7.23.

Methyl (*E*)- and (*Z*)-6-(*p*-Chlorophenyl)-5,6-dideoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hex-5-enofuranoside (4b and 5b). Condensation of **2a** (576 mg, 1.0 mmol) with *p*-chlorobenzaldehyde afforded a total of 245 mg (79%) of **4b** and **5b** after separation by preparative TLC.

4b (29%): mp 58–59.5 °C; IR (KBr) 3005, 2995, 2940, 2905, 2832, 1654, 1593, 1490, 1382, 1218, 1100 cm^{-1}; NMR δ 7.25 (s, 4, ArH), 6.71 (d, 1, J = 11 Hz, H_6, A of ABX), 5.73–6.1 (m, 1, H_5, B of ABX), 4.91 (s, 1, H_1), 4.47–4.77 (m, 3, H_2, H_3, H_4), 3.35 (s, 3, OCH_3), 1.33 and 1.52 [2 s, 6, $C(CH_3)_2$].

Anal. Calcd for $C_{16}H_{19}ClO_4$: C, 61.83; H, 6.16. Found: C, 62.01; H, 6.30.

5b (50%): mp 70.5–72 °C; IR (KBr) 3072, 3045, 3028, 2990, 2978, 2960, 2930, 2895, 2835, 1655, 1592, 1495, 1375, 1105 cm^{-1}; NMR δ 7.30 (s, 4, ArH), 6.68 (d, 1, J = 15.5 Hz, H_6, A of ABX), 6.05–6.43 (m, 1, H_5, B of ABX), 4.92 (s, 1, H_1), 4.42–4.77 (m, 3, H_2, H_3, H_4), 3.37 (s, 3, OCH_3), 1.31 and 1.49 [2 s, 6, $C(CH_3)_2$].

Anal. Calcd for $C_{16}H_{19}ClO_4$: C, 61.83; H, 6.16. Found: C, 62.11; H, 6.32.

Methyl (*E*)- and (*Z*)-5,6-Dideoxy-2,3-*O*-isopropylidene-6-(*p*-methoxyphenyl)-α-L-*lyxo*-hex-5-enofuranoside (4c and 5c). Condensation of **2a** (1.728 g, 3.0 mmol) with *p*-methoxybenzaldehyde affords 727 mg (79%) of a **4c** and **5c** mixture (an oil), which is partially separable: IR (mixture, neat) 3040, 2990, 2935, 2840, 1645 (br), 1608, 1513, 1387, 1378, 1260, 1103 cm^{-1}; NMR (**4c**) δ 7.07 (m, 4, ArH), 6.78 (d, 1, J = 11.5 Hz, H_6, A of ABX), 5.68–6.02 (m, 1, H_5, B of ABX), 4.95 (s, 1, H_1), 4.53–4.92 (m, 3, H_2, H_3, H_4), 3.83 (s, 3, $ArOCH_3$), 3.38 (s, 3, OCH_3), 1.35 and 1.53 [2 s, 6, $C(CH_3)_2$]; NMR (**5c**) δ 7.07 (m, 4, ArH), 6.66 (d, 1, J = 15.5 Hz, H_6, A of ABX), 5.96–6.34 (m, 1, H_5, B of ABX), 4.90 (s, 1, H_1), 4.39–4.75 (m, 3, H_2, H_3, H_4), 3.80 (s, 3, $ArOCH_3$), 3.37 (s, 3, OCH_3), 1.32 and 1.50 [2 s, 6, $C(CH_3)_3$].

Anal. (mixture) Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.23. Found: C, 66.29; H, 7.16.

Methyl 5,6,7,8-Tetradeoxy-2,3-*O*-isopropylidene-8-phenyl-α-L-*lyxo*-hept-5-enofuranoside (7a). Condensation of **2a** (360 mg, 0.625 mmol) with 3-phenylpropionaldehyde affords 161 mg (85%) of one oily isomer: IR (neat) 3085, 3065, 3030, 2990, 2935, 2860, 2835, 1686, 1603, 1498, 1456, 1383, 1375, 1100 cm^{-1}; NMR δ 7.18 (s, 5, ArH), 5.42–5.98 (m, 2, H_5, H_6), 4.83 (s, 1, H_1), 4.15–4.67 (m, 3, H_2, H_3, H_4), 3.28 (s, 3, OCH_3), 2.25–2.93 [m, 4, $-(CH_2)_2-$], 1.28 and 1.44 [2 s, 6, $C(CH_3)_2$].

Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 71.05; H, 8.00.

Methyl 5,6,7,8,9-Pentadeoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-non-5-enofuranoside (7b). Condensation of **2a** (1.077 g, 1.87 mmol) with butyraldehyde affords 300 mg (66%) of one oily isomer: IR (neat) 3035, 2990, 2958, 2935, 2875, 2835, 1660, 1463, 1387, 1377, 1216, 1109 cm^{-1}; NMR δ 5.47–6.02 (m, 2, H_5, H_6), 4.92 (s, 1, H_1), 4.58–4.85 (m, 3, H_2, H_3, H_4), 3.33 (s, 3, OCH_3), 1.92–2.38 (m, 2, allylic CH_2), ca. 1.48 (m, partially hidden, 2, $CH_2CH_2CH_3$), 1.33 and 1.48 [2 s, 6, $C(CH_3)_2$], 0.93 (t, 3, J = 6 Hz, CH_2CH_3).

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.43; H, 9.15. Found: C, 64.59; H, 9.19.

Methyl 5,6,7,8,9,10-Hexadeoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-dec-5-enofuranoside (7c). Condensation of **2a** (360 mg, 0.625 mmol) with *n*-pentanal affords 104 mg (65%) of one oily isomer: IR (neat) 3040, 2990, 2955, 2935, 2878, 2865, 2835, 1661, 1471, 1462, 1387, 1377, 1216, 1107 cm^{-1}; NMR δ 5.43–6.0 (m, 2, H_5, H_6), 4.90 (s, 1, H_1), 4.49–4.86 (m, 3, H_2, H_3, H_4), 3.37 (s, 3, OCH_3), 1.89–2.52 (m, 2, allylic CH_2), 1.41 (m, partially hidden, 4, $-CH_2CH_2CH_3$), 1.33 and 1.48 [2, s, 6, $C(CH_3)_2$], 0.91 (t, 3, J = 6 Hz, CH_2CH_3).

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 65.75; H, 9.55.

Epimerization of 2a. Formation of Methyl 5-Deoxy-2,3-*O*-isopropylidene-5-(triphenylphosphonio)-α-L-lyxofuranoside Iodide (6c). To a solution of 360 mg (0.625 mmol) of phosphonium salt **2a** in 7 mL of THF at −40 °C was added 0.7 mmol of *n*-BuLi. After 3 min an excess of Dowex 50 (H^+) was added with stirring. The resin was filtered off and washed with THF, and the filtrate was evaporated to dryness. Purification by preparative TLC (elution with 95:5 CH_2Cl_2–CH_3OH) gave 184 mg (51%) of the colorless epimerized semisolid salt: IR (KBr) 3053, 2990, 2935, 2868, 2835, 1587, 1488, 1450, 1388, 1098, 1013 cm^{-1}; NMR (100 MHz) δ 7.44–8.06 (m, 15, ArH), 5.10 (m, 1, H_3), 4.75 (s, 1, H_1), 4.53 (d, 1, J = 6 Hz, H_2), 4.44–4.93 (m, 2, partially hidden, H_5, $H_{5'}$), 3.61–3.90 (m, 1, H_4), 2.64 (s, 3, OCH_3), 1.32 and 1.51 [2, s, 6, $C(CH_3)_2$]. Phosphorus decoupling (100 MHz) simplified H_3 (dd, $J_{2,3}$ = 6 Hz, $J_{3,4}$ = 3 Hz), H_4, H_5, and $H_{5'}$.

Self-condensation of Ylide 10. Production of Methyl 5,6,9,10-Tetradeoxy-2,3:7,8-di-*O*-isopropylidene-D-*glycero*-β-D-*gulo*-deca-5,9-dienofuranoside (14). To a solution of 360 mg (0.625 mmol) of phosphonium salt **2a** in 3 mL of 2:1 THF–HMPA at −50 °C under nitrogen was added 0.726 mmol of *n*-BuLi. After 3 min, 0.5 g of Dowex 50 (H^+) was added, the solution gradually lightening to a pale yellow. The solution was warmed to −10 °C, benzene added, and the resin filtered off and washed. The organic layer was washed with H_2O, dried, and concentrated. Purification was accomplished by preparative TLC (elution with 3:1 petroleum ether–ether) to afford 65 mg (64%) of a colorless oil: IR (neat) 3085, 3050, 2990, 2935, 2835, 1646, 1607, 1597, 1457, 1378 cm^{-1}; ^1H NMR δ 4.45–6.12 (m, 10, H_{2-9}, H_{10}, $H_{10'}$), 4.85 (s, 1, H_1), 3.33 (s, 3, OCH_3), 1.29, 1.40, 1.45, 1.50 [4 s, 12, 2 $C(CH_3)_2$]; ^{13}C NMR (multiplicity in off resonance decoupling measurement) δ 25.0, 25.6, 26.2, 28.1 [4 q, 2 $C(CH_3)_2$], 54.7 (q, OCH_3), 74.9, 75.5, 79.9, 81.3 (4 d, C_2, C_3, C_7, C_8), 85.3 (d, C_4), 107.4 (d, C_1), 109.0, 112.6 [2, s, 2 $C(CH_3)_2$], 117.9 (t, CH_2=CH), 127.2, 130.9, 134.3 (3 d, 3 CH=).

Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.79; H, 7.92.

Hydrogenation of 14. Formation of Methyl 5,6,9,10-Tetradeoxy-2,3:7,8-di-*O*-isopropylidene-D-*glycero*-β-D-*gulo*-decofuranoside (15). A mixture of 80 mg of **14** (0.245 mmol) and 10 mg of 10% Pd/C in 4 mL of ethanol was hydrogenated (Parr shaker) at 2 atm for several hours. The catalyst was filtered off and washed with ethanol. Removal of solvent was followed by purification by preparative TLC (elution with 4:1 petroleum ether–ether) afforded 58 mg (72%) of oily **15**: NMR δ 4.83 (s, 1, H_1), 4.45–4.69 (m, 2, H_2, H_3), 3.78–4.25 (m, 3, H_4, H_7, H_8), 3.31 (s, 3, OCH_3), 1.68 (m, partially hidden, 6, 3 CH_2), 1.30, 1.33, 1.46 [3 s, 12, 2$C(CH_3)_2$], 0.98 (t, 3, CH_3CH_2); mass spectrum calcd m/e 330.2042; found m/e 330.2048.

General Procedure for Ozonolysis–Reduction of 4a–4c, 5a–5c, 7a–7c, and 14. Formation of Methyl 2,3-*O*-Isopropylidene-α-L-lyxofuranoside (6a). Ozone was passed through a hexane solution of the olefinic carbohydrate derivative for 5 min at 0 °C; nitrogen gas was then passed through, and an excess of an ethereal solution of $LiAlH_4$ was added at −30 °C. The solution was warmed to RT, heated at reflux 1 h, and worked up by addition of H_2O to quench the excess $LiAlH_4$ followed by dilution with ether and extraction. The organic layer was dried and concentrated, and the alcohol **6a**[14] was separated by preparative TLC (elution with 1:2 petroleum ether–ether): ^{13}C NMR δ 24.7, 26.0 [$C(CH_3)_2$], 54.7 (OCH_3), 61.0 (C_5), 79.6, 80.3, 85.3 (C_2, C_3, C_4), 107.2 (C_1), 112.8 [$C(CH_3)_2$]. For comparison purposes: ^{13}C NMR (**2c**) δ 24.7, 26.3 [$C(CH_3)_2$], 55.4 (OCH_3), 64.0 (C_5), 81.4, 85.7, 88.3 (C_2, C_3, C_4), 110.0 (C_1), 112.1 [$C(CH_3)_2$]. Specific assignments for C_2, C_3, and C_4 in both cases are not known.

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Registry No.—**2a**, 63559-65-5; **2b**, 38838-06-1; **4a**, 63599-66-6; **4b**, 63599-67-7; **4c**, 63599-68-8; **5a**, 63599-69-9; **5b**, 63599-70-2; **5c**, 63599-71-3; **6a**, 5531-21-5; **6c**, 63599-72-4; **7a**, 63599-73-5; **7b**, 63599-74-6; **7c**, 63599-75-7; **10** ylide, 63599-76-8; **10** unchanged, 63599-77-9; **14**, 63599-78-0; **15**, 63599-79-1; triphenylphosphine, 603-35-0; benzaldehyde, 100-52-7; *p*-chlorobenzaldehyde, 104-88-1; *p*-methoxybenzaldehyde, 123-11-5; 3-phenylpropionaldehyde, 104-53-0; butyraldehyde, 123-72-8; pentanal, 110-62-3.

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Organoboranes. 23. Reaction of Organolithium and Grignard Reagents with α-Bromoalkylboronate Esters. A Convenient, Essentially Quantitative Procedure for the Synthesis of Tertiary Alkyl-, Benzyl-, Propargyl-, and Stereospecific Allylboranes

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Treatment of trimethylene α-bromoalkylboronate esters in ether at −78 °C with a wide variety of organolithium and Grignard reagents results in an essentially quantitative replacement of the α-bromine substituent by the corresponding organic group. Simple distillation provides, in high yield and purity, many novel, highly substituted organoboronate esters not available via hydroboration.

Organoboronate esters, $RB(OR')_2$, are becoming increasingly important as intermediates in organic synthesis. For example, their reaction with lithium aluminum hydride, $LiAlH_4$, or aluminum hydride, AlH_3, provides essentially quantitative yields of the corresponding monoalkylboranes, RBH_2.[2] Their reaction with Grignard reagents provides a route to mixed trialkylboranes.[3] In addition, organoboronate esters can make more efficient use of the boron-bound alkyl groups in certain synthetic transformations involving organoboranes where the utilization of only one alkyl group is inherent in the reaction. In these particular cases, only one-half of the alkyl groups, R, in dialkylborinates, R_2BOR', and only one-third of the alkyl groups in trialkylboranes, R_3B, would be utilized.[4–6] This would seriously limit the synthetic utility of the reaction if the alkyl group was derived from a valuable intermediate. The promising synthetic potential of organoboronate esters in such situations has recently been demonstrated by D. A. Evans.[4] It was shown that in stereospecific olefin syntheses leading to prostaglandins the use of organoboronate esters can overcome the inefficient utilization of the alkyl group in trialkylboranes.

Perhaps the most convenient route to organoboronate esters is via hydroboration of olefins and acetylenes with catecholborane[7] or dihaloboranes[8] followed by esterification (eq 1).

$$X_2BH + CH_2{=}CHR \rightarrow X_2BCH_2CH_2R \qquad (1)$$

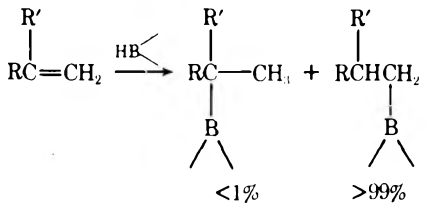
Hydroboration of olefins followed by subsequent redistribution of the trialkylboranes with boron halides[9] or borate esters[10] also provides a facile route to alkylboronate esters (eq 2).

$$BH_3 + 3CH{=}CHR \longrightarrow B(CH_2CH_2R)_3 \xrightarrow{2BX_3} 3X_2BCH_2CH_2R \qquad (2)$$

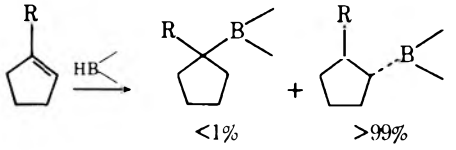
However, certain organoboronate esters cannot be obtained directly by hydroboration due to the remarkable regioselectivity inherent in the hydroboration reaction.[6] Hydroboration of terminal olefins places the boron predominantly at the terminal carbon. Hydroboration of 1-substituted cycloalkenes places the boron nearly exclusively at the 2 position. While this exceptional regioselectivity has important implications in organoborane chemistry, it precludes, with few exceptions,[6,11] the synthesis of tertiary organoboranes by direct hydroboration (eq 3 and 4).

Furthermore, certain groups, such as methyl, alkynyl, benzyl, propargyl, and many allyl, cannot be attached to boron through the hydroboration reaction.

A great deal of progress has been made in the synthesis of "mixed" trialkylboranes possessing groups not available via simple hydroboration.[12–15] However, the synthesis of organoborate esters of this class is quite limited.[16]

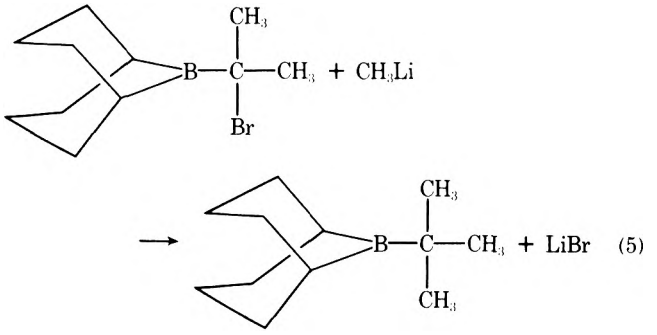


(3)



(4)

Possible routes to these organoboronate esters have been suggested in the literature. We reported that treatment of *B*-α-bromoisopropyl-9-borabicyclo[3.3.1]nonane with methyllithium provides an essentially quantitative yield of *B*-*tert*-butyl-9-borabicyclo[3.3.1]nonane, unavailable via hydroboration (eq 5).[12]

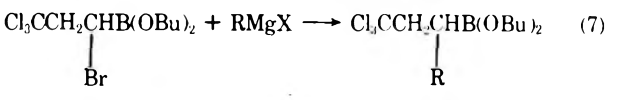


(5)

Rathke reported that diisopropyl dichloromethylboronate reacts with organolithium and organomagnesium reagents to provide secondary organoboronate esters (eq 6).[17]

$$Cl_2CHB(OR)_2 + 2n\text{-}C_4H_9Li \rightarrow (n\text{-}C_4H_9)_2CHB(OR)_2 \quad (6)$$
$$45\%$$

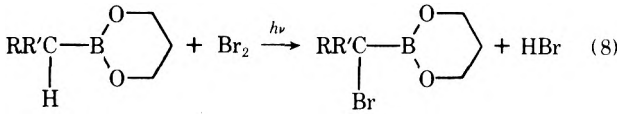
Matteson observed that the α-bromine in dibutyl 1-bromo-3,3,3-trichloropropylboronate could be substituted in variable yields by ethyl and certain aryl Grignard reagents (eq 7).[18]



(7)

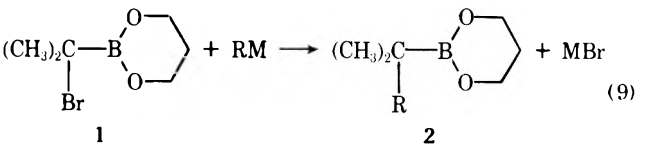
Unfortunately, the full synthetic scope and generality of these potentially valuable reactions have not yet been examined. This may have been due in part to the limited number of synthetic routes to the α-haloalkylboronate ester precursors.

We recently reported a convenient procedure for the synthesis of a wide variety of α-bromoalkylboronate esters in high yields (eq 8).[19]



(8)

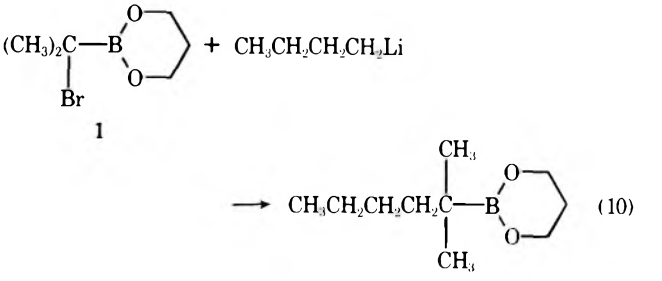
These easily obtainable α-bromoalkylboronate esters should permit a facile entry into previously unattainable organoboranes. However, most of these compounds possess a tertiary α-bromine, a feature not present in previous reactions of organometallics with α-haloalkylboronate esters. Thus, investigation appeared desirable to determine if such tertiary α-bromoalkylboronate esters **1** could be converted into new, highly substituted organoboronate esters **2** by reaction with representative organometallics (eq 9).



1 2 (9)

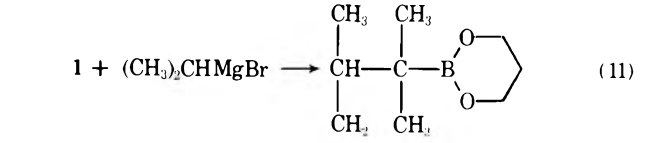
Results and Discussion

2-(1-Bromo-1-methylethyl)-1,3,2-dioxaborinane (**1**) (trimethylene α-bromoisopropylboronate) was selected as a representative substrate for study. Treatment of **1** in ether at −78 °C with methyl lithium or primary alkyl lithium reagents such as *n*-butyllithium results in quantitative substitution of the α-bromine by the organometallic reagent. Simple distillation provides the highly substituted alkylboronates in high yield and purity (eq 10).



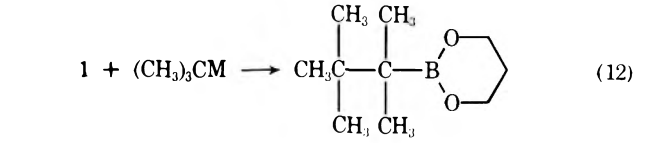
(10)

More reactive lithium reagents, such as isopropyllithium, give substantially lower yields of alkylated product. However, the corresponding Grignard reagent provides an essentially quantitative yield of the thexylboronate ester (eq 11).



(11)

Only with the exceptionally hindered reagents, *tert*-butyllithium and *tert*-butylmagnesium chloride, does the reaction, at present, fail to provide high yields (eq 12).

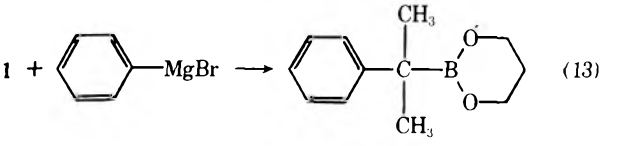


(12)

M = MgCl, 11%
M = Li, 7%

Perhaps, even these low yields might be considered acceptable in view of the anticipated difficulties in making the exceptionally hindered triptylboronate ester by other methods.

Aryl organometallics, such as phenylmagnesium bromide, react cleanly with **1** to provide high yields of organoboronate esters with α-aryl substitution (eq 13).



(13)

Propargylboronate esters have been shown to undergo 1,2 additions to aldehydes and ketones,[20] but the synthesis of propargylboronate esters is generally difficult.[21] Yet, alkynyllithium reagents, such as 1-hexynyllithium, readily react with **1** to provide high yields of the corresponding propargylboronate ester (eq 14).

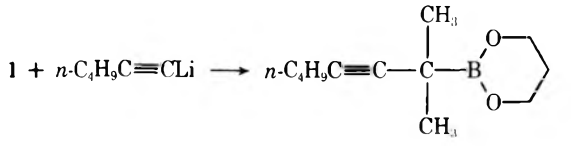
Alkenyllithium reagents react with **1** to provide tertiary allylboronate esters which cannot be obtained via hydrobo-

Table I. Preparation of 2-Alkyl-1,3,2-dioxaborinanes by Reaction of Organolithium and Grignard Reagents with 2-(1-Bromoalkyl)-1,3,2-dioxaborinanes

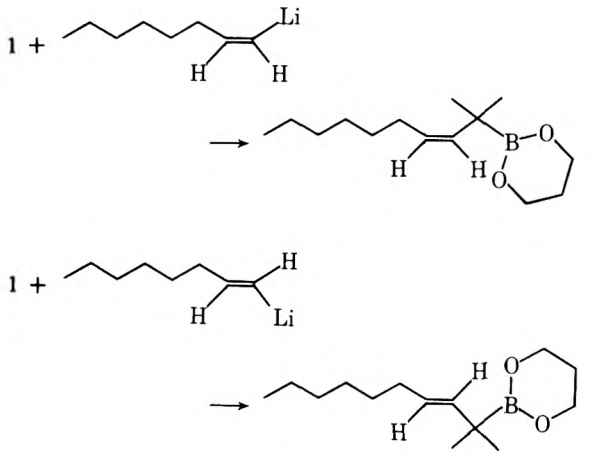
2-(1-Bromoalkyl)-1,3,2-dioxaborinane	Registry no.	Organolithium or Grignard reagent	Registry no.	2-Alkyl-1,3,2-dioxaborinane *B*-alkyl	Yield,[a] % (isolated)	Bp, °C (mm, Hg)
1	62930-29-4	RM		2		
1		CH_3Li	917-54-4	1,1-Dimethylethyl	100 (90)	78–80 (72)
1		n-C_4H_9Li	109-72-8	1,1-Dimethylpentyl	100	
1		i-C_3H_7MgBr	75-26-3	1,1,2-Trimethylpropyl	97[b] (88)	74–75 (13)
1		t-C_4H_9MgCl	507-20-0	1,1,2,2-Tetramethylpropyl	11[c]	
1		C_6H_5MgBr	108-86-1	1-Methyl-1-phenylethyl	96[d] (92)	67–68 (0.05)
1		n-$C_4H_9C{\equiv}CLi$	17689-03-1	1,1-Dimethyl-2-heptynyl	91	
1		*cis*-(n-C_6H_{13})-CH=CH(Li)	56318-79-7	(*Z*)-1,1-Dimethyl-2-nonenyl	85[e] (77)	79–80 (0.04)
1		*trans*-(n-C_6H_{13})-CH=CH(Li)	37730-25-9	(*E*)-1,1-Dimethyl-2-nonenyl	85[f] (73)	83–85 (0.05)
3	62930-31-8			4		
3		CH_3Li		1-Methylcyclopentyl	99 (89)	53–56 (3)
3		n-C_4H_9Li		1-Butylcyclopentyl	99 (90)	85–87 (3)
3		C_6H_5MgBr		1-Phenylcyclopentyl	94 (97)	64–67[g]

[a] GLC yields for 2-mmol reactions. Isolated yields for 20–30-mmol reactions. [b] Isopropyllithium gave 17%. [c] *tert*-Butyllithium gave 7%. [d] Phenyllithium gave 71%. [e] Product is ≥95% Z isomer. [f] Product is ≥95% E isomer. [g] Melting point from petroleum ether.

ration or the reaction of the corresponding allylic organometallic reagents with boronate esters or boron halides. Significantly, (*Z*)- or (*E*)-1-octenyllithium reacts with complete retention of configuration. Such a development holds great promise for natural products and pharmaceutical chemistry (eq 15 and 16).



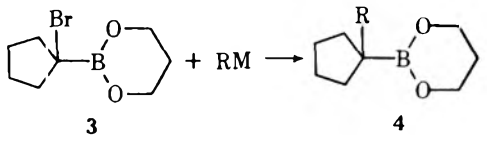
(14)



(15)

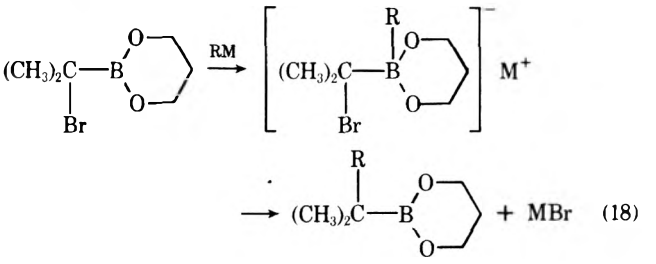
(16)

The alkylation reaction of lithium and Grignard reagents with trimethylene α-bromocyclopentylboronate also gives excellent results (eq 17). It should be applicable to other α-bromoalkylboronate esters, thus providing a facile procedure for the synthesis of a wide variety of novel, highly substituted organoboronate esters not readily available by other methods. We have thus far explored the reaction from the standpoint of its synthetic applications. It appears the mechanism would be the same as previously proposed by Matteson (eq 18).[18]



(17)

3 4



(18)

The results of this study are summarized in Table I.

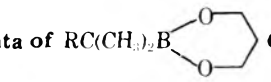
Summary

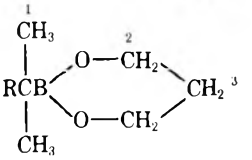
It is evident that the substitution of the α-bromine in α-bromoalkylboronate esters by reaction with organolithium and Grignard reagents provides a convenient procedure for the synthesis of many highly substituted organoboronate esters not readily available via hydroboration or other methods. Such novel organoboranes as tertiary alkyl-, benzyl-, and propargyl-, and stereospecific allylboronate esters are now available for the expanding scope of organoborane chemistry.

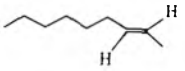
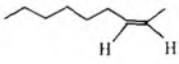
As a synthetic tool, alkyl halides are among the most versatile class of organic compounds. Likewise, organoboranes are exceedingly useful intermediates for further synthetic transformations. The α-bromoboranes are a class of easily obtained compounds possessing both of these desirable functionalities. Undoubtedly, they hold great promise for future synthetic developments.

Experimental Section

General Comments. General procedures for the manipulation of air-sensitive materials have been described elsewhere.[6] Trimethylene α-bromoalkylboronate esters were synthesized as described previously.[19] Methyl, *n*-butyl-, isopropyl-, and phenyllithium were commercially available (Alfa, Aldrich) and standardized by the Watson–Eastham method.[22] The 1-hexynyllithium was prepared as a 0.5 M ether solution by a literature method.[15] The (*Z*)- and (*E*)-1-octenyllithium reagents were prepared as 0.5 M ether solutions from the pure (*Z*)- and (*E*)-1-iodooctenes[23] by the method of Corey and Beames.[24] The Grignard reagents were prepared by the usual procedures[25] and standardized by the Watson–Eastham method. ^1H NMR spectra were recorded on a Varian T-60 (60 MHz) in $CDCl_3$ using $(CH_3)_4Si$ (δ 0 ppm) as an internal standard. Infrared spectra were

Table II. Selected ^{1}H NMR Spectral Data of  Obtained From Reaction of 1 with RM



R	Registry no	δ	δ C-1 (s, 6 H)	δ C-2 (t, 4 H)	δ C-3 (quin, 2 H)
CH_3–	63689-73-6	0.87 (s, 3 H)	0.87	3.97	1.88
$(CH_3)_2CH$–,	63689-74-7	0.77 (d, 6 H) 1.51 (m, ~1 h)	0.87	3.97	1.88
	63869-75-8	7.0–7.4 (m, 5 H)	1.30	3.85	1.73
	63689-76-9	0.88 (t, ~3 H) 1.6–2.3 (m, ~2 H) 1.32 (br s, ~8 H) 5.54 (d, J = 15 Hz) 5.15 (pair of t, J = 15 and 5 Hz)	0.93	3.97	1.95
	63689-77-0	0.97 (t, ~3 H) 1.6–2.3 (m, ~2 H) 1.33 (br s, ~8 H) 5.32 (d, J = 11 Hz) 5.12 (pair of t, J = 11 and 5.5 Hz)	1.00	4.00	1.90

recorded on a Perkin-Elmer 137 spectrophotometer and GLC analyses were performed on a Hewlett-Packard 5750-B dual thermal-conductivity gas chromatograph using a clean 6 ft × 0.25 in. stainless steel column packed with 10% SE-30 on acid-washed, DMCS treated Chromosorb W for borane analyses and 10% DC 710 for alcohol analyses. Normal hydrocarbons (Phillips 99%) were used as internal standards. Correction factors were determined using isolated organoboranes or alcohols. Boiling points are uncorrected.

General Procedure. A dry flask equipped with magnetic stirrer, septum inlet, and pressure-equalized addition funnel was flushed with dry nitrogen and maintained under a positive pressure of nitrogen gas. The flask was charged with the appropriate trimethylene α-bromoalkylboronate ester and enough absolute ethyl ether to make the solution ca. 0.5 M in borane. The flask was cooled in a dry ice/acetone cold bath and 1 equiv of the organolithium or Grignard reagent was added to the addition funnel and diluted to ca. 0.5 M with ether (for methyl- and phenyllithium and Grignard reagents) or pentane (for *n*-butyl-, isopropyl-, and *tert*-butyllithium). The organometallic reagent was then added dropwise over 10–15 min while maintaining the reaction mixture at −78 to −60 °C.[26] After the organometallic reagent had been added, the addition funnel was washed out with a small portion of the appropriate solvent and added over 3–5 min. In the case of 1-hexynyllithium and the (*Z*)- and (*E*)-1-octenyllithium reagents, the reagents were prepared as 0.5 M ether solutions in a separate flask at −78 °C and transferred directly to the reaction mixture over 3–5 min by a cold, double-ended needle. The reaction mixture was stirred at −78 °C for 10 min and warmed to room temperature where stirring was continued for 1.5–2 h. For reaction mixtures analyzed by GLC (2-mmol scale), an internal standard was added and the yield of borane determined directly. Alternatively, the success of the reaction was determined by oxidation of the reaction mixture with alkaline hydrogen peroxide[6] and analyzing for the corresponding alcohols by GLC analysis. In preparative reactions (20–30-mmol scale), the reaction mixture was freed of partially dissolved magnesium or lithium salts by removing volatile components by aspirator vacuum and taking up the residue in 30–40 mL of pentane, allowing the salts to settle, and transferring the supernatant to a nitrogen-flushed, simple distillation apparatus. In order to ensure quantitative transfer of the product, the salts were washed one or two times with pentane (20 mL) and the washings transferred to the distillation assembly.[27] The pentane was removed by aspirator and the residual material vacuum distilled. Purities were ≥95% by GLC or ^{1}H NMR analysis.

Product Identification. Organoborane products were characterized spectroscopically by their ^{1}H NMR (Table II) and infrared spectra. Further confirmation of the structures was obtained by alkaline hydrogen peroxide oxidation to give the corresponding alcohols in quantitative yields.[6] The alcohols were compared to authentic samples either commercially available or obtained through the reaction of the lithium or Grignard reagent with the appropriate ketone.[28] The trimethylene 1,1,2-trimethylpropylboronate, prepared by the reaction of isopropylmagnesium bromide and **1**, was identical to a sample prepared by the reaction of 1,3-propanediol with thexylborane.[6,11] Stereochemistry of the trimethylene (*E*)- and (*Z*)-1,1-dimethyl-2-nonenylboronates was established by their ^{1}H NMR and infrared spectra.[29] The ^{1}H NMR of the E isomer showed resonances at δ 5.15 (1 H, doublet of triplets, J = 15 and 5 Hz) and 5.54 (1 H, doublet, J = 15 Hz), and the infrared spectra showed medium absorption at 10.2 μm. The ^{1}H NMR of the Z isomer showed resonances at δ 5.12 (1 H, doublet of triplets, J = 11 and 5.5 Hz) and 5.32 (1 H, doublet, J = 11 Hz), and the infrared spectrum showed medium absorption at 13.4 μm and none at 10.2 μm. The two isomers were stereochemically pure (≥95%) by ^{1}H NMR.

Registry No.—Isopropyllithium, 1888-75-1; *tert*-butyllithium, 594-19-4; phenyllithium, 591-51-5.

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(26) Rapid addition of concentrated organometallics (~2 M) gave substantially lower yields (50–70%).
(27) The washing procedure can be hastened by transferring the entire mixture through a large bore double-ended needle into dry, nitrogen-flushed, 50-mL centrifuge tubes capped with rubber septa. The solid can be removed from the wash liquid by centrifuging.
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Synthesis and Reactions of 7,10-Methano-7,8,9,10,11,11-hexachloro-7,10-dihydrofluoranthene[1]

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Received June 6, 1977

The synthesis of 7,10-methano-7,8,9,10,11,11-hexachloro-7,10-dihydrofluoranthene (3) is reported and its properties are studied. The absorption spectrum of this orange substance shows an enhanced K band that may reflect an intramolecular charge-transfer process. When 3 is irradiated with 360-nm light, no quadricyclene is detected nor does 3 show any other photochemical reaction at 360 nm. The reaction of 3 with methoxide, ethoxide, and isopropoxide nucleophiles occurs in a stereospecific manner to produce 7,10-methano-6b-alkoxy-7,8,9,10,11,11-hexachloro-6b,7,10,10a-tetrahydrofluoranthene.

We synthesized a quantity of 7,10-methano-7,8,9,10,-11,11-hexachlorofluoranthene (3) as a compound for photochemical study. A molecule containing a norbornadiene moiety fused through the 1,2-bridge of acenaphthylene seemed a potentially rich source of photochemical intrigue.[4] It was hoped that such a substance would exhibit photochemistry similar to that of norbornadiene-1,2-dicarboxylic acid anhydride[5] and thus be convertible to a quadricyclene derivative.[6] The bright orange crystals of 3 have currently resisted a variety of photolytic ring-closing conditions. However, we have found some interesting ground-state chemistry associated with 3.

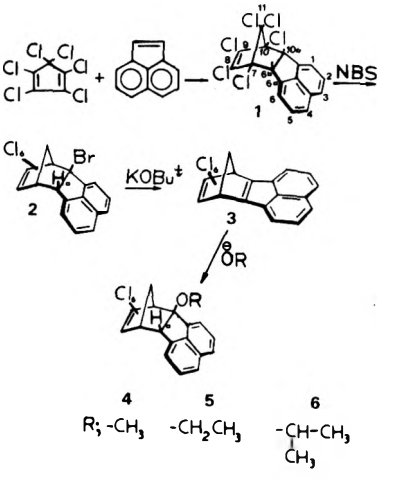
The study of the ground-state properties of 3 described herein has its genesis in our early attempts to synthesize 3. During these initial studies, by-products were isolated that suggested that alkoxy groups were incorporated into the structure. Thus, the recent report by Davies and Adams[8] concerning the reaction of nucleophiles with chlorine-substituted norbornadienes stimulated us to explore in detail the similar reaction upon 3.

Results and Discussion

The synthesis of 3 involves the thermal [4 + 2] cycloaddition of hexachlorocyclopentadiene to acenaphthylene to form *endo*-7,10-methano-7,8,9,10,11,11-hexachloro-6b,7,10,10a-tetrahydrofluoranthene (1).[9,10] This compound was treated with NBS in refluxing carbon tetrachloride to form the crude monobrominated derivative 2. Subsequent treatment of crude 2 with warm potassium *tert*-butoxide in *tert*-butyl alcohol produced 3 in good yield. The mass spectrometric examination of 3 showed the expected isotopic cluster for a six chlorine atom containing molecule at M^+ of 420 through 426. The base peak at *m/e* 387 (M − 35) showed the isotopic clustering characteristic of five chlorine atoms.[13] A minor M − 105 grouping occurred at *m/e* 315, 317, and 319, suggesting a fragment with three chlorine atoms lost. The NMR spectrum of 3 showed only the typical aromatic resonances at 7.2–7.8 ppm.

The UV–visible spectrum of a cyclohexane solution of 3 is shown in Figure 1 as compared to acenaphthylene dissolved in the same solvent. The feature of major interest is the bathochromic shift and hyperchromic modification of the absorption band of acenaphthylene between 400 and 450 nm. This band has been classified as a K transition by Michl[14] and theoretical CI-SCF-P-P-P calculations indicate that this transition involves substantial intramolecular charge transfer from the peri bridge to the naphthalene chromophore. The enhancement of the K band in 3 may represent additional charge transfer involving homoconjugation of the remote dichloroethene π system with the peri bridge of the acenaphthylene unit. The recent synthesis and characterization of 8*H*-cyclopent[*a*]acenaphthylene as orange needles[15] casts some doubt on the existence of this proposed homoconjugative interaction because the remote double bond at position 8 and 9 is saturated in this molecule. We hope that studies now in progress will clarify the spectral interpretations.

The reaction of 3 with various alkoxides was pursued



analogous to the procedure in prior studies[8] by refluxing an alcoholic mixture of 3 with the appropriate sodium alkoxide. We observed that there were qualitative rate differences and that the reaction of 3 with alkoxides occurred in the order $CH_3O^- > CH_3CH_2O^- > (CH_3)_2CHO^- >>> (CH_3)_3CO^-$. Methoxide and ethoxide addition proceeded smoothly. The addition of isopropoxide proceeded with difficulty, and some

Table I. Proton NMR Data, δ Values

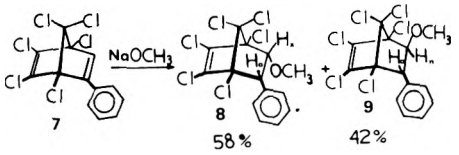
Compd	Registry no.	H_a	CH	CH_2	CH_3
1	63784-80-5	4.80			
2	63784-81-6	5.05			
4	63784-83-8	4.18			2.92 (s)
5	63784-84-9	4.18		3.00 (q)	1.15 (t)
6	63784-85-0	4.20	3.30 (m)		0.83, 0.95 (d)
8[a]	37053-27-3	4.48			3.16
9[b]	36964-07-5	4.71			3.51

[a] H_x = 3.98. [b] H_n = 3.22.

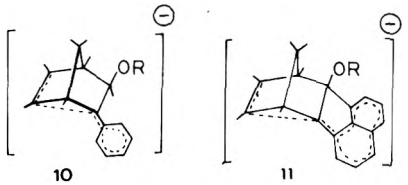
decomposition was found. Within the limits of detection we could not find any addition of *tert*-butoxide to **3**.

All reactions showed a high degree of stereospecificity with the major isomer being the only product that was isolated. GLC analysis of the crude product mixture verified that the total percentage of minor components was always less than 10%. Of the minor components detected, about 30% seemed to be one isomer.

The selectivity of the reaction that produces the major stereoisomer is supported by several observations. The alkoxy adduct is a pure white crystalline substance indicating that the ethylene bridge common to acenaphthylene and norbornadiene is now saturated. The elemental analysis of the product is indicative of the retention of all six chlorine atoms. If alkoxide were to add at the dichloroethene bridge, β elimination of HCl would be anticipated and this is not found. The addition of methoxide to 5-phenylhexachloronorbornadiene (**7**) is also selective with the phenyl-substituted double bond being the site of reaction.[8]



The factors that contribute to the selectivity of alkoxide addition to **3** are analogous to those that cause more exo product than is normally found when **7** is subjected to nucleophilic substitution. The transition states leading to the alkoxy derivatives of **3** are likely stabilized by significant resonance delocalization in the acenaphthylene group as suggested in **11**. Since the π system of acenaphthylene can



stabilize negative charge through resonance, the alternative addition of alkoxide to the dichloroethylene bridge of **3** is expected to have a greater activation energy because chlorine will not be as effective in stabilizing negative charge when compared to acenaphthylene. Thus, the selectivity is readily rationalized and supported by analogy to the transition state **10** for reaction of **7**.

Discrete rather than nonclassical carbanions have been proposed for the Birch reduction of benzonorbornadiene.[16] Therefore, it is probable that **3** may also form such intermediates.

The endo or exo geometry adopted by the attacking nucleophile upon **3** is subject to both steric and electronic demands made in the transition state. Careful study of molecular models allows no clear decision as to which stereoisomer is produced during these reactions.[17]

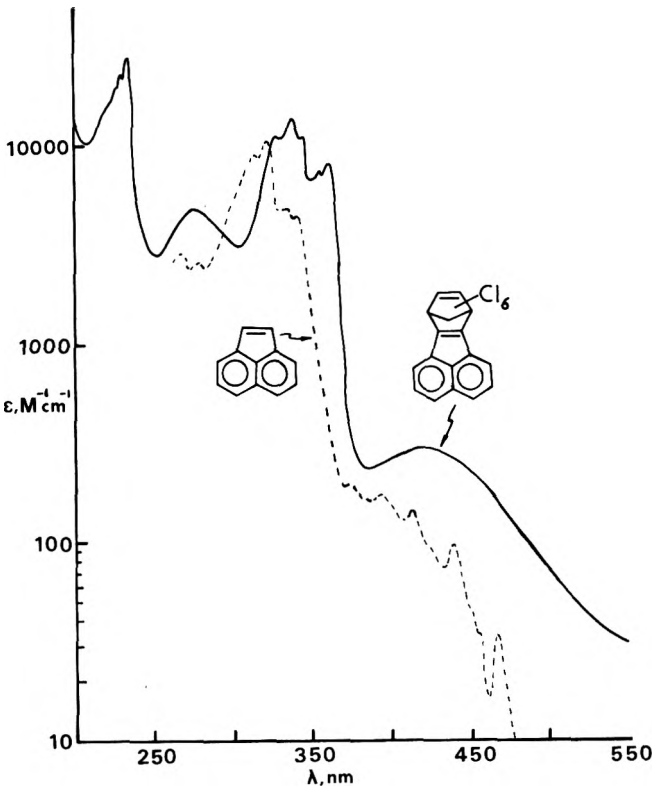


Figure 1. The ultraviolet–visible absorption spectrum of acenaphthylene and 7,10-methano-7,8,9,10,11,11-hexachloro-7,10-dihydrofluoranthene.

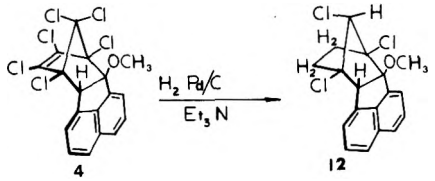
We attempted to synthesize structures **4**, **5**, and **6** by an alternate route. We envisaged that a Diels–Alder reaction between 1-methoxyacenaphthylene and hexachlorocyclopentadiene would produce the desired compound whose stereochemistry would be predictable from the Alder Rule.[11] Unfortunately, the reactions studied to date have not satisfactorily produced the product we desire.

The ^1H NMR spectra of the various compounds are recorded in Table I. The chemical shifts for proton H_a are consistent for the compounds **4**, **5**, and **6**, suggesting identical geometry for all the adducts. We have tried to find other model systems for a comparison of chemical shifts in the hope that NMR data would indicate a trend that would allow us to make stereochemical assignments. The H_a protons for **8** and **9** resonate at lower field and differ substantially in their environment from adducts **4**, **5**, and **6**. The [4 + 2] endo adduct derived from tetrachlorocyclopentadienone and acenaphthylene shows a chemical shift for H_a of 4.35 ppm while the analogous exo adduct has a shift for H_a of 4.49 ppm.[18] The endo and exo [4 + 2] products derived from the reaction of acenaphthylene and cyclopentadiene show chemical shifts of 4.04 and 3.52 for H_a, respectively.[19] These bridge protons show nonsystematic behavior, and consequently are not reliable indicators of endo or exo stereochemistry.

The chemical shifts and multiplicities of the various alkoxy compounds are those expected for these substituents. The NMR spectrum of isopropoxy adduct **6** shows clear evidence of the diastereotopic relationship of the two methyl groups. The quasitriplet at a field width of 500 Hz is resolved upon scale expansion into a set of close-lying doublets, J = 4.8 Hz. We have also observed that scale expansion of the proton resonance for H_a in **4**, **5**, and **6** shows a perturbation of this signal. We surmise that some weak long-range coupling is occurring. Perhaps the closest ortho hydrogen to H_a undergoes a weak spin–spin interaction with H_a.

We are currently studying reductive dehalogenation of the structures **3**, **4**, **5**, and **6** and wish to report an initial experiment. We initiated these studies in the hope that the reduced products would lead to a prediction of the endo or exo geometry of the alkoxy substituent. The results are interesting but not definitive.

When methoxy compound **4** is treated with hydrogen over Pd/C in the presence of triethylamine (TEA) and the hydrogenation interrupted early in the reaction, NMR analysis of the crude product shows the presence of one hydrogen atom at δ 3.75. as well as H_a at δ 4.0. We suggest that the chlorine at the 11 position anti to the dichloroethene bond is first to be removed by virtue of homoconjugative assistance from the 8,9 π bond. Subsequent attack by hydrogen is then anti to the π bond. Further reduction occurs at the dichloroethene bond to form compound **12**.



4 **12**

Dissolving metal reductions have been shown to selectively substitute the anti-chlorine with hydrogen in 1,2,3,4,7,7-hexachloro-5-*endo*-acetoxybicyclo[2.2.1]2-heptene.[20] However, when these same investigators used TEA and H_2/Pd/C they found that chlorine removal from the geminal position did not occur in competition with saturation of the ethene bridge.

Our results are contrary to this observation but seem internally consistent if the peri-fused naphthalene is endo to the 8,9 π bond of **4**. This endo position would add some steric interference to catalytic hydrogenation of the 8,9 π bond of **4** allowing the rate of hydrogenation of the 11-geminal chlorine group to become competitive as enhanced by homoconjugative assistance.

The NMR spectrum of **12** is complex with a series of overlapping multiplets occurring in the range δ 2.0–3.05 and overlapping the methoxy protons at δ 2.92. Two perturbed singlets occur at δ 3.35 and 3.75. We tentatively conclude that the δ 3.75 signal is associated with the 11-bridge proton and that the perturbation of this singlet results from long-range W coupling with the endo protons now at positions 8 and 9. The perturbed singlet at δ 3.35 is therefore assigned to bridge proton H_a whose chemical shift is affected by the loss of the unsaturation and chlorine atoms and whose perturbation results from weak W coupling[21] with the exo bridge protons at positions 8 and 9 as well as with the ortho hydrogen on the aromatic ring.

We shall report in future publications the results of continuing studies on the synthesis of complex strained-ring derivatives of **3** as well as their attendant chemistry.

Experimental Section[22]

Materials. Acenaphthylene (Tech) was repeatedly crystallized from methanol and treated with charcoal. Hexachlorocyclopentadiene (Aldrich) was vacuum distilled. *N*-Bromosuccinimide was recrystallized from water and dried. Fresh potassium *tert*-butoxide was used directly from the bottle.

***endo*-7,10-Methano-6b-bromo-7,8,9,10,11,11-hexachloro-6b,7,10,10a-tetrahydrofluoranthene (2).** A mixture of 8.5 g (0.02 mol) of 1,[9] 150 mL of carbon tetrachloride, 0.10 g of azobis(isobutyronitrile) and 7.12 g (0.04 mol) of *N*-bromosuccinimide was refluxed by the radiant energy from a 150-W sun lamp for 26 h. At 6-h intervals an additional 0.1 g of AIBN was added. The cooled, brown solution was suction filtered, the filtrate was treated with decolorizing carbon, and after a second filtration the filtrate was subjected to vacuum rotary evaporation. The resulting pale yellow solid was recrystallized from cyclohexane to produce 6.3 g (70%) of off-white crystals: mp 185–190 °C; IR (KBr) 3035, 2945, 1590 cm^{-1}; NMR (CCl_4)δ 7.3–7.8 (ArH), 5.05 (ArCH) ppm.

7,10-Methano-7,8,9,10,11,11-hexachloro-7,10-dihydrofluoranthene (3). A solution of 40.5 g (0.08 mol) of **2** and 10.2 g (0.09 mol) of potassium *tert*-butoxide in 750 mL of dried *tert*-butyl alcohol was heated to 50 °C and magnetically stirred under a nitrogen atmosphere for 6 h. After cooling to room temperature, the excess alkoxide was destroyed by adding 20 mL of ice water. The solution was then made neutral by the addition of cold 6 N HCl and the solids were collected by filtration. The filtrate was vacuum rotary evaporated yielding an orange solid. All collected solids were combined and suspended in boiling hexane which was filtered hot to remove inorganic salts. The filtrate upon cooling to −10 °C for 24 h produced orange crystals: mp 169.4–169.9 °C (90%); $\lambda_{max}^{C_6H_{12}}$ nm (ϵ, M^{-1} cm^{-1}) 281 (5600), 340 (14 000), 357 (7200), 363 (7200), 400 (300); IR (KBr) 3045, 1580 cm^{-1}; NMR δ 7.3–7.95 (ArH); mass spectrum, 70 eV, *m/e* (relative intensity) 426 (3), 425 (1), 424 (6), 423 (1), 422 (8), 421 (1), 420 (3), 391 (21), 390 (13), 389 (70), 388 (20), 387 (100), 386 (13), 385 (64), 342 (2), 340 (6), 338 (5), 319 (6), 318 (3), 317 (20), 316 (3), 315 (20).

Anal. Calcd for $C_{17}H_6Cl_6$: C, 48.27; H, 1.43; Cl, 50.29. Found: C, 48.37; H, 1.35; H, 1.35; Cl, 50.30.

Synthesis of 7,10-Methano-6b-alkoxy-7,8,9,10,11,11-hexachloro-6b,7,10,10a-tetrahydrofluoranthene. A mixture of 1.0 g (2.37 mM) of **3** and 50 mL of absolute alcohol solvent containing 0.5 g (22 mM) of dissolved sodium was refluxed gently for 6 and 24 h, depending upon the alkoxide used. The bright orange diene slowly dissolved and the mixture became pale yellow to dark brown, depending upon the alcohol used. After reflux, the cooled mixture was carefully quenched with 100 mL of ice-cold 0.1 N HCl. This mixture was extracted with three 50-mL portions of dichloromethane, and the combined CH_2Cl_2 extracts were treated with decolorizing carbon, dried over anhydrous $MgSO_4$, filtered, and vacuum rotary evaporated. The resulting off-white solid was dissolved in a minimum amount of hot methanol and allowed to crystallize at 0 °C for 24 h. The methoxy, ethoxy, and isopropoxy substituents were made in this manner.

Methoxy Substituent 4: mp 132–133 °C (90%); NMR δ 2.95 (3 H, CH_3, s), 4.1 (1 H, ArCH, s), 7.35–7.9 (6 H, ArH); IR (KBr) 3045, 2940, 2925, 2810, 1595, 1190, 1155, 1110, 1040, 975, 905, 780 cm^{-1}. Anal. Calcd for $C_{18}H_{10}Cl_6O$: C, 47.51; H, 2.22; Cl, 46.53. Found: C, 47.66; H, 2.19; Cl, 46.75.

Ethoxy Substituent 5: mp 111–112 °C (25%); NMR δ 1.15 (3 H, CH_3, t), 3.0 (2 H, CH_2, q), 4.1 (1 H, s), 7.4–7.9 (6 H, ArH, m); IR (KBr) 3045, 2960, 2920, 2880, 1595, 1240, 1200, 1170, 1108, 1050, 910, 865, 775 cm^{-1}. Anal. Calcd for $C_{19}H_{12}Cl_6O$: C, 48.67; H, 2.56; Cl, 45.36. Found: C, 48.48; H, 2.77; Cl, 44.73.

Isopropoxy Substituent 6: mp 159–160 °C (10%); NMR δ 0.83 (3 H, CH_3, d), 0.95 (3 H, CH_3, d), 3.30 (1 H, (O)C(H)>, m), 4.1 (1 H, ArCH, s), 7.4–7.9 (6 H, ArH, m); IR (KBr) 3045, 2960, 2910, 1595, 1240, 1205, 1170, 1125, 1100, 1060, 1055, 950, 845, 780 cm^{-1}. Anal. Calcd for $C_{20}H_{14}Cl_6O$: C, 49.74; H, 2.90; Cl, 44.05. Found: C, 49.90; H, 2.90; Cl, 43.75.

7,10-Methano-6b-methoxy-7,10-11,trichloro-6b,7,8,9,10,10a-hexahydrofluoranthene (12). A mixture of 15 mL of absolute methanol, 0.175 g (0.38 mM) of **4**, 0.1 g (0.95 mM) of triethylamine, and 20 mg of 10% Pd/C catalyst was placed in a Parr medium-pressure hydrogenator. The system was pressurized to 50 psi with H_2 and shaken. After 2 h of agitation, an additional 20 mg of catalyst was added, and the system was repressurized to 50 psi and shaken an additional 2.5 h. The mixture was filtered and the filtrate vacuum rotary evaporated to produce a pale yellow oil. This oil was mixed with 50 mL of CCl_4 and washed with three 25-mL portions of H_2O, and the organic phase was dried over $MgSO_4$. Vacuum rotary evaporation of the dry CCl_4 solution produced an off-white crystalline substance that was vacuum dried at 1 mmHg. The solid was recrystallized from hexane to produce 0.072 g (53%) of **12**: mp 119–120 °C; NMR δ 1.95–3.05 (4 H, CH_2CH_2, m) 2.95 (3 H, OCH_3, s), 3.35 (1 H, s), 3.8 (1 H, s), 7.2–7.8 (6 H, ArH); IR (KBr) 3045, 2995, 2947, 2820, 1590, 1295, 1245, 1230, 1178, 1090, 1032, 984, 922, 875, 785, cm^{-1}. Anal. Calcd for $C_{18}H_{15}Cl_3O$: C, 61.16; H, 4.24; Cl, 30.08. Found: 61.10; H, 4.18; Cl, 29.98.

Acknowledgment. We thank the Robert A. Welch Foundation for partial support of this work. We thank the National Science Foundation for a summer URP grant and for matching funds to purchase the Cary 118C spectrophotometer. We thank Dr. Bill Stavinoha for obtaining mass spectrometric data.

Registry No.—**3**, 63784-82-7; **12**, 63784-86-1.

References and Notes

(1) Presented in part at the 172nd National Meeting of the American Chemical Society, San Francisco, 1976.
(2) (a) Robert A. Welch Postgraduate Fellow; (b) taken in part from the Master's Thesis of D.M.C., Trinity University, 1970.
(3) (a) NSF Undergraduate Research Participant; (b) Robert A. Welch Undergraduate Scholar.
(4) The interesting photochemical properties of acenaphthylene may be found in references in the following papers: (a) W. I. Ferree, Jr., B. F. Plummer, and W. W. Schloman, Jr., *J. Am. Chem. Soc.*, **96**, 7741 (1974). (b) D. O. Cowan and J. Kozlar, *ibid.*, **98**, 1001 (1976).
(5) J. R. Erdman and H. E. Simmons *J. Org. Chem.*, **33**, 3808 (1968).
(6) It has not escaped our attention that compound 3 offers potential for the storage of solar energy[7] and we are continuing our efforts to find suitable photochemical conditions for its transformation.
(7) (a) G. Jones and B. R. Ramachandran, *J. Org. Chem.*, **41**, 798 (1976). (b) D. P. Schwendeman and C. Kutal, *Inorg. Chem.*, **16**, 719 (1977).
(8) (a) D. R. Adams and D. I. Davies, *J. Chem. Soc., Perkin Trans. 1*, 2012, (1974); (b) *ibid.*, 1237, (1972).
(9) D. C. Morrison, *J. Org. Chem.*, **25**, 1665 (1960).
(10) The assignment of endo orientation to **1** is based upon the classical Alder Rule[11] and the theoretical framework of Woodward–Hoffmann formalism.[12]
(11) K. Alder and G. Stein, *Angew. Chem.* **50**, 514 (1937).
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(16) M. N. Paddon-Row, D. N. Butter, and R. N. Warrener, *J. Chem. Soc., Chem. Commun.* 741 (1976).
(17) The diagrams we have chosen for illustration are arbitrarily illustrated with the alkoxy group in the exo position for clarity of presentation. We shall attempt to identify the correct geometry for these adducts when subsequent studies are finished.
(18) (a) M. Akhtar, D. M. Bratby, J. C. Chadwick, and G. I. Fray, *Tetrahedron*, **32**, 2265 (1976). (b) L. S. Besford, R. C. Cookson, and J. Cooper, *J. Chem. Soc. C*, 1385 (1967).
(19) R. Baker and T. J. Mason, *J. Chem. Soc. C*, 596 (1970).
(20) K. L. Williamson, Y. Hsu, and E. I. Young, *Tetrahedron*, **24**, 6007 (1968).
(21) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon, New York, N.Y., 1969, p 334–344.
(22) Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded in KBr pellets on a Perkin-Elmer 337 or 283. NMR spectra were obtained in dilute solutions of $CDCl_3$ or CCl_4 with internal Me_4Si on a Varian T-60. UV–visible spectra were obtained on a Cary 118C. GLC analyses were run on a Varian Hy-Fl 2400 with a flame-ionization detector and a 5 ft × 0.125 in. column of 1.5% OV-101 on Chromosorb G. Mass spectra were recorded on a Finnegan 1015 C system/150 Quadrupole spectrometer at 70 eV. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Versatile Allene and Carbon Dioxide Equivalents for the Diels–Alder Reaction

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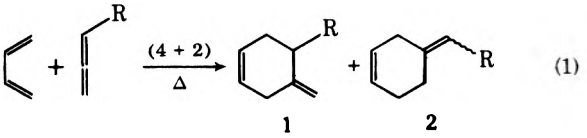
Received May 10, 1977

The Diels–Alder cycloaddition of vinyltriphenylphosphonium bromide (4) with a variety of 1,3-dienes generated the unsaturated cyclic phosphonium salts 3 in excellent yield. Wittig condensation of the ylides of 3 with aldehydes afforded the alkylidene derivatives. In addition, the known Diels–Alder adducts 13 were prepared from diethyl ketomalonate (12) and 1,3-dienes. These dihydropyrans could be transformed, via diacids 14, to β,γ-unsaturated valerolactones 15 by either lead tetraacetate mediated oxidative decarboxylation or by the Curtius degradation.

The Diels–Alder reaction figures prominently in the arsenal of organosynthetic reactions, and a wealth of knowledge exists concerning reactivity profiles, regioselectivity, and stereochemistry of the 4 + 2 cycloaddition reaction.[2] In recent years the construction of synthetic equivalents for unreactive dienophiles such as ketene[3] and allene[4] has extended the scope of this cyclization reaction to the production of cyclohexene systems not normally generated by this thermal process. This report relates the development of two such Diels–Alder equivalents: an allene equivalent[5] capable of introducing the $-CH_2C(=CHR)-$ group in a Diels–Alder sense, and a carbon dioxide equivalent[6] which places the $-OC(=O)-$ group into the cycloadduct.

Results and Discussion

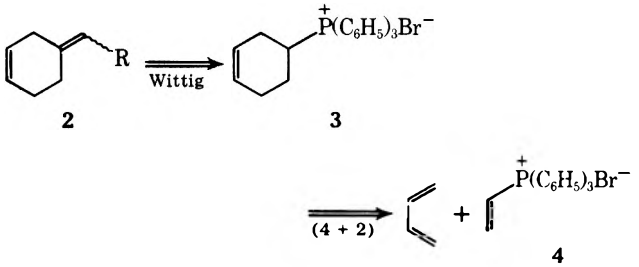
General Allene Equivalent. Two isomeric Diels–Alder products may be realized from the 4 + 2 cyclization between alkyl-substituted allenes and 1,3-dienes (eq 1).[7] It was felt that



1 2 (1)

an allene equivalent capable of producing the alkylidene moiety in 2 might be obtained from the intermediate 3 via a Wittig transformation (Scheme I). Cycloadduct 3 might then

Scheme I

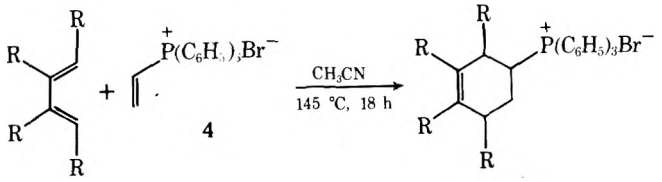


2 3 4

be obtained using the Diels–Alder transform, thus requiring a 1,3-diene and vinyltriphenylphosphonium bromide (4) as starting materials.

Indeed, vinyltriphenylphosphonium bromide[8] underwent smooth Diels–Alder reaction with a number of dienes at elevated temperatures to afford the desired adducts in excellent yield as shown in Table I. Cycloadducts **3a–e** were recovered as powders after recrystallization. These new phosphonium salts could be readily converted to the ylides by treatment with lithium diisopropylamide at −78 °C in tetrahydrofuran. Addition of a slight excess of aldehyde at 0 °C followed by warming to room temperature afforded the alkylidene derivatives as shown in Table II. Formaldehyde, aliphatic and aromatic aldehydes, and α,β-unsaturated aldehydes underwent condensation and the desired olefins were obtained in good yield although, in some cases, product volatility con-

Table I. Diels-Alder Adducts of 4 with 1,3-Dienes



Registry no.	Diene	Adduct	Yield,[a] %
106-99-0	1,3-Butadiene	3a	93
78-79-5	Isoprene	3b	90[b]
513-81-5	2,3-Dimethyl-1,3-butadiene	3c	92
542-92-7	Cyclopentadiene	3d	90[c]
592-57-4	1,3-Cyclohexadiene	3e	96[c]

[a] Yields are reported after recrystallization from $CHCl_3$–Et_2O. [b] The para isomer was found in greater than 90% excess over the meta isomer. See ref 14. [c] Both ^1H and ^{31}P NMR methods failed to allow analysis of endo:exo isomer ratio. ^{13}C NMR spectrometry did reveal a ratio of approximately 80:20; however, exact structure assignment was not possible.

tributed to substantial decreases in the actual quantity isolated.

It is well documented that allenes possessing electron-withdrawing groups undergo Diels–Alder reactions in generally good yield across the α,β portion of the allenic π-bond system.[7b] Condensation of the ylide of the bicyclic phosphonium salt **3d** with glyoxal monodiethyl acetal[9] led to isolation of a mixture of *Z* and *E* isomers of the conjugated aldehyde **6** (required for another study) following treatment of the crude acetal Wittig product with silica gel in pentane (eq 3). Mild

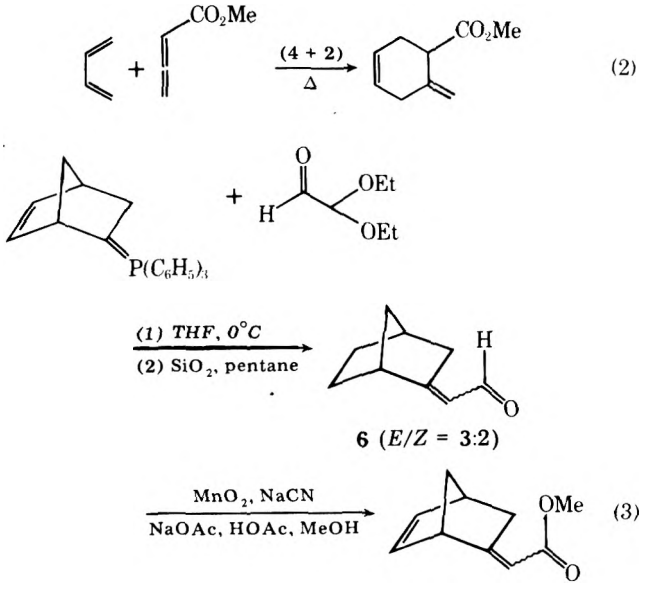
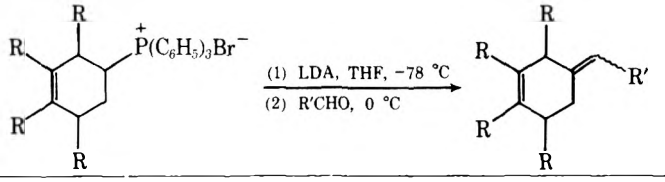


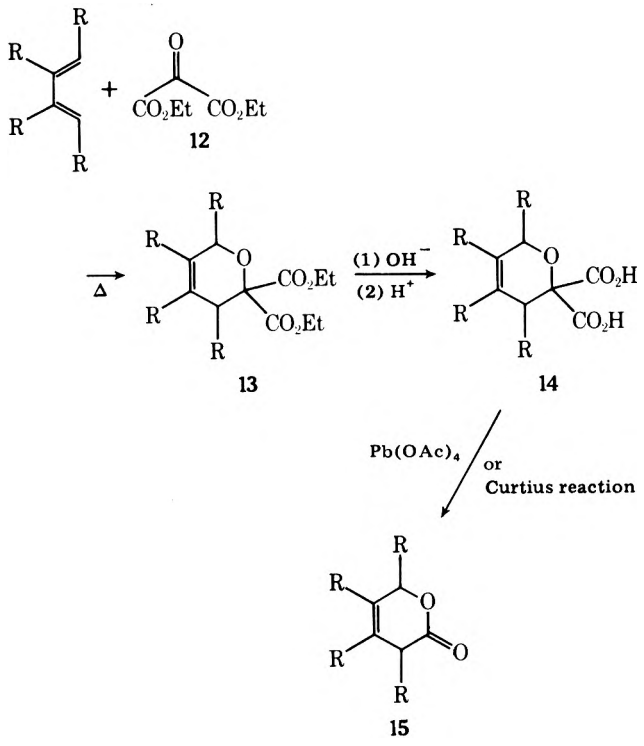
Table II. Wittig Condensations of 3a–e with Aldehydes



Registry no.	Phosphonium salt	Registry no.	Aldehyde	Product[a]	Yield,[b] %
63797-62-6	3a	100-52-7	C_6H_5CHO	5a	78
63797-63-7	3b		C_6H_5CHO	5b	80
54222-64-9	3c		C_6H_5CHO	5c	75
	3d		C_6H_5CHO	5d	81
	3d	5344-23-0	$(C_2H_5O)_2CHCHO$	6 (*E* = 60%, *Z* = 40%)	35
	3e		C_6H_5CHO	5e	85
	3e	50-00-0	CH_2O(g) or $(CH_2O)_n$	7	50
	3e	111-71-7	n-$C_6H_{13}CHO$	8	63
	3e	4170-30-3	$CH_3CH{=}CHCHO$	9	30

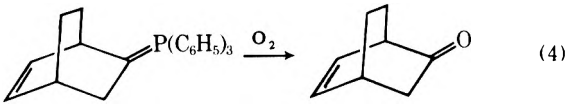
[a] Amounts of *Z* and *E* isomers were not determined except in **6**. [b] Yields are reported after chromatographic purification.

Scheme II



oxidation of this aldehyde using activated manganese dioxide and sodium cyanide[10] afforded the methyl ester in excellent yield.

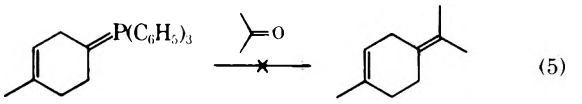
Furthermore, vinyltriphenylphosphonium bromide may also be considered as a ketene equivalent as demonstrated below using **3e** (eq 4). By bubbling a stream of oxygen through



(4)

a solution of the ylide at room temperature,[11] the bicyclic ketone **10** could be generated.

One particular limitation of the Wittig reaction is its failure to allow formation of tetrasubstituted olefins.[12] For example,



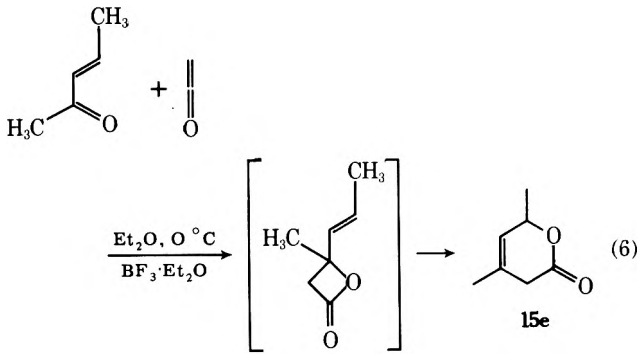
(5)

an attempt at the synthesis of the natural product terpinolene[13] **11** by condensation of acetone with the ylide of **3b** led to recovery of starting material after 24 h.

Carbon Dioxide Equivalent. To complete the triad of Diels–Alder equivalents for carbon and oxygen cumulated systems, a study was undertaken to develop a method for the introduction of the -OC(=O)- group into the 4 + 2 cycloadduct. Of the myriads of known carbonyl compounds, only a few have been shown to act as dienophiles in the Diels–Alder reaction.[15] Diethyl ketomalonate[8] (**12**) is one such species, and its Diels–Alder adducts with a variety of 1,3-dienes have been well characterized.[16]

As can be seen in Scheme II, we envisioned the conversion of the biscarboethoxy group of cycloadduct **13** to the lactone carbonyl of **15** to proceed by either lead tetraacetate mediated oxidative decarboxylation[17] of diacid **14** or by the classical Curtius degradation[18] of the same intermediate.

Although a number of syntheses of β,γ-unsaturated valerolactones are known,[19] one in particular is capable of generating only dialkyl-substituted species such as **15e** in high yield (eq 6). This method involves the addition of ketene to γ-alkyl-α,β-unsaturated ketones.[19a]

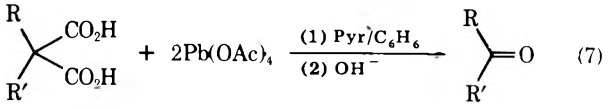


(6)

Diels–Alder Adducts of Diethyl Ketomalonate (12). The 4 + 2 cycloaddition products were made by dissolving **12** and an excess of the 1,3-diene in acetonitrile and heating the solution at 130–135 °C for the designated period of time in a sealed tube (Table III). The diesters **13a–f** were then hydrolyzed to the biscarboxylic acids **14a–f** in good overall yield based on diethyl ketomalonate.

Conspicuously absent from Table III is the cyclopentadiene adduct. Cycloaddition of this normally reactive diene had been reportedly unsuccessful.[16a] We also attempted the cyclization of monomeric cyclopentadiene with **12** at various temperatures ranging from −20 to 135 °C, but we were unable to isolate the cycloadduct. Apparently, if the adduct is formed, thermodynamic instability results in facile cycloreversion. Anthracene also failed to form a product with the carbonyl substrate.

Lactone Carbonyl Release. Lead Tetraacetate Method. Alkyl-substituted malonic acids undergo oxidative decarboxylation to form aldehydes or ketones upon treatment with lead tetraacetate,[20] LTA (eq 7). When similarly applied to



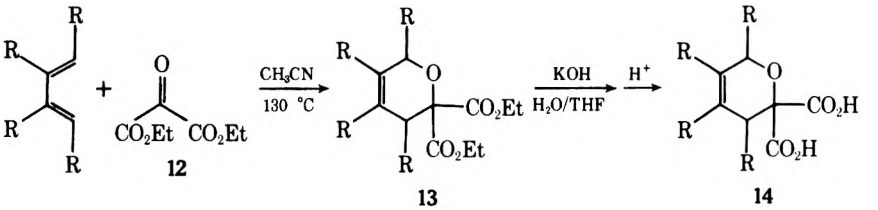
(7)

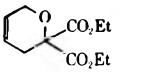
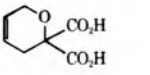
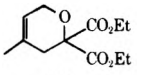
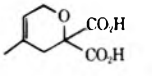
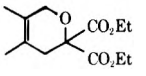
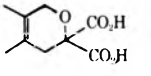
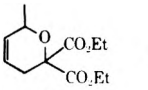
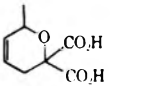
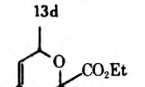
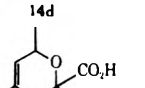
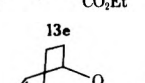
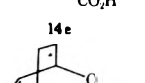
diacid **14c** (see Table IV), this procedure allowed isolation of the desired lactone in 20% yield after aqueous workup. Following numerous attempts to improve the yield of valerolactone **15c**, the best conditions were found to be a variation of a procedure developed by Cope and co-workers[21] utilizing sodium acetate to facilitate carboxyl ligand transfer to Pb^{IV}, a prerequisite for successful oxidation.[17] (Pyridine also functions in this manner.) However, due to limited success in generation of other valerolactones with lead tetraacetate, the Curtius degradation was explored.

Trimethylsilyl Azide Method. The essential feature of the Curtius degradation of carboxylic acids is the thermal rearrangement of an acyl azide to the isocyanate, and numerous approaches to the synthesis of acyl azides are known.[22] One procedure which has been developed recently is the one-pot conversion of an acid chloride to the isocyanate using trimethylsilyl azide (TMSA).[23] (See Scheme III.)

Upon treatment of a warm cyclohexane solution[24] of the bisacid chloride of **14c** with an excess of TMSA, the bisacyl azide was rapidly formed as evidenced by infrared spectroscopy (λ_{max} 4.67 and 5.80 μm). On further warming, stepwise rearrangement to the bisisocyanate apparently occurred. Within 15 min strong isocyanate infrared absorptions (λ_{max} 4.40 and 4.46 μm) were seen which were equal in intensity to those of the acyl azide. After about 30 min of heating, no acyl azide remained. Removal of solvent, followed by mild hydrolysis of a tetrahydrofuran solution of the bisisocyanate with either aqueous acetic acid or aqueous oxalic acid generated

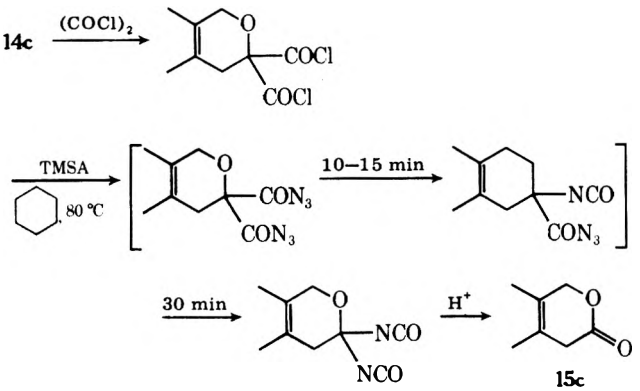
Table III. Diels-Alder Adducts of 12 and 1,3-Dienes



Registry no.	Diene[a]	Diester (%)[b,g]	Diacid (%)[c]	Mp, °C
	1,3-Butadiene (16 h)	 (78)	 (63)	Oil
		13a	14a	
	Isoprene (4 h)	 (80)[d]	 (64)	Oil
		13b	14b	
	2,3-Dimethyl-1,3-butadiene (4 h)	 (86)	 (70)	138-140
		13c	14c	
504-60-9	Piperylene (4 h)	 (85)[e]	 (66)	124-126
		13d	14d	
1118-58-7	2-Methyl-1,3-pentadiene (1.5 h)	 (95)[f]	 (90)	146-147
		13e	14e	
	1,3-Cyclohexadiene (4 h)	 (84)	 (74)	128-130
		13f	14f	

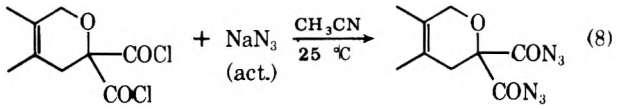
[a] Reaction time in parentheses. [b] Yields reported after distillation. [c] Overall yield based on 12. [d] NMR analysis revealed 11:1 ratio of para:meta isomers. [e] NMR analysis revealed 95% ortho isomer. [f] No meta isomer detected by NMR analysis. [g] Registry no.: 13c, 24588-60-1; 13d, 36749-08-3; 13e, 63797-64-8; 13f, 24588-62-3.

Scheme III



valerolactone **15c** in 55% yield after distillation. Similar treatment of diacid **14b** produced **15b** in only 30% yield.

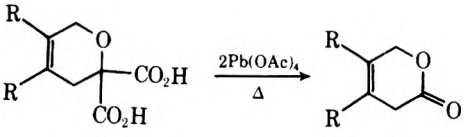
Sodium Azide Method. Alternatively, excellent conversion of the acid chloride to the acyl azide could be accomplished under mild conditions by stirring an acetonitrile solution of the acid chloride with an excess of activated sodium azide[25] at room temperature (eq 8). Within 40 min substitution was



(8)

complete and filtration of the reaction mixture to remove insoluble sodium salts, followed by thorough concentration at room temperature, generated the viscous product (λ_{max} 4.67 μm).

Table IV. LTA Oxidation of Diacids 14a-c



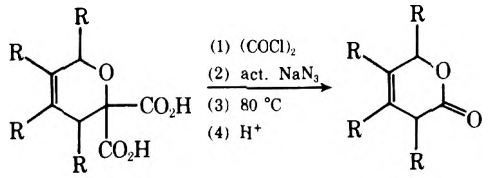
Diacid	Method	Lactone (%)[a]
14c	2 equiv of Pyr, C_6H_6, 80 °C, 3 h[b]	15c (20)
14c	NaOAc, HOAc, C_6H_6, 40 °C, 1 h[c]	15c (63)
14b	NaOAc, HOAc, C_6H_6, 40 °C, 1 h[c]	15b (40)
14a	NaOAc, HOAc, C_6H_6, 40 °C, 1 h[c]	15a (0)

[a] Yields reported after distillation. [b] Tufariello and Kissel, ref 20. [c] Cope, Park, and Scheiner, ref 21.

Without further purification, careful addition of cyclohexane to the potentially explosive acyl azide followed by rapid stirring at 80 °C for 40 min resulted in formation of the insoluble isocyanate. Hydrolysis of this material as before led to isolation of **15c** in 72% yield (Table V) based on diacid. Extension of this method to other diacids resulted in improved yields of the desired valerolactones.

However, when the sodium azide method was applied to the bisacid chlorides of **14d** and **14e**, the dienoic acids **16d** and **16e** were recovered along with the lactone in the case of the latter material. Perhaps stabilization of an incipient cation by the allylic methyl group allows this rearrangement to take place during isocyanate hydrolysis (eq 9 and 10).

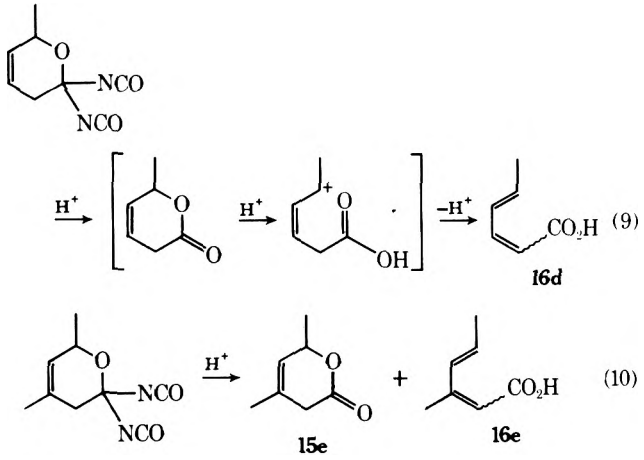
Table V. Lactone Formation by the Sodium Azide Method



14 15

Registry no.	Diacid	Hydrolysis method[a]	Time, min	Lactone (%)[b]	Other products (%)
57668-92-5	14a	A	40	15a (52)	.....
57668-93-6	14b	A	50	15b (60)	.....
57668-94-7	14c	A	60	15c (72)	.....
828-50-2	14d	B	60	.....	16d (55)
63797-65-9	14e	A	40	15e (30)	16e (34)
61779-36-0	14f	C		15f (7)	.....

[a] Method A: aqueous oxalic acid/THF/25 °C; method B: hydrolysis was run under a variety of conditions ranging from mildly acidic to mildly basic ($NaHCO_3$); method C: 5% aqueous $NaHCO_3$/THF/25 °C/18 h followed by acidification to pH 2. [b] Yields are reported after distillation and are based on diacid.



Synthetic Transformations of Lactone 15c. The synthetic versatility of these lactones is outlined in Scheme IV where lactone **15c** was subjected to a variety of chemical manipulations.

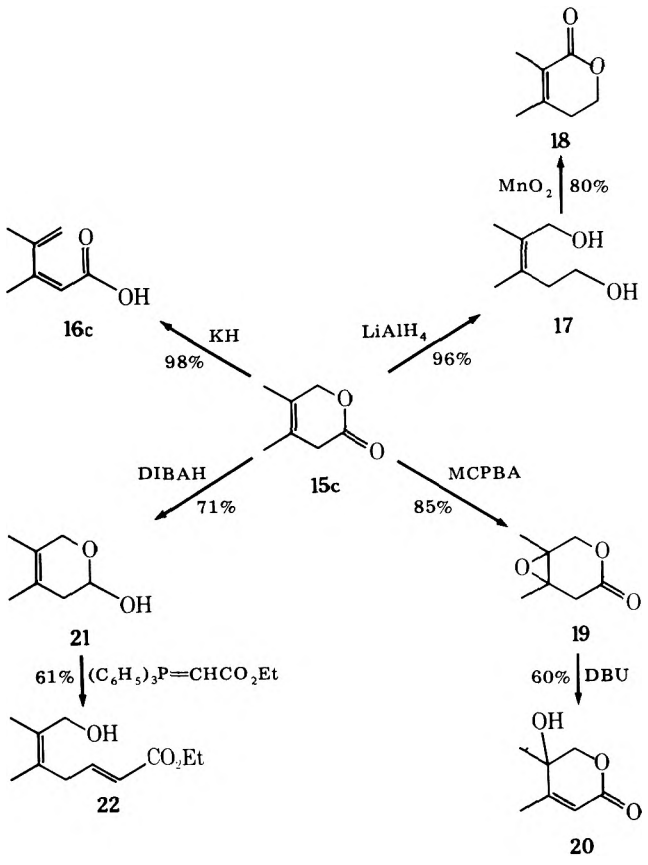
Production of 3,4-dimethyl-2(*Z*),4-pentadienoic acid (**16c**) was cleanly accomplished by treatment of the lactone with 1 equiv of potassium hydride in THF at 0 °C.

Lithium aluminum hydride reduction of the lactone in THF at room temperature afforded diol **17** in excellent yield. This product could be transformed to the α,β-unsaturated valerolactone **18** upon selective oxidation of the allylic alcohol using activated manganese dioxide.[26]

Epoxylactone **19** was prepared by oxidation of **15c** with *m*-chloroperbenzoic acid in dichloromethane at 0 °C. Treatment of the crystalline epoxide with diazabicyclo[5.4.0]-undec-5-ene (DBU) in THF generated the rearranged alcohol **20** in good yield.[27]

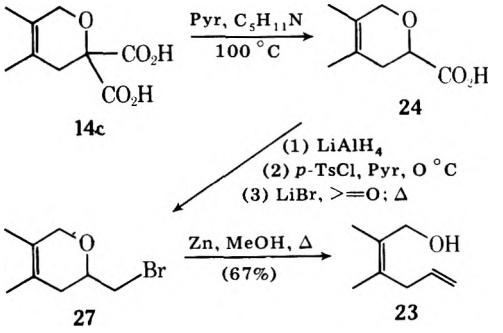
Reduction of **15c** to the cyclic hemiacetal **21** was achieved at −20 °C in ether using diisobutylaluminum hydride

Scheme IV

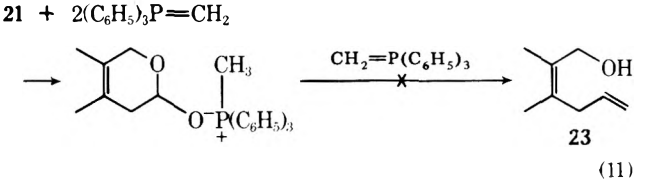


(DIBAH). Wittig condensation of the weakly basic stabilized ylide carboethoxyethylidene triphenylphosphorane with **21** generated the 1,4-diene **22** in 61% yield. Attempted Wittig reaction of **21** with the unstabilized ylide methylene tri-

Scheme V



phenylphosphorane led to recovery of starting material (eq 11). Diene **23** could be obtained by a different route starting



(11)

with the diacid **14c**. This compound could be monodecarboxylated using pyridine and a few equivalents of piperidine at 100 °C as shown in Scheme V. The new carboxylic acid **24** was then reduced to the alcohol **25** using LAH in ether. Conversion to the *p*-toluenesulfonate **26** was accomplished using standard procedures, and displacement by lithium bromide in refluxing acetone then generated the primary bromide in 70% overall yield from **25**. Zinc-mediated fragmentation of the bromide was performed in refluxing methanol to afford the desired product.

Experimental Section

Reactions were carried out under a nitrogen atmosphere unless otherwise noted. Melting points were taken on a Fisher-Johns hot stage apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer 137 spectrophotometer. NMR spectra were taken on either Varian T-60 or A-60A spectrometers with tetramethylsilane as an internal standard. In describing NMR chemical shifts, peaks are reported by indicating the center of the pattern. The multiplicity of the peak is abbreviated as s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Mass spectra were obtained using a Hitachi Perkin-Elmer Model RMU-7E spectrometer. Elemental analyses were determined by Robertson Laboratory, Florham Park, N.J. Micro thin-layer chromatography was performed on Eastman Chromatogram Sheets No. 960 precoated with silica gel and fluorescent indicator. Preparative thick-layer chromatography was done on precoated Silica Gel G-200 plates with fluorescent indicator as supplied by Brinkman Instruments, Inc. Column chromatography was conducted with Grace silica gel, grade 923, 100–200 mesh.

All chemicals were commercial samples unless reference is given to their preparation. They were used as received unless otherwise noted. Anhydrous solvents were obtained by distillation from the specified substances: acetonitrile, chloroform, and dichloromethane from P_2O_5; benzene and methanol from calcium hydride; cyclohexane from sulfuric acid; ether and tetrahydrofuran (THF) from sodium benzophenone ketyl.

General Procedure for Cycloaddition of Vinyltriphenylphosphonium Bromide with 1,3-Dienes. A solution of an excess of freshly distilled 1,3-butadiene (precooled to −78 °C), vinyltriphenylphsophonium bromide (2.50 g, 7 mmol), and a trace of hydroquinone in 5 mL of acetonitrile was heated in a sealed tube at 145 °C. After 20 h the tube was opened and the contents were removed with CH_2Cl_2. Following concentration at reduced pressure, the gummy residue was dissolved in a minimal volume of $CHCl_3$ and triturated with Et_2O to afford, after drying under vacuum, 2.90 g (93%) of cyclohex-3-enyltriphenylphosphonium bromide (**3a**): mp 240–241 °C dec; NMR ($CDCl_3$) δ 5.70 (br s, 2 H), 5.00–5.50 (br m, 1 H), 1.90–3.00 (complex m, 6 H). Anal. Calcd for $C_{24}H_{24}BrP$: C, 68.09; H, 5.71. Found: C, 67.66; H, 5.26.

In a similar fashion, the following phosphonium salts were prepared.

Table VI. Spectral and Analytical Data

Compound	NMR (δ)[a]	Analysis,[b] mol wt
5a	5.70–6.0 (m, 3 H)	Calcd: 170.2588 Found: 170.2610
5b	6.15 (br s, 1 H), 5.70 (br s, 1 H), 1.75 (br s, 3 H)	Calcd: 183.2796 Found: 183.2808
5c	6.20 (br s, 1 H), 1.70 (br s, 6 H)	Calcd: 198.1401 Found: 198.1392
5d	6.30 (br s, 1 H), 6.02 (ABq, J = 2 Hz, 2 H)	Calcd: 182.1093 Found: 182.1102
5e	6.10–6.25 (m, 3 H), 3.09 (br s, 1 H), 2.71 (br s, 1 H)	Calcd: 196.1262 Found: 196.1279
7	6.20–6.35 (m, J = 3.5 Hz, 2 H), 4.55, 4.70 (2m, 2 H)	Calcd: 120.1963 Found: 120.1982
8	6.24 (m, J = 4 Hz, 2 H), 5.15 (br t, 1 H)	Calcd: 204.3571 Found: 204.3558
9	6.25 (m, J = 4 Hz, 2 H), 5.13–6.05 (m, 3 H), 1.75 (d, J = 6 Hz, 3 H)	Calcd: 160.2689 Found: 160.2702
10	6.40 (q, 2 H), 3.02 (br m, 2 H), 1.95 (d, J = 3 Hz, 2 H), 0.95–1.85 (complex m, 2 H)	Calcd: 122.0731 Found: 122.0720

[a] Spectra taken in CCl_4. [b] By mass spectral analysis.

4-Methylcyclohex-3-enyltriphenylphosphonium bromide (3b): mp 232–235 °C dec; NMR ($CDCl_3$) δ 5.30–5.60 (br s, 1 H), 4.40–4.95 (br m, 1 H), 2.00–3.00 (br m, 6 H), 1.65 (br s, 3 H). Anal. Calcd for $C_{25}H_{26}BrP$: C, 68.65; H, 5.99. Found: C, 68.04; H, 5.16.

3,4-Dimethylcyclohex-3-enyltriphenylphosphonium bromide (3c): mp 114–115 °C dec; NMR ($CDCl_3$) δ 6.23 (s, 1 H), 2.90 (br s, 2 H), 1.90–2.56 (br m, 4 H), 1.55 (s, 6 H). anal. Calcd for $C_{26}H_{28}BrP$: C, 69.18; H, 6.25. Found: C, 70.04; H, 5.98.

Bicyclo[2.2.1]hept-5-enyl-2-triphenylphosphonium bromide (3d): mp 220–223 °C dec; NMR ($CDCl_3$) δ 5.10–5.95 (br m, 3 H). Anal. Calcd for $C_{25}H_{24}BrP$: C, 68.97; H, 5.55. Found: C, 69.10; H, 5.93.

Bicyclo[2.2.2]oct-5-enyltriphenylphosphonium bromide (3e): mp 263–266 °C; NMR ($CDCl_3$) δ 5.10–6.03 (br m, 3 H). Anal. Calcd for $C_{26}H_{26}BrP$: C, 69.49; H, 5.83. Found: C, 70.05; H, 6.18.

General Procedure for Wittig Condensation. To a cooled solution (0 °C) of the phosphorane of **3e** (0.442 g, 1 mmol) in 10 mL of THF (prepared by addition of 1.1 mmol of lithium diisopropylamide in THF to a suspension of phosphonium salt in the same solvent at −78 °C) was added 0.127 g (1.2 mmol) of benzaldehyde. After stirring overnight at 25 °C, the product was diluted with pentane and the organic layer was washed many times with water, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The pure olefin was obtained by column chromatographic purification over silica gel using hexane as eluent. Thus, 2-benzylidenebicyclo[2.2.2]oct-5-ene (**5e**) was obtained (0.166 g, 85%) as a colorless oil. Anal. Calcd for $C_{15}H_{16}$: mol wt, 196.1279. Found: mol wt (MS), 196.1262.

Table VI contains spectral and analytical data for Wittig products **5a-d**, **7**, **8**, **9**, and **10**.

Bicyclo[2.2.2]oct-5-en-2-one (10). Phosphorane **3e** (0.442 g, 1 mmol) was prepared as above. Oxygen was bubbled into the stirring suspension until the characteristic deep red color of the ylide disappeared. After 24 h, the resulting mixture was directly filtered through silica gel to afford 0.024 g (20%) of ketone **10**: IR (hexane) 5.78, 6.2 μm.

Bicyclic Aldehyde (6). To a cooled solution (0 °C) of the ylide of phosphonium salt **3d** (1.254 g, 3 mmol) in 50 mL of THF was added glyoxal monodiethyl acetal[9] (0.53 g, 4 mmol). After stirring overnight, the product was diluted with pentane and the organic layer was repeatedly washed with water and dried over $MgSO_4$. The crude diethyl acetal was obtained by removal of solvent by distillation at atmospheric pressure. The volatile product was redissolved in pentane and stirred overnight with 3 g of silica gel at room temperature. After filtration and concentration at atmospheric pressure, the crude aldehyde was purified by thick-layer chromatography using 4:1 hexane–ether

as developing solvent and obtained as a colorless volatile liquid (0.14 g, 35%, a mixture of *Z* and *E* isomers); IR (CH_2Cl_2) 5.97, 6.07, and 6.17 μm; NMR ($CDCl_3$) δ 9.80 (d, *J* = 8.5 Hz, C*H*O, *Z* isomer): 9.60 (d, *J* = 8.5 Hz, C*H*O, *E* isomer), 4.22 (m, doubly allylic methine *Z* isomer), 3.42 (m, doubly allylic methine *E* isomer); mp (semicarbazide) 207–208 °C dec. Anal. Calcd for $C_{10}H_{13}N_3O$: mol wt, 191.2258. Found: mol wt, 191.2284.

General Procedure for Cycloaddition of Diethyl Ketomalonate with 1,3-Dienes. Freshly distilled 1,3-butadiene (an excess) was condensed into a Carius tube containing a trace of hydroquinone, diethyl ketomalonate (1.82 mL, 12 mmol) and 4 mL of acetonitrile. The tube was sealed and after heating at 135 °C for 16 h, the product was isolated with CH_2Cl_2. After concentration, approximately 50 mL of 95% EtOH was added to precipitate polymeric material and the resulting white suspension was vacuum-filtered through Celite and then concentrated. Evaporative distillation produced diethyl 3,6-dihydropyran-2,2-biscarboxylate (**13a**) (2.17 g, 78%) as a colorless liquid; bp 100 °C (0.8 mm); IR (neat) 5.71 μm; NMR (CCl_4) δ 5.79 (s, 2 H), 4.23 (q and buried s, 6 H), 2.65 (m, 2 H) and 1.27 (t, 6 H). Anal. Calcd for $C_{13}H_{20}O_5$: mol wt, 256.1317. Found: mol wt, 256.1320.

In a similar fashion the following known compounds were prepared.

Diethyl 4-Methyl-3,6-dihydropyran-2,2-biscarboxylate (13b). Isoprene (2.7 mL, 27 mmol) and diethyl ketomalonate (1.82 mL, 12 mmol) were treated as above. After 4 h of heating, identical workup afforded **13b** as a colorless liquid after distillation (2.4 g, 80%). Para:meta isomer ratio was 11:1 as determined by NMR analysis: bp 110 °C (1.0 mm); IR (neat) 5.70 μm; NMR (CCl_4) δ 5.38 (s, 1 H), 4.23 (q and buried s, 6 H), 2.50 (s, 2 H), 1.76 (s, *p*-CH_3), 1.65 (s, *m*-CH_3).

Diethyl 4,5-Dimethyl-3,6-dihydropyran-2,2-biscarboxylate (13c). 2,3-Dimethyl-1,3-butadiene (2.7 mL, 25 mmol) and diethyl ketomalonate (1.82 mL, 12 mmol) were treated as above. After 4 h heating, similar workup afforded **13c** (2.64 g, 86%): bp 120 °C (1.0 mm); IR (neat) 5.72 μm; NMR (CCl_4) δ 4:20 (q and buried s), 2.46 (s, 2 H), 1.68 and 1.52 (2s, 6 H).

Diethyl 6-Methyl-3,6-dihydropyran-2,2-biscarboxylate (13d). Piperylene (2.7 mL, 27 mmol) and diethyl ketomalonate (1.55 mL, 10.2 mmol) were treated as above to afford **13d** (2.19 g, 85%): bp 105 °C (1.5 mm); IR (neat) 5.73 μm; NMR (CCl_4) δ 5.62 (m, 2 H), 4.20 (q and buried m, 5 H), 2.58 (m, 2 H) and 1.30 (m, 9 H). No 3-methyl isomer was detected by NMR analysis.

Diethyl 4,6-Dimethyl-3,6-dihydropyran-2,2-biscarboxylate (13e). 2-Methyl-1,3-pentadiene (4 mL, 40 mmol) and diethyl ketomalonate (2.7 mL, 18 mmol) were treated as above to produce, after 90 min heating, adduct **13e** (4.50 g, 95%): bp 112 °C (1.0 mm); IR (neat) 5.73 μm; NMR (CCl_4) δ 5.38 (m, 1 H), 4.33 (q and buried m, 5 H), 2.58 (m, 2 H), 1.78 (s, 3 H). No 4,6-dimethyl isomer was detected by NMR analysis.

2-Oxa-3,3-dicarboethoxybicyclo[2.2.2]oct-5-ene (13f). 1,3-Cyclohexadiene (2.7 mL, 27 mmol) and diethyl ketomalonate (1.82 ml, 12 mmol) were treated as above. After 4 h heating, similar workup afforded **13f** (2.86 g, 84%): bp 120 °C (0.8 mm); IR (neat) 5.72 μm; NMR (CCl_4) δ 6.43 (m, 2 H), 4.50 (br m, 1 H), 4.15 (m, 4 H), 3.30 (br m, 1 H), 1.6–2.5 (complex m, 4 H).

General Procedure for Hydrolysis of Diester 13 to Diacid 14. To a solution of diester **13a** (0.821 g, 3.4 mmol) in 30 mL of THF was added 30 mL of 10 N KOH and the resulting mixture was stirred at room temperature for 30 h. Acidification to pH 1 with 2 N HCl was followed by thorough extraction with Et_2O and the combined organic extracts were dried over Na_2SO_4. Complete removal of solvent afforded 3,6-dihydropyran-2,2-biscarboxylic acid (**14a**) as a golden viscous oil (0.50 g, 80%) (dry by NMR analysis) which resisted numerous crystallization attempts: IR (Et_2O) 5.78 μm; NMR ($CDCl_3$) δ 5.78 (s, 2 H), 4.42 (s, 2 H) and 2.78 (s, 2 H).

4-Methyl-3,6-dihydropyran-2,2-biscarboxylic Acid (14b). Diester **13b** (0.968 g, 4 mmol) was treated as above. The resulting diacid **14b** was also obtained as a golden viscous oil (0.670 g, 85%): IR (neat) 5.75 μm; NMR ($CDCl_3$) δ 5.57 (s, 1 H), 4.53 (s, 2 H), 2.78 (s, 2 H), 1.90 (s, *p*-vinyl CH_3) and 1.88 (*m*-vinyl CH_3).

4,5-Dimethyl-3,6-dihydropyran-2,2-biscarboxylic Acid (14c). Diester **13c** (2.640 g, 10.3 mmol) was treated as above. Diacid **14c** was isolated as crystals and recrystallization from Et_2O–petroleum ether afforded 1.80 g (87%) of product: IR (CH_2Cl_2) 5.75 μm; NMR ($CDCl_3$) δ 4.25 (s, 2 H), 2.63 (s, 2 H) and 1.70, 1.55 (2s, 6 H).

6-Methyl-3,6-dihydropyran-2,2-biscarboxylic Acid (14d). Diester **13d** (2.187 g, 9.5 mmol) was treated as above. Diacid **14d** was obtained as a powdery solid after recrystallization (1.38 g, 78%): NMR ($CDCl_3$) δ 5.75 (m, 2 H), 4.67 (br m, 1 H), 2.72 (ABq, J_{AB} = 15 Hz, 2 H) and 1.33 (d, *J* = 6 Hz, 3 H).

4,6-Dimethyl-3,6-dihydropyran-2,2-biscarboxylic Acid (14e). Diester **13e** (4.50 g, 16.9 mmol) was treated as above to afford diacid **14e** (3.24 g, 90%) as a powder: NMR ($CDCl_3$) δ 5.35 (m, 1 H), 4.58 (br m, 1 H), 2.65 (ABq, J_{AB} = 18 Hz, 2 H), 1.78 (s, 3 H) and 1.30 (d, *J* = 6 Hz, 3 H).

2-Oxa-3,3-dicarboxybicyclo[2.2.2]oct-5-ene (14f). Diester **13f** (2.50 g, 8.8 mmol) was treated as above to generate diacid **14f** (1.78 g, 90%) as a powder: IR (CH_2Cl_2) 5.68 μm; NMR ($CDCl_3$) δ 6.10 (complex m, 2 H), 5.17 (br m, 1 H), 2.7 (br m, 1 H).

Lactone Carbonyl Release—Representative Procedures. 3,4-Dimethyl-3,4-dehydrovalerolactone (15c). Lead Tetraacetate Oxidation. Lead tetraacetate (1.00 g, 2 mmol, 90% in acetic acid) was added to a flask containing a suspension of excess anhydrous NaOAc in 2 mL of dry benzene and 1 mL of glacial HOAc. The mixture was then heated to 65 °C. Diacid **14c** (0.10 g, 0.5 mmol) was dissolved in 2 mL of glacial HOAc and then introduced into the preheated mixture. Immediate CO_2 evolution was observed and the oxidation was allowed to proceed for 1 h.

Upon cooling, the resulting white suspension was extracted with Et_2O and washed with water, neutralized with aqueous $NaHCO_3$, washed with brine, and dried over $MgSO_4$. After concentration and Kugelrohr distillation of the residue, lactone **15c** was recovered in 63% yield (0.040 g, yield based on diacid): bp 105 °C (1.0 mm); IR (neat) 5.75, 5.98 μm; NMR (CCl_4) δ 4.60 (s, 2 H), 2.85 (s, 2 H) and 1.70 (s, 6 H); *m/e* 126, 110, 108, 82, 69, 67, 55, 54, 53. Anal. Calcd for $C_7H_{10}O_2$: mol wt, 126.0681. Found: mol wt, 126.0667.

Trimethylsilyl Azide Method. To a stirring suspension of diacid **14c** (0.1 g, 0.5 mmol) in 25 mL of benzene containing a catalytic amount of pyridine was added 0.254 g (2 mmol) of oxalyl chloride. The reaction mixture was heated at reflux temperature until formation of acid chloride was complete, i.e., 2 h (IR, 5.59 μm). After removal of solvent and traces of oxalyl chloride, the acid chloride was dissolved in cyclohexane and heated to reflux. A solution of trimethylsilyl azide (0.180 g, 1.5 mmol) in 5 mL of cyclohexane was then added. Isocyanate formation was accomplished in about 40–50 min (IR, 4.40 and 4.46 μm).

After the product was allowed to cool, 10 mL of a 2:1 HOAc–H_2O solution was added and the mixture was stirred for 1 h at 25 °C. Following thorough Et_2O extraction, the combined organic portions were washed with water, neutralized with aqueous $NaHCO_3$, washed with brine, and dried over $MgSO_4$. Concentration afforded lactone **15c** in 57% yield (0.035 g, based on diacid).

Sodium Azide Method. (These bisacyl azides are potentially explosive and should be handled behind a safety shield.) The bisacid chloride of diacid **14c** (0.189 g, 0.95 mmol) was prepared as above using 0.30 g (2.3 mmol) of oxalyl chloride. After isolation of the crude product, the resulting oil was redissolved in dry acetonitrile (25 mL) and activated sodium azide[25] (0.25 g, 3.8 mmol) was added. The suspension was stirred at room temperature for 45 min (IR 4.67, 5.81, and 5.85 μm).

The reaction mixture was quickly filtered and then concentrated at room temperature under reduced pressure to afford a gummy golden residue of the bisacyl azide. (CAUTION! The bisacyl azide is shock sensitive. Cover with solvent before introduction of magnetic stirring bar.)

Curtius rearrangement was effected as before by vigorously stirring the insoluble residue in dry cyclohexane at reflux temperature. Formation of the insoluble bisisocyanate normally required 45–50 min (IR 4.40 and 4.46 μm). After concentration and redissolution in THF, hydrolysis was accomplished using 3 mL of 5% aqueous oxalic acid and stirring at 25 °C for 1 h.

Isolation of lactone **15c** was performed according to the same procedure as above generating 0.086 g (72%, based on diacid) of the desired compound.

3,4-Dehydrovalerolactone (15a). The sodium azide method was employed as above. Diacid **14a** (0.5 g, 2.8 mmol) afforded 0.120 g (52%) of the desired lactone **15a**. Hydrolysis time was shortened to 40 min: bp 97–100 °C (0.8 mm); IR (neat) 5.69 μm; NMR (CCl_4) δ 5.88 (s, 2 H), 4.83 (m, 2 H), and 2.98 (m, 2 H); *m/e* 98, 70, 54, 43, 39. Anal. Calcd for $C_5H_6O_2$: mol wt, 98.0368. Found: mol wt, 98.0404.

3-Methyl-3,4-dehydrovalerolactone (15b). The sodium azide method was employed as above. Diacid **14b** (0.130 g, 0.7 mmol) generated 0.042 g, (60%) of the desired lactone **15b**. Hydrolysis time was 50 min: bp 100–102 °C (1.0 mm); IR (neat) 5.76 μm; NMR (CCl_4) δ 5.60 (s, 1 H), 4.79 (s, 2 H), 2.91 (s, 2 H) and 1.80 (s, 3 H); *m/e* 112, 84, 82, 69, 55, 41. Anal. Calcd for $C_6H_8O_2$: mol wt, 112.0524. Found: mol wt, 112.0518.

3,5-Dimethyl-3,4-dehydrovalerolactone. (15e). The sodium azide method was employed as above. Diacid **14e** (0.2 g, 1 mmol) afforded 0.034 g (30%) of the desired lactone **15e**. Hydrolysis time was

45 min: bp 98–101 °C (1.0 mm); IR (neat) 5.74 μm; NMR (CCl_4) δ 5.58 (m, 1 H), 5.10 (m, 1 H), 2.98 (m, 2 H), 1.80 (s, 3 H) and 1.45 (d, 3 H); *m/e* 126, 110, 98, 83, 67, 55, 43. Anal. Calcd for $C_7H_{10}O_2$: mol wt, 126.0681. Found: mol wt, 126.0674.

3-Methylhexa-2,4-dienoic Acid (16e). Upon concentration of the crude parent lactone **15e** during the isolation procedure above, a solid appeared. Following addition of 5 mL of Et_2O, the supernatant containing the lactone was removed. Recrystallization of the solid from $CHCl_3$–Et_2O produced the dienoic acid **16e** (0.036 g, 34%): mp 119–121 °C; IR (CH_2Cl_2) 5.87 μm; NMR ($CDCl_3$) δ 7.58 (m, 1 H),[28] 6.60–5.46 (m, 3 H, vinyl H and OH) and 1.97 (m, 6 H). Anal. Calcd for $C_7H_9O_2$: (M − 1)/e, 125.0602. Found: (M − 1)/e, 125.0586.

Hexa-2,4-dienoic Acid (16d). The sodium azide method was employed as above using diacid **14d** (0.186 g, 1 mmol). Following hydrolysis, extraction and isolation afforded the dienoic acid **16d**, presumably a mixture of isomers, after recrystallization from $CHCl_3$–Et_2O (0.061 g, 55%). No lactone precursor was found: mp 115–117 °C; NMR ($CDCl_3$) δ 7.43 (m, 1H),[28] 6.60–5.50 (complex m, 4 H, vinyl H and OH), and 1.82 (d, 3 H); *m/e* 112, 111, 92, 67, 41, 29. Anal. Calcd for $C_6H_8O_2$: mol wt, 112.0524. Found: mol wt, 112.0514.

Bicyclic Lactone (15f). The sodium azide method was used as shown above. Diacid **14f** (0.35 g, 1.7 mmol) afforded the bisacid chloride (5.58 μm) after 24 h at reflux, then the bisacyl azide (4.63 and 5.81 μm) and the bisisocyanate (4.39 and 4.43 μm). Lactone carbonyl release was effected by dissolution of the bisisocyanate in 20 mL of THF followed by addition of 10 mL of 5% aqueous $NaHCO_3$. After stirring at 25 °C overnight, the biphasic mixture was acidified to pH 2 and thoroughly extracted into Et_2O. Drying (Na_2SO_4) and concentration led to recovery of a golden oil. Evaporative distillation afforded the lactone **15f** as a colorless liquid (0.015 g, 7% from diacid): IR (neat) 5.71, 6.20, 11.48 μm; NMR (CCl_4) δ 6.50 (m, 2 H), 5.10 (br m, 1 H), 3.40 (br m, 1 H) and 1.35–2.30 (complex m, 4 H); *m/e* 124, 96, 80, 79, 78, 77, 68. Anal. Calcd for $C_7H_8O_2$: mol wt, 124.0524. Found: mol wt, 12.0558.

***cis*-2,3-Dimethylpent-2-ene-1,5-diol (17).** To a suspension of lithium aluminum hydride (0.046 g, 1.2 mmol) in 40 mL of dry THF at 25 °C was slowly added a THF solution of lactone **15c** (0.126 g, 1 mmol). The reduction was allowed to proceed overnight. After addition of 2 mL of 10% aqueous NaOH, followed by stirring for 10 min, the contents were repeatedly extracted into Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford diol **17** (0.114 g, 96%) as a colorless oil which needed no further purification: IR (neat) 3.0 and 6.04 μm; NMR (CCl_4) δ 4.47 (s, 2 H), 3.93 (s, 1 H), 3.57 (t, 2 H), 2.29 (t, 2 H), 1.76 and 1.70 (2s, 6 H); *m/e* 130, 112, 97, 84, 82, 67, 55. Anal. Calcd for $C_7H_{14}O_2$: mol wt, 130.0994. Found: mol wt, 130.0982.

2,3-Dimethyl-2,3-dehydrovalerolactone (18). A solution of diol **17** (0.038 g, 0.29 mmol) in 6 mL of CH_2Cl_2 was stirred at room temperature. Excess activated manganese dioxide (0.35 g, 4 mmol) was slowly added and the mixture was stirred overnight. Isolation of lactone **18** was accomplished by dilution of the suspension with 10 mL of CH_2Cl_2 and then filtration through Celite. After removal of solvent, the product was obtained in 80% yield (0.029 g): IR (neat) 5.83 μm; NMR (CCl_4) δ 4.27 (t, 2 H), 2.38 (t, 2 H), 1.96 and 1.86 (2s, 6 H); *m/e* 126, 96, 81, 68, 67, 53, 41. Anal. Calcd for $C_7H_{10}O_2$: mol wt, 126.0681. Found: mol wt, 126.0678.

3,4-Dimethyl-2(*Z*),4-pentadienoic Acid (16c). Potassium hydride (0.03 g, 1 mmol, 24% in oil) was washed three times with petroleum ether and then suspended in 10 mL of THF. A solution of lactone **15c** (0.063 g, 0.5 mmol) was added to the stirring mixture with immediate evolution of H_2 accompanied by formation of a pale yellow solid. Following acidification with dilute HCl, the contents were extracted with Et_2O and the organic layer was washed with water and brine and then dried over Na_2SO_4. After removal of solvent, feathery white crystals were isolated. Recrystallization from $CHCl_3$–Et_2O afforded the *cis*-dienoic acid **16c** in 98% yield (0.062 g): mp 54.5–56 °C; IR (CH_2Cl_2) 5.89, 6.05, and 6.08 μm; NMR ($CDCl_3$) δ 5.68 (m, 1 H), 4.88 (m, 1 H), 4.70 (m, 1 H), and 1.98 (m, 6 H); *m/e* 126, 125, 111, 79, 55, 53. Anal. Calcd for $C_7H_{10}O_2$: mol wt, 126.0681. Found: mol wt, 126.0677.

3,4-Dimethyl-3,4-epoxyvalerolactone (19). A solution of lactone **15c** (0.126 g, 1 mmol) in 20 mL of CH_2Cl_2 was cooled to 0 °C; 100% *m*-chloroperbenzoic acid[29] (0.344 g, 2 mmol) was then added as a solution in CH_2Cl_2. After 4 h, excess oxidizing agent was destroyed with 10 mL of saturated $NaHSO_3$ solution. Isolation was accomplished with CH_2Cl_2 extraction. After neutralization of the organic extract with aqueous $NaHCO_3$ and drying over $MgSO_4$, the solvent was removed to afford white needle crystals (0.120 g, 85%) of epoxide **19**: mp 49–51 °C; NMR (CCl_4) δ 4.28 (ABq, J_{AB} = 12 Hz, 2 H), 2.76 (s, 2 H) and 1.22 (s, 6 H); *m/e* 112, 99, 83, 69, 43. Anal. Calcd for $C_6H_8O_2$ (M − 30): 112.0524. Found: 112.0532. Loss of CH_2O produces the major fragment.

3,4-Dimethyl-4-hydroxy-2-dehydrovalerolactone (20). Epoxide **19** (0.044 g, 0.35 mmol) was dissolved in 10 mL of THF. 1,5-Diazabicyclo[5.4.0]undec-5-ene (DBU) (0.053 g, 0.35 mmol) was introduced into the solution and the reaction was allowed to proceed at 25 °C for 3 h. Dilute HCl (5 mL) was added and the contents of the flask were extracted into CH_2Cl_2. After the organic layer was washed with water and dried over Na_2SO_4, concentration led to recovery of 0.032 g (60%) of hydroxylactone **20** as a colorless liquid: IR (neat) 2.98 and 5.80 μm; NMR ($CDCl_3$) δ 5.74 (m, J_{AX} = 0.7 Hz, 1 H, vinyl H), 4.17 (s, 2 H), 2.74 (br s, 1 H), 2.01 (d, J_{AX} = 0.7 Hz, 3 H, vinyl CH_3) and 1.37 (s, 3 H). Anal. Calcd for $C_7H_{10}O_3$: mol wt, 142.1523. Found: mol wt, 142.1514.

3,4-Dimethyl-3,4-dehydrovalerolactol (21). Lactone **15c** (0.252 g, 2 mmol) was dissolved in 10 mL of dry Et_2O and cooled to −20 °C. Diisobutylaluminum hydride (4 mL, 5.2 mmol, 20% in hexane) was slowly added by syringe to the precooled solution and after 30 min, 2 mL of MeOH was introduced. The mixture was stirred overnight and, after dilution with Et_2O, the organic layer was washed with brine, dried over $MgSO_4$, and filtered through Celite. Concentration led to recovery of the crude product. Purification was accomplished by column chromatographic separation over silica gel. Lactol **21** was eluted with Et_2O and obtained as a colorless liquid (0.18 g, 71%): IR (neat) 2.90 μm; NMR ($CDCl_3$) δ 5.01 (t, 1 H), 3.99 (br s, 2 H), 2.10 (br s, 2 H) and 1.58 (d, 6 H); *m/e* 110, 95, 82, 77, 64, 51, 41. Anal. Calcd for $C_7H_{10}O$: (M − 18), 110.0732. Found: 110.0737. Loss of H_2O produces the major fragment.

Ethyl 5,6-Dimethyl-7-hydroxyhepta-2 (*E*),5(*Z*)-dienoate (22). Lactol **21** (0.064 g, 0.5 mmol) was dissolved in 15 mL of benzene contained in a 25-mL two-neck flask fitted with a reflux condenser. A benzene solution of carboethoxyethylidene triphenylphosphorane was then added to the reaction flask and heated to reflux. After 20 h, the mixture was cooled and then diluted with H_2O. Following extraction with Et_2O and drying over Na_2SO_4, the organic extract was concentrated to furnish the crude product. Preparative thick layer chromatography on silica gel afforded, after development with 1:1 hexane–Et_2O, diene **22** as a colorless liquid (0.058 g, 61%); IR (neat) 2.90, 5.80 and 5.85 μm; NMR ($CDCl_3$) δ 6.95 (d of t, J_{AB} = 14 Hz, J_{AC} = 7 Hz, 1 H), 5.80 (d, 1 H), 3.0 (d, 2 H), 4.20 (m, 5 H), 1.75 (d, 6 H), 1.22 (t, 3 H). Anal. Calcd for $C_{11}H_{18}O_3$: mol wt. 198.2620. Found: mol wt, 198.2603.

Production of Monocarboxylic Acid 24. A solution of diacid **14c** (1.40 g, 7.0 mmol) in 40 mL of dry pyridine containing 1 mL of piperidine was heated at 100 °C for 5 h. After the reaction mixture was allowed to cool, it was diluted with Et_2O and thoroughly extracted with dilute HCl to remove traces of base. The remaining Et_2O layer was washed with H_2O, then with brine, and dried over Na_2SO_4. Removal of solvent led to recovery of the monocarboxylic acid **24** as white crystals (0.940 g, 86%): mp 84.5–85 °C; IR (CH_2Cl_2) 5.72 μm; NMR ($CDCl_3$) δ 4.27 (partially buried t, 1 H), 4.13 (br s, 2 H), 2.30 (br d, 2 H), 1.68 and 1.53 (2s, 6 H); *m/e* 156, 138, 111, 110, 109, 96, 95, 83, 67, 55. Anal. Calcd for $C_8H_{12}O_3$: mol wt, 156.0796. Found: mol wt, 156.0812.

LAH Reduction of 24. LAH (0.5 g, 5 mmol) was suspended in Et_2O and the mixture was stirred at 0 °C for 20 min. An ethereal solution of carboxylic acid **24** (1.1 g, 5.5 mmol) was added dropwise to the hydride suspension and the mixture was then stirred for 2 h at 25 °C. Excess hydride was quenched by cautious addition of H_2O, followed by 10 mL of 0.1 N NaOH. After stirring for 30 min, the contents were extracted with Et_2O. The organic layer was washed with H_2O, then with brine, and dried over $MgSO_4$. Concentration and evaporative distillation led to recovery of 0.58 g (74%) of alcohol **25** as a colorless liquid: bp 105 °C (2 mm); IR (neat) 2.90 μm; NMR (CCl_4) δ 3.94 (br s, 2 H), 3.48 (br s and buried m, 4 H), 1.8–1.96 (br m, 2 H), 1.54 and 1.65 (2s, 6 H). Anal. Calcd for $C_8H_{14}O_2$: mol wt, 142.0998. Found: mol wt, 142.1013.

Preparation of Tosylate 26 and Bromide 27. To a solution of alcohol **25** (0.46 g, 3.2 mmol) in 10 mL of pyridine cooled to 0 °C was added 1.25 g (6.5 mmol) of *p*-toluenesulfonyl chloride. After 8 h at 0 °C, ice chips were added to destroy excess *p*-tosyl chloride, and the product was isolated with Et_2O. Yield of crude tosylate **26**, 0.81 g (83%); IR (CH_2Cl_2) 8.39 and 8.47 μm; NMR (CCl_4) δ 7.23 and 7.67 (centers of 2d of ABq, J_{AB} = 8 Hz, 4 H), 2.40 (s, 3 H).

The crude tosylate (0.81 g, 2.74 mmol) was then dissolved in 30 mL of anhydrous acetone. Lithium bromide (0.952 g, 11 mmol) was added and the solution was heated at reflux for 20 h. The solution was allowed to cool and, after removal of acetone, the residue was extracted with Et_2O. After drying over Na_2SO_4, the organic extract was concentrated to a brown liquid. Filtration through silica gel and Celite

afforded bromide **27** (0.475 g, 85%): IR (CCl_4) 7.98 and 8.08 μm; NMR (CCl_4) δ 3.95 (br s, 2 H), 3.61 (m, 1 H), 3.20–3.30 (m, 2 H), 2.0 (br m, 2 H), and 1.62 and 1.50 (2s, 6 H).

1-Hydroxy-2,3-dimethylhexa-2(*Z*),5-diene (23). Bromide **27** (0.40 g, 1.94 mmol) was dissolved in 25 mL of dry methanol. Activated zinc (2.80 g, prepared by stirring zinc dust for 5 min in glacial HOAc and then washing with several portions of methanol) was then added to the solution and stirred at reflux temperature for 20 h. After the reaction mixture had cooled, it was filtered through Celite to remove the zinc. The product (0.160 g, 67%) was obtained after Et_2O extraction and distillation (bp 92 °C (2 mm)) using a Kugelrohr apparatus: IR (CH_2Cl_2) 2.89, 6.00, and 6.10 μm; NMR (CCl_4) δ 5.37–6.03, 5.0, and 4.79 (3 m, 3 H), 3.96 (s, 2 H), 3.43 (s, 1 H), 2.80 (d, J = 6 Hz, 2 H) and 1.63 and 1.70 (2d, 6 H). Anal. Calcd for $C_8H_{14}O$: mol wt, 126.1045. Found: mol wt, 126.1034.

Acknowledgment. We thank Dr. Dorothy Z. Denney for taking ^{31}P and ^{13}C NMR spectra. R.B. would like to thank Mr. Larry Weiss for bringing her attention to the reagent glyoxal monodiethyl acetal. She is also grateful to Professor Bruce Ganem for his support during preparation of this manuscript. Grateful acknowledgment is made to Research Corporation, the Rutgers University Research Council, and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

Registry No.—*exo*-**3d**, 63797-66-0; *endo*-**3d**, 63797-67-1; *exo*-**3e**, 63864-73-3; *endo*-**3e**, 63864-74-4; **4**, 5044-52-0; (*E*)-**5a**, 63797-68-2; (*Z*)-**5a**, 63797-69-3; (*E*)-**5b**, 63797-70-6; (*Z*)-**5b**, 63797-71-7; (*E*)-**5c**, 63797-72-8; (*Z*)-**5c**, 63797-73-9; (*E*)-**5d**, 28764-49-0; (*Z*)-**5d**, 28764-48-9; (*E*)-**5e**, 63797-74-0; (*Z*)-**5e**, 63797-75-1; (*E*)-**6**, 63797-76-2; (*Z*)-**6**, 63797-77-3; 6 semicarbazide, 63797-78-4; **7**, 19386-05-1; (*E*)-**8**, 63797-79-5; (*Z*)-**8**, 63797-80-8; **9**, 54222-72-9; **10**, 2220-40-8; **12**, 609-09-6; **13a**, 24588-58-7; **13b**, 24588-59-8; **15a**, 26677-08-7; **15b**, 10021-22-4; **15c**, 22937-02-6; **15e**, 22936-96-5; **16c**, 63797-81-9; (*E*)-**16d**, 110-44-1; (*Z*)-**16d**, 5309-57-9; (*E*)-**16e**, 63797-82-0; (*Z*)-**16e**, 26050-06-6; **17**, 63797-83-1; **18**, 57668-96-9; **19**, 63797-84-2; **20**, 63797-85-3; **21**, 63797-86-4; **22**, 63797-87-5; **23**, 63797-88-6; **24**, 27944-71-4; **25**, 63797-89-7; **26**, 63797-90-0; **27**, 63797-91-1; carboethoxyethylidenetriphenylphosphorane, 1099-45-2; diethyl 5-methyl-3,6-dihydropyran-2,2-biscarboxylate, 63797-92-2.

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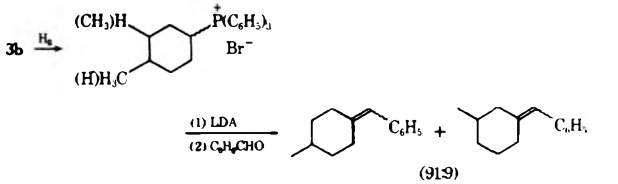

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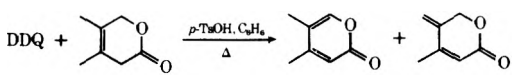

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Alkylation of Arylacetic Esters by Phase-Transfer Catalysis and Sodium Hydride: Activation and Stereochemical Effects of the Chromium Tricarbonyl Group

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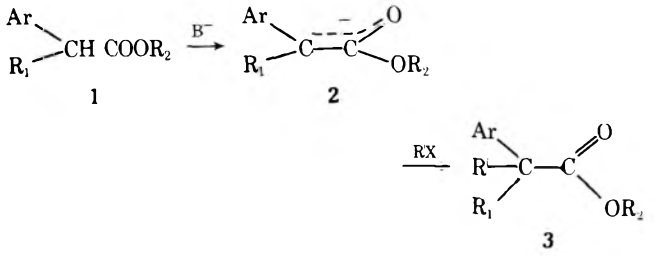
Methyl arylacetate–chromium tricarbonyl complexes and related compounds can be readily alkylated either by phase-transfer catalysis or by sodium hydride in *N*,*N*-dimethylformamide. The electron-withdrawing character of the $Cr(CO)_3$ group has a significant influence on the generation of the ester carbanion, and on its subsequent reaction with an alkyl halide. Alkylation of cyclic ester complexes is stereospecifically exo (with respect to the $Cr(CO)_3$ group), while acyclic analogues undergo alkylation with considerable stereoselectivity.

There has been considerable interest, particularly from a pharmacological viewpoint, in the alkylation of arylacetic esters (**1**) and related compounds.[1,2] Alkylation is generally



effected by generation of an enolate anion (**2**) from the ester, followed by reaction with an alkyl halide. Strong bases are required for enolate anion formation, including sodamide (in liquid ammonia)[3] and lithium *N*-cyclohexyl-*N*-isopropylamide (tetrahydrofuran, −78 °C).[4] Due to the sensitivity of methyl esters (**1**, $R_2 = CH_3$) toward alkaline hydrolysis,[5] only the tertiary butyl esters [**1**, $R_2 = C(CH_3)_3$] can be alkylated by phase-transfer catalysis.[5]

We now report[6] that these alkylation reactions can be greatly improved by the use of the chromium tricarbonyl [$Cr(CO)_3$] moiety as a temporary complexing group of the aromatic ring.[7] Complexation of arylacetic esters can be readily effected using $Cr(CO)_6$, often giving high yields of arene chromium tricarbonyl complexes (see Experimental Section). Furthermore, liberation of the arene ligand from the complex is simple and quantitative, either by chemical[7a] or photochemical[8-10] oxidation.

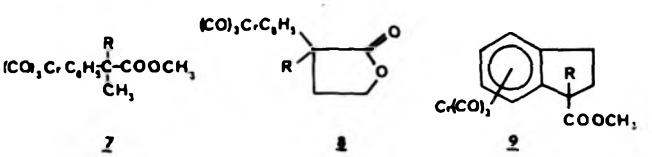
Both electronic and steric effects of the $Cr(CO)_3$ group are useful in the alkylation reactions. The former enhances the acidity of the esters, allowing a facile alkylation of methyl esters, with different alkylating agents [either by phase-transfer catalysis or by sodium hydride in *N*,*N*-dimethylformamide (DMF)]. Steric effects may induce stereospecific alkylations, some examples of which are given below.

Electronic Activation

Several studies have indicated the substantial electron-withdrawing influence of the $Cr(CO)_3$ group when attached to a benzene ring.[11] This effect is also significant in the phase-transfer-catalyzed methylation of some diarylacetic esters (Table I). Compounds **4–6** were each methylated by treatment with 50% sodium hydroxide, cetyltrimethylammonium bromide (CTAB, 40% of the ester concentration) as the catalyst, a stoechiometric amount of methyl iodide, and stirring 45 min at room temperature.

Clearly, the kinetic acidity of arylacetic esters, which is important in phase-transfer catalysis, is greatly enhanced by complexation of one or both arene sites. Evidence for the operation of a phase-transfer system rather than a micellar catalysis in these reactions comes from a study of the effect of the catalyst concentration on the alkylation of **6** (Table II): as the ratio of CTAB/**6** increases, the yield of alkylated material increases. Here the CTAB concentration covers a range of approximately 10^{-3}–10^{-2} M, higher than its critical micellar concentration ($\simeq 10^{-3}$ M at 25 °C).[12]

Several other related ester complexes (**7–9**, R = H) were



subjected to phase-transfer-catalyzed alkylation, and the yields are listed in Table III. In all but one instance, alkylation of **7–9** is faster than hydrolysis. Further hydrolysis of the alkylated compounds is negligible, due to the increased steric hindrance of the ester or lactone groups. *None* of the noncomplexed analogues of **7–9** (R = H) could be alkylated by phase-transfer catalysis, since hydrolysis is more facile than alkylation.

As compared with the preceding method, alkylation of noncomplexed analogues of **7–9** (R = H) using NaH/DMF is a poor reaction. Complexes **7–9** (R = H) are very reactive toward NaH/DMF, rapidly affording stable enolates in quantitative yields at room temperature, and alkylation of these formed enolates with different halides (RX = CH_3I, $PhCH_2Br$, $CH_2{=}CHCH_2Br$, $HC{\equiv}CCH_2Br$, $BrCH_2COOCH_3$) is also fast (<5 min) and quantitative at room temperature. The complexed enolate anions are, in fact, weaker nucleophiles than the corresponding noncomplexed species. This point was demonstrated by competitive reaction of equal amounts of a complexed and noncomplexed anion with a limited amount of methyl iodide (Table IV). The uncomplexed anion, in both instances, was alkylated to a greater extent than the complexed anion, the dicomplexed anion not undergoing any methylation. These results are principally due to the electron-attracting influence of the $Cr(CO)_3$ group, rather than to the steric bulk of this group: as noted below the R of RX becomes attached to the enolate on the side opposite to that of the $Cr(CO)_3$ group.

Using an appropriate substrate, the stereochemistry of the phase-transfer and NaH/DMF methods could be compared. Generation of the anion of **10** by phase-transfer catalysis and subsequent reaction with 1,4-dibromopentane gives **11** and **12** in a ratio of 72:28 (total yield 45%). A 76:24 ratio of **11**/**12** (total yield 100%) resulted with the use of NaH/DMF. These results are consistent with literature data[13] indicating the similarity between phase-transfer catalysis and S_N2 reactions

Table I. Methylation of Diarylacetic Esters

Reactant	Yield (%)
$Ph_2CHCOOCH_3$ (4)	2.5
$(CO)_3CrC_6H_5CHCOOCH_3$ (5)	60
Ph	
$[(CO)_3CrC_6H_5]_2CHCOOCH_3$ (6)	100

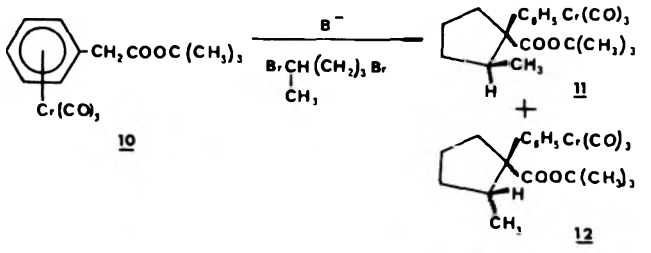
Table II. Effect of CTAB Concentration on Alkylation of 6

CTAB/6, %	5	10	20	30	40
Methylation %	25	30	60	80	100

Table III. Alkylation of 7-9

RX	7-9, R =	% Yield[a] 7	8	9
CH_3I	CH_3	70 (30)	40 (60)	100
$PhCH_2Br$	$PhCH_2$	100	60 (40)	100
CH_2=CHC-H_2Br	CH_2=CH-CH_2	100	90 (10)	100
$HC{\equiv}CCH_2Br$	$HC{\equiv}CCH_2$	100	100	100

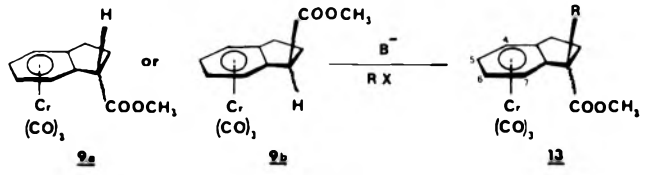
[a] Yields given using stoichiometric quantities of RX. Yields in brackets are for hydrolysis of starting materials.



conducted in a dipolar aprotic solvent; in both instances, few tight ion pairs exist between the carbanion and the counterion. Note that **10**, without the $Cr(CO)_3$ group, does not undergo cyclization with 1,4-dibromopentane by phase-transfer catalysis.

Stereochemical Effects

A. The Carbanionic Carbon Is Part of a Ring. In addition to the electronic effects noted above, the $Cr(CO)_3$ group may act as a stereodirecting unit when complexation of the arene site is diastereogenic. For example, complex **9** exists in two isomeric forms **9a** and **9b**, and alkylation should give two isomers **13**. In fact, the reaction is stereospecifically exo,



whatever the alkylating agent or the process used to effect alkylation.

The configurations of **9a** and **9b** were previously determined by Jackson and co-workers.[14] The spectral properties of **9a**, **9b**, and **13** display some interesting trends. An infrared (IR) study of the ester carbonyl absorption showed the presence of two such bands for **9a** and for **13** in CCl_4, a nonpolar solvent (Table V). Complex **9b**, containing the ester function exo to the $Cr(CO)_3$ group, shows only one absorption band in CCl_4. In the more polar solvent $CHCl_3$, only one broad ester carbonyl absorption was observed for **9a**, **9b**, or **13**.[15] The nuclear magnetic resonance (NMR) spectra of complexes **9a** and **13** gave a doublet signal for H_7 in the region of δ 5.62–6.11, which is deshielded relative to H_4, H_5, and H_6 (see Experimental Section). The relative abundances of the principal peaks in the mass spectra of **9a** and **13** (R = CH_3) are similar (Table VI), but distinct from those of **9b**.

Table IV. Competitive Alkylation of Enolate Anions by CH_3I

Enolate pair	% yield
$Ph_2\bar{C}COOCH_3$	38
Ph	
$\bar{C}COOCH_3$	2
$(CO)_3CrC_6H_5$	
$Ph_2\bar{C}COOCH_3$	32
$[(CO)_3CrC_6H_5]_2\bar{C}COOCH_3$	0

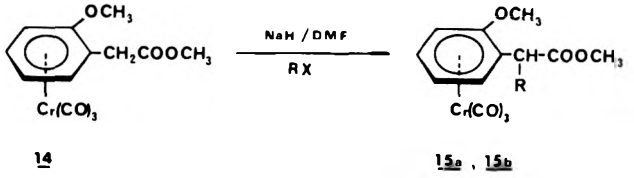
Table V. IR Ester Carbonyl Stretching Bands

Compd	$\nu_{C=O}$, cm^{-1} CCl_4	$CHCl_3$
9a	1755, 1739	1751
9b	1748	1741
13, R = CH_3	1748, 1738	1738
13, R = $PhCH_2$	1752, 1737	1738
13, R = $CH_2CH{=}CH_2$	1751, 1737	1741
13, R = $CH_2C{\equiv}CH$	1751, 1738	1738

Table VI. Mass Spectra Data for 9a, 9b, and 13 (R = CH_3)

	% Rel abundance 9b	9a	13
$M^{\cdot+}$	22.29	13.25	12.21
$(M - CO)^{+\cdot}$	0	2.41	3.49
$(M - 2CO)^{+\cdot}$	1.20	6.02	5.81
$(M - 3CO)^{+\cdot}$	100	100	100
$(M - COOCH_3)^+$	1.80	2.41	2.33

B. The Carbanionic Carbon Is Part of a Chain. The readily available complex **14** was chosen for this study. Here,



monoalkylation of **14** by phase-transfer catalysis proved tedious. Efficient methylation of **14** by NaH/DMF and methyl iodide gave two diastereoisomers (**15a**, **15b**, R = CH_3) in a 82:18 ratio. With $PhCH_2Br$, only one of the two diastereoisomers was produced. Only one stereoisomer, **16**, was obtained by treatment of either **15** (**a** or **b**, R = CH_3) with NaH/DMF and $PhCH_2Br$, or **15** (**a** or **b**, R = CH_2Ph) with NaH/DMF and CH_3I. These alkylation reactions are quite stereoselective. The stereochemical assignments were more difficult to establish for **15a,b** than for **9a**, **9b**, or **13**, but NMR provided useful structural information. When deuteriochloroform is used as the solvent for the NMR spectral determinations, the chemical shifts of the two methoxy groups (ester

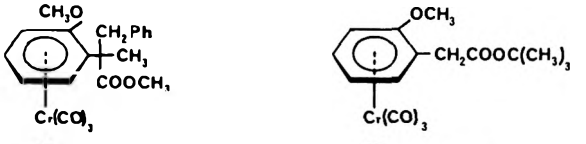


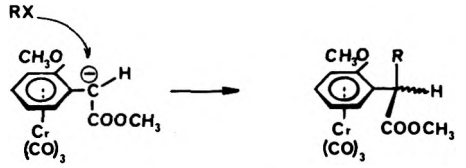
Table VII. Chemical Shifts for Complexes 14–17

Compd	δ $Cr(CO)_3ArOCH_3$			δ OCH_3 ester		
	$CDCl_3$	C_6D_6	Δ	$CDCl_3$	C_6D_6	Δ
14	3.85	3.03	0.82	3.85	3.45	0.4
17	3.88	3.00	0.88			
15a, R = CH_3	3.95[a]	3.18	0.77	3.96[a]	3.75	0.21
15b, R = CH_3	3.83[a]	3.05	0.78	3.88[a]	3.38	0.50
15a, R = CH_2Ph	3.88	3.01	0.87	3.88	3.66	0.22
15b, R = CH_2Ph	3.88	3.00	0.88	3.88	3.25	0.63
16	3.83	3.05	0.78	3.83	3.63	0.20

[a] Signals too close to be ascertained.

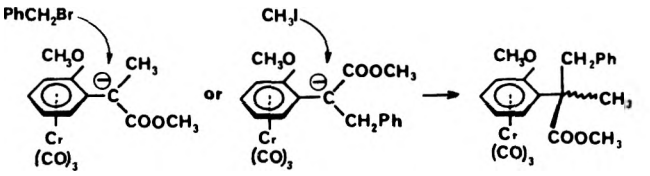
and aromatic) of **14–16** are very similar, if not identical. Differentiation of the two methoxy groups can be made by use of a strong anisotropic solvent such as benzene-d_6. Complex **17**, the *tert*-butyl analogue of **14**, displays only one methoxy signal, but at quite different chemical shifts in C_6D_6 (δ 3.00) and $CDCl_3$ (δ 3.88), i.e., $\Delta(CDCl_3 - C_6D_6) = 0.88$.

Similar pronounced solvent effects were observed for **14–16** (Table VII). The solvent effect is not as great for the ester methoxy group, and in three cases (**15a**, R = CH_3; **15a**, CH_2Ph; **16**) $\Delta(CDCl_3 - C_6D_6)$ was 0.22 or less. For **15b** (R = CH_3, CH_2Ph), $\Delta(CDCl_3 - C_6D_6)$ was considerably larger (0.5–0.63). Therefore, it is proposed that **15a** (R = CH_3, CH_2Ph) and **16** are of one configuration, while **15b** (R = CH_3, CH_2Ph) are of another. This assignment is consistent with exo attack of RX on the enolate (previously demonstrated with **9**), the enolate being in a stable conformation. The most stable conformation of the enolate derived from **14** should be **18**, where the ortho



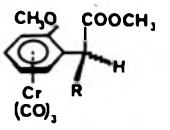
18 **15a** R = CH_3, CH_2Ph

effect is minimized by placing the smallest group attached to the carbanionic carbon near the aromatic methoxy group (H for **18**, CH_3 for **19**, $COOCH_3$ for **20**). The most likely structure



19 **20** **16**

for **15b** has the carbomethoxy group on the "top" of the mol-



15b; R = CH_3, CH_2Ph

ecule, permitting closer contact with the anisotropic solvent than in **15a**, and consequently a larger $\Delta(CDCl_3 - C_6D_6)$.

Experimental Section

General. All melting points were determined on a Kofler bank and are uncorrected. NMR spectra were recorded on a Varian A60A spectrometer. Chemical shifts are given as δ units, Me_4Si being used as internal standard (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet). Precise IR data were determined with a Beckman IR 12 spectrophotometer on diluted solutions. UV analyses were made with a Beckman DK2 apparatus. Mass spectra were recorded on a Varian MAT 311 spectrometer; the energy of the electronic beam was 70 eV.

Starting materials were commercially available or prepared according to literature methods (2-phenylpropanoic acid,[16] 2-phenylbutyrolactone,[17] 1-indancarboxylic acid[18a–c]). Chromium hexacarbonyl was purchased from Strem Inc. and used as received.

Complexes 5–10, 14, and 17. The following procedure for (methyl 1-indancarboxylate) chromium tricarbonyl is typical (previously prepared by a slightly different process).[14] A mixture of methyl 1-indancarboxylate (2 g, 0.011 mol), $Cr(CO)_6$ (3 g, 0.013 mol), heptane (70 mL), hexane (20 mL), and di-*n*-butyl ether (70 mL) was heated under N_2 for 3 days at 127 °C in a Strohmeir[19] type apparatus. After filtration of the solution and evaporation in vacuo, the crude product was chromatographed on silica gel. Elution with ether–petroleum ether (ratio 3:7) first gave **9a** (1.46 g, 42%) followed by **9b** (1.69 g, 49%). The complexes were recrystallized from ether–petroleum ether. Yields and physical and analytical data are in Table VIII.

Phase-Transfer Alkylation of 5–10, 11, 12, and 14. Into a 25-mL Erlenmeyer flask (N_2 atmosphere) was placed 50% aqueous NaOH (5 mL), benzene (5 mL) or CH_2Cl_2 for 8, complex (0.25 mmol), alkylating agent RX (0.25 mmol), and CTAB (36 mg). The reaction

Table VIII. Complexed Starting Materials, Yields, and Analytical and Physical Data[a]

Registry no.	Compd	% yield	Mp, °C	NMR data, δ ($CDCl_3$)
63703-98-0	**5**	41[b]	80	3.8 (s, 3 H, OCH_3), 4.7 (s, 1 H, CH), 5.1–6 (m, 5 H, $PhCr(CO)_3$), 7.45 (s, 5 H, Ph)
63703-99-1	**6**	17[b]	201	3.85 (s, 3 H, OCH_3), 4.15 (s, 1 H, CH), 5.1–6 (m, 10 H, $PhCr(CO)_3$)
63704-00-7	**7** (R = H)	71	26	1.5 (d, 3 H, CH_3, J = 7 Hz), 3.36, 3.46, 3.6, 3.73 (q, 1 H, CH), 5.6 (s, 5 H, $PhCr(CO)_3$)
63704-01-8	**8** (R = H)	54	121	2.2–3.2 (m, 2 H), 4.3–4.8 (m, 2 H, CH_2CH_2O), 3.5–3.9 (q, 1 H, CH), 5.6 (s, 5 H, $PhCr(CO)_3$)
12215-81-5	**9a**	42[b]	87	2.1–2.75 (m, 4 H, CH_2CH_2), 3.6 (s, 3 H, OCH_3), 3.7 (t, 1 H, CH), 4.75–5.70 (m, 4 H, $C_6H_4Cr(CO)_3$)
12215-80-4	**9b**	49[b]	70	2.15–2.45 and 2.6–2.95 (m, 4 H, CH_2CH_2), 3.5 (s, 3 H, OCH_3), 3.5 (t, 1 H, CH), 4.9–5.45 (m, 4 H, $PhCr(CO)_3$)
63704-02-9	**10**	66	63	1.5 (s, 9 H, $C(CH_3)_3$), 3.38 (s, 2 H, CH_2), 5.52 (s, 5 H, $PhCr(CO)_3$)
63704-03-0	**14**	73	69	2.7, 3.3, 3.62, 3.92 (q, 2 H, CH_2), 3.03 (s, 3 H, $ArOCH_3$), 3.45 (s, 3 H, $COOCH_3$), 4.3 (t), 4.83 (t), 5.18 (d, 4 H, $PhCr(CO)_3$)[c]
63704-04-1	**17**	70	81	

[a] Satisfactory analytical data (±0.3% for C and H) for all compounds (except as noted) were submitted for review. Exception, compound **10**: calcd C, 54.90; H, 4.87; found C, 54.29; H, 4.78. [b] **5** and **6** were obtained from one starting material in the same experiment, and then separated by TLC as described above; the same for **9a** and **9b**. [c] Solvent C_6D_6.

Table IX. Alkylated Products from 7, 8 (R = H), and 9: Analytical and Physical Data[a]

Registry no.	Compd, R =	Mp, °C	NMR data, δ ($CDCl_3$)
58482-52-3	7, CH_3	55	1.6 (s, 3 H, CH_3), 3.8 (s, 3 H, OCH_3), 5.2–6 (m, 5 H, $PhCr(CO)_3$)
63704-05-2	7, CH_2Ph	100	1.45 (s, 3 H, CH_3), 2.95, 3.18, 3.45, 3.68 (q, 2 H, CH_2), 3.9 (s, 3 H, OCH_3), 5.2–6.2 (m, 5 H, $PhCr(CO)_3$), 7–7.6 (m, 5 H, Ph)
63704-06-3	7, $CH_2CH{=}CH_2$	61	1.55 (s, 3 H, CH_3), 2.2–3.2 (m, 2 H, CH_2), 3.9 (s, 3 H, OCH_3), 4.8–6.1 (m, 8 H, $CH{=}CH_2$ and $PhCr(CO)_3$)
63704-07-4	7, $CH_2C{\equiv}CH$	65	1.70 (s, 3 H, CH_3), 2.10 (s, 1 H≡CH), 2.75–3.1 (m, 2 H, CH_2), 3.9 (s, 3 H, OCH_3), 5.2–6 (m, 5 H, $PhCr(CO)_3$)
63704-08-5	7, CH_2COOCH_3	100	1.68 (s, 3 H, CH_3), 2.58, 2.85, 3.13, 3.40 (q, 2 H, CH_2), 3.7 (s, 3 H, OCH_3), 3.8 (s, 3 H, OCH_3), 5–5.9 (m, 5 H, $PhCr(CO)_3$)
63704-09-6	8, CH_3	128	1.7 (s, 3 H, CH_3), 2.2–3.1, 4.3–4.8 (m, 4 H, CH_2CH_2O), 5.2–6.2 (m, 5 H, $PhCr(CO)_3$)
63703-90-2	8, CH_2Ph	206	Insoluble in usual solvents
63703-91-3	8, $CH_2CH{=}CH_2$	106	2.3–2.9 (m, 4 H, $2CH_2$), 4.2–4.8 (m, 2 H, CH_2O), 5.0–6.6 (m, 8 H, $CH{=}CH_2$ and $PhCr(CO)_3$)
63703-92-4	8, $CH_2C{\equiv}CH$	152	2.0–3.0 (m, 5 H, $2CH_2$ and ≡CH), 4.5–4.9 (m, 2 H, CH_2O), 5.3–6.5 (m, 5 H, $PhCr(CO)_3$)
63703-93-5	8, CH_2COOCH_3	142	2.85 (m), 4.7 (m, 4 H, CH_2CH_2O), 3.1 (s, 2 H, CH_2Ph), 3.85 (s, 3 H, OCH_3), 5.3–6.4 (m, 5 H, $PhCr(CO)_3$)
57628-76-9	13, CH_3	86	1.4 (s, 3 H, CH_3), 1.6–2.75 (m, 4 H, CH_2CH_2), 3.6 (s, 3 H, OCH_3), 4.75–5.25 (m, 3 H), 5.65 (d, 1 H, J = 6 Hz, $C_6H_4Cr(CO)_3$))
61168-83-0	13, CH_2Ph	98	2.0–3.4 (m, 6 H, $PhCH_2$ and CH_2CH_2), 3.87 (s, 3 H, OCH_3), 5.1–5.8 (m, 3 H), 6.11 (d, 1 H, J = 6 Hz, $C_6H_4Cr(CO)_3$)), 7.0–7.6 (m, 5 H, C_6H_5)
63730-30-3	13, $CH_2CH{=}CH_2$	65	1.9–3.0 (m, 6 H, CH_2 and CH_2CH_2), 3.8 (s, 3 H, OCH_3), 4.85–5.85 (m, 6 H), 5.95 (d, 1 H, J = 6 Hz, $C_6H_4Cr(CO)_3$ and $CH{=}CH_2$)
63730-31-4	13, $CH_2C{\equiv}CH$	112	1.9–3 (m, 5 H, ≡CH and CH_2CH_2), 3.87 (s, 3 H, OCH_3), 5.00–5.60 (m, 3 H), 5.90 (d, 1 H, J = 6 Hz, $C_6H_4Cr(CO)_3$)
63730-32-5	13, CH_2COOCH_3	80	1.80–3.4 (m, 6 H, CH_2 and CH_2CH_2), 3.8 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 5.1–5.85 (m, 3 H), 6.10 (d, 1 H, J = 6 Hz, $C_6H_4Cr(CO)_3$)

[a] Satisfactory analytical data (±0.4% for C and H) for all compounds were submitted for review.

Table X. Physical and Analytical Data for the Alkylated Complexes 11, 12, 15a, 15b (R = CH_3 or CH_2Ph), and 16[d]

Registry no.	Compd	Mp, °C	NMR data, δ ($CDCl_3$ or C_6D_6)
63703-94-6	11	86	0.75 (d, 3 H, CH_3, J = 7 Hz), 1.58 (s, 9 H, $C(CH_3)_3$), 1.6–2.9 (m, 7 H, $(CH_2)_3$ and ≡CH), 5.3–5.95 (m, 5 H, $PhCr(CO)_3$)[a]
63730-33-6	12	133	1.21 (d, 3 H, CH_3, J = 7 Hz), 1.45 (s, 9 H, $C(CH_3)_3$), 1.6–2.9 (m, 7 H, $(CH_2)_3$ and CH), 5.25–5.85 (m, 5 H, $PhCr(CO)_3$)[a]
63703-95-7	15a (R = CH_3)	98	1.32 (d, 3 H, CH_3, J = 7 Hz), 3.18 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.80, 3.92, 4.05, 4.17 (q, 1 H, CH), 4.2–4.5 (m), 5.08 (t), 5.9 (d, $C_6H_4Cr(CO)_3$)[b]
	15b (R = CH_3)	77	1.4 (d, 3 H, CH_3, J = 8 Hz), 3.05 (s, 3 H, OCH_3), 3.38 (s, 3 H, OCH_3), 3.9–4.45 (m), 4.9 (t) and 5.51 (d, $C_6H_4Cr(CO)_3$ and CH)[b]
63703-96-8	15a (R = CH_2Ph)	127	2.7, 2.92, 3.1, 3.32 (q, 2 H, CH_2), 3.01 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3), 4.1–4.65 (m), 4.95 (t), 6.15 (d, $C_6H_4Cr(CO)_3$), 7.25–7.60 (m, 5 H, Ph)[b]
	15b (R = CH_2Ph)	110	3.00 (s, 3 H, OCH_3), 3.25 (s, 3 H, OCH_3, CH_2,[c] 4.1–4.6 (m), 4.9 (t), 5.75, (d, $C_6H_4Cr(CO)_3$ and CH), 7.1–7.75 (m, 5 H, Ph)
63703-97-9	16	175	1.42 (s, 3 H, CH_3), 2.68, 3.0, 3.58, 3.8 (q, 2 H, CH_2), 3.05 (s, 3 H, OCH_3), 3.63 (s, 3 H, OCH_3), 4.00–4.30 (m), 4.98 (t), 5.42 (d, $C_6H_4Cr(CO)_3$), 7.48 (s, 5 H, Ph)[b]

[a] Solvent $CDCl_3$. [b] Solvent C_6D_6. [c] Quartet mixed with precedent signals. [d] Satisfactory analytical data (±0.3% for C and H) for all compounds were submitted for review.

mixture was stirred at room temperature and its progress was checked with TLC. After complete disappearance of starting material, a spectrophotometric titration at 407 nm on a diluted aliquot of organic layer was used to determine the yield of alkylated product (the spectrophotometer was previously standardized with a known solution of alkylated product). In those experiments alkylated products are easily isolated after drying and evaporation of the organic layer, and chromatographic purification on silica gel. In experiments given in Tables I and II, crude products were photochemically decomplexed according to ref 7e, and then analyzed by GC with an added internal standard [diphenylacetonitrile; column DEGS (diethylene glycol succinate) 3 m, T = 170 °C].

Alkylation of complex **10** with 1,4-dibromopentane needed 3 days of stirring, then giving **11** and **12**. Separation by TLC (eluent ether–petroleum ether 1:9) yields **11** (higher R_f, 34%) and **12** (lower R_f, 11%). The NMR spectra of the decomplexed ligands (according to ref 7e) were found consistent with those given in the literature for the corresponding acids:[20] ligand desired from **11**, δ_{CH_3} 0.60 (d, J = 7 Hz); from **12**, δ_{CH_3} 1.18 (d, J = 7 Hz).

Alkylation of Complexes 5–10, 11, 12, 14, 16 by NaH/DMF/RX System. The following procedure is typical. A mixture of anhydrous DMF (3 mL), complex **7** (R = H, 0.25 mmol), and an equivalent amount of NaH was stirred under N_2 for 10 min at room temperature. The alkyl halide was then added and the mixture was stirred for 5 min. The mixture was poured on ice, extracted several times with benzene, and worked up as previously described. If desired, the crude product may be purified on thick-layer chromatograph using silica gel, followed by recrystallization from petroleum ether, ether–petroleum ether, or benzene–heptane. Usually, "in situ" yields given by GC after decomplexation are quantitative. Due to the workup, yields of isolated

products are slightly lower. Ratios of stereoisomers **11** and **12**, 72:28.

15a and **15b** (R = CH_3) were obtained from complex **14**, the alkylating agent being CH_3I, and separated on TLC (eluent ether–petroleum ether 1:7). The higher band gave pure **15a** (63%). The lower band gave both **15b** (14%) and **14** (23%). The best way to get **15b** was found to epimerize pure **15a** (NaH/DMF and further hydrolysis). Alkylation of **14** with benzyl bromide only gave one isomer **15a** (R = CH_2Ph). **15b** (R = CH_2Ph) was produced by epimerization of **15a** as described above, and then was separated from **15a** by TLC (eluent ether–petroleum ether 1:4). Ratio **15a/15b**, 72:28.

Complex **16** was prepared starting from **15** (R = CH_3; benzyl bromide) or **15** (R = CH_2Ph; CH_3I) and then purified from ether, yield 70%.

Analytical and physical data are given in Tables IX and X.

Competitive Methylation of Enolates Shown in Table IV. Equivalent amounts of methyl diphenylacetate enolate and mono- (or di-) complexed enolate (from **5** or **6**) were prepared in the usual way with equivalent amounts of NaH (completion of the reaction after 10 min can be checked in a side experiment by methylation with excess CH_3I). About 30–40% of the equivalent quantity of CH_3I vs. one enolate is injected with a syringe. After stirring for 10 min and usual workup, the crude mixture was separated on a thick-layer plate of silica gel (eluent: ether–petroleum ether 20:80). Two bands were observed: one contained a mixture of noncomplexed alkylated and nonalkylated products, while the other contained the same for complexed products. The later mixture was decomplexed according to literature methods.[7d] Every fraction was analyzed by GC after adding the same quantity of internal standard (diphenylacetonitrile) as described above.

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Registry No.—**4**, 3469-00-9; NaH, 7646-69-7; $Cr(CO)_6$, 13007-92-6; CH_3I, 74-88-4; $PhCH_2Br$, 100-39-0; $CH_2{=}CHCH_2Br$, 106-95-6; $HC{\equiv}CCH_2Br$, 106-96-7; $BrCH_2COOCH_3$, 96-32-2; $PhMeACCO_2Me$, 31508-44-8; $PhCH_2COOC(Me)_3$, 16537-09-0; $MeOC_6H_4$-*o*-CH_2COOMe, 27798-60-3; $MeOC_6H_4$-*o*-$CH_2COOC(Me)_3$, 63730-75-6; methyl 1-indancarboxylate, 26452-96-0; 3-phenyldihydro-3*H*-furan-2-one, 6836-98-2.

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Stereochemistry and Absolute Configuration in Homoadamantane and Protoadamantane Derivatives[1]

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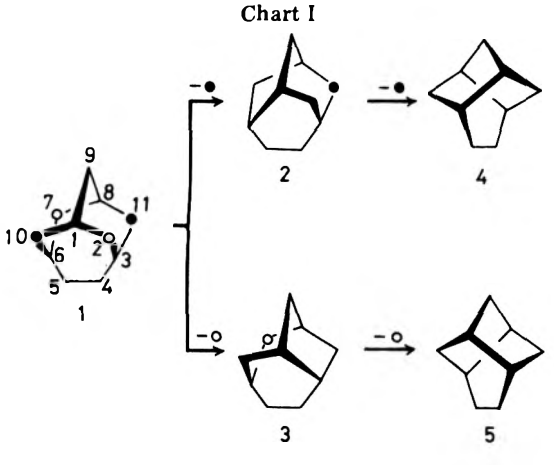
Double Favorskii rearrangement of (+)-3,6-dibromohomoadamantane-2,7-dione (**6**) eventually led to (+)-(1*S*,3*R*,6*R*,8*S*)-twist-brendane (**4**), assigning the (1*R*,3*S*,6*S*,8*R*) configuration to the (+)-dibromodione **6**. (−)-Protoadamantane (tricyclo[4.3.1.0^{3,8}]decane) **3** was obtained by the sequence of reactions involving single Favorskii rearrangement of the (−)-dibromodione **6**, and this correlation gave the (1*R*,3*S*,6*R*,8*R*) configuration to (−)-protoadamantane. Temperature-dependent circular dichroism spectrum analyses of (+)-homoadamantane-2,7-dione (**15**) and (+)-homoadamantan-2-one (**23**) suggested the C_{2v} untwisted conformation to the homoadamantane (tricyclo[4.3.1.1^{3,8}]undecane) (**1**) molecule.

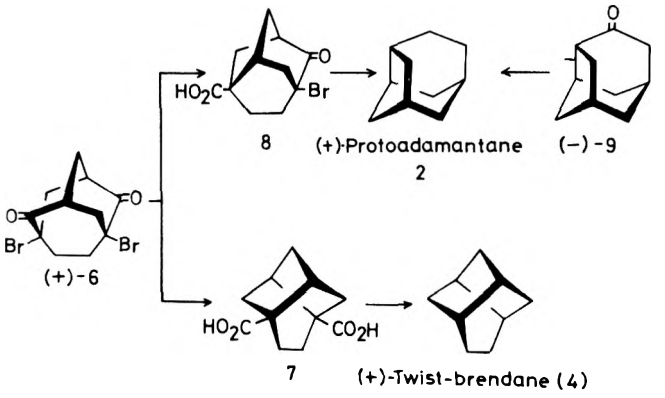
On ring expansion of adamantane by one carbon atom, the high-symmetry T_d inherent to this molecule permits homoadamantane (**1**)[2] to emerge as a sole product. Although an inspection of the molecular model indicates a flexible structure, for convenience of discussion homoadamantane (**1**) will be regarded as a rigid molecule with C_{2v} symmetry until we shortly return to discuss this conformational complexity (vide infra) (Chart I).

In the C_{2v} molecular model **1**, we can discern two sets of homotopic methylene groups: $C_2{=}C_7$ and $C_{10}{=}C_{11}$. Since the molecule possesses two planes of symmetry which contain the C_2 axis and are mutually perpendicular, these four methylene

Chart I



Scheme I



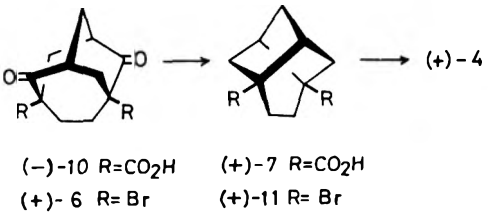
groups also form four sets of enantiotopic methylene groups: C_2/C_{11}, C_7/C_{10}, C_2/C_{10}, and C_7/C_{11}. Removal of one of these methylene groups destroys the C_{2v} symmetry, furnishing asymmetric (C_1 symmetry) protoadamantane[3] **2** or **3**, and which methylene group in each of these sets of enantiotopic groups is removed determines the chiralities of the enantiomeric protoadamantane molecules. Removal of two homotopic methylene groups, on the other hand, conserves the original C_2 axis of homoadamantane (**1**) to give twist-brendane[4] **4** or **5** with C_2 symmetry.

This time again, the chiralities of the enantiomeric twist-brendane molecules are determined by the choice of the set of homotopic methylene groups to be removed, C_2=C_7 or C_{10}=C_{11}.

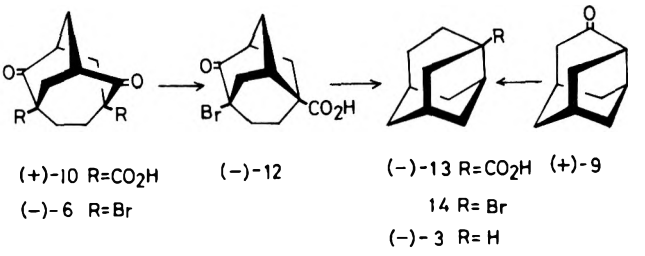
Consideration on these molecular geometries permitted us to choose optically active 3,6-dibromohomoadamantane-2,7-dione (**6**) as a go-between whose single and double Favorskii rearrangements[5] should correlate the absolute configurations of optically active protoadamantane **2** and twist-brendane **4**, via the carboxylic acids **7** and **8**, respectively (Scheme I).

Our continuing interests[4,6] on the syntheses and chiroptical properties of high-symmetry chiral (gyrochiral[6b]) cage-shaped molecules currently center on the microbiological reduction of carbonyl groups constrained in various chiral cage-shaped molecular frameworks, and during these experiments[7] (+)-protoadamantan-4-one (**9**) [the enantiomer of (−)-**9** in Scheme I] was isolated from a culture solution containing (±)-protoadamantan-4-one[8] as the substrate. Information about the absolute configuration of this optically active protoadamantan-4-one (**9**) was required to formulate a rule which specifies stereoselectivity in phytochemical reduction, and in this paper we report the configurational relationship between optically active twist-brendane **4** and protoadamantane **2** following the sequence outlined in Scheme I, which eventually leads to the absolute configuration of protoadamantan-4-one (**9**); also reported is an examination of the conformational mobility of

Scheme II



Scheme III



the homoadamantane framework by means of temperature-dependent circular dichroism (CD) measurements on (+)-homoadamantane-2,7-dione (**15**) and (+)-homoadamantan-2-one (**23**).

Results and Discussion

Configurational Correlation between (−)-Homoadamantane-2,7-dione-3,6-dicarboxylic Acid (10) and (+)-Twist-brendane 4. Optical resolution of (±)-homoadamantane-2,7-dione-3,6-dicarboxylic acid (**10**)[5b] was accomplished by working with cinchonidine as the resolving agent. Crystallization of the salt from ethanol followed by recrystallization of the separated dicarboxylic acids from acetone–ether resulted in fairly good resolution, as evidence by optical rotations of the resolved dicarboxylic acids, $[\alpha]_D$ +41.1° and $[\alpha]_D$ −43.7°, obtained respectively from the sparingly soluble and the soluble cinchonidine salts.

The silver salt, prepared from the (−)-dicarboxylic acid **10**, $[\alpha]_D$ −43.7°, was treated with bromine in carbon tetrachloride to afford the (+)-dibromide **6**, $[\alpha]_D$ +34.0°, whose double Favorskii type ring contraction[5b] with ethanolic potassium hydroxide gave an 82% yield of (+)-twist-brendane-3,6-dicarboxylic acid (**7**). The second Hunsdiecker reaction carried out on the silver salt of (+)-twist-brendane-3,6-dicarboxylic acid (**7**) provided (+)-3,6-dibromo-twist-brendane (**11**) which was refluxed with sodium in *tert*-butyl alcohol to give (+)-twist-brendane **4**: mp 163.5–164.5 °C; $[\alpha]_D$ +280° (98% optical purity[4a]) (Scheme II).

Since our unambiguous synthesis starting from the precursor with known absolute configuration has assigned the (1*S*,3*R*,6*R*,8*S*) configuration to (+)-twist-brendane **4**, the configurational correlation in Scheme II indicates the (1*R*,3*S*,6*S*,8*R*) configuration to (−)-homoadamantane-2,7-dione-3,6-dicarboxylic acid (**10**).

Configurational Correlation between (+)-Homoadamantane-2,7-dione-3,6-dicarboxylic Acid (10) and (−)-Protoadamantane (3). In operating a one carbon atom ring contraction on the homoadamantane framework, we started again from the optically active 2,7-dione-3,6-dicarboxylic acid **10**. In contrast to Scheme II, however, the dextrorotatory dicarboxylic acid **10** was our starting material in this correlation experiment (Scheme III).

The Hunsdiecker reaction converted (+)-homoadamantane-2,7-dione-3,6-dicarboxylic acid (**10**), $[\alpha]_D$ +30.0°, into the (−)-dibromide **6** which was, following Vogt's procedure,[5a] refluxed with 10% sodium bicarbonate solution in ethanol to give a 71% yield of the (−)-monobromoketocarboxylic acid **12**. Clemmensen reduction of (−)-**12** furnished (−)-protoadamantan-3-carboxylic acid (**13**) whose carboxyl group was re-

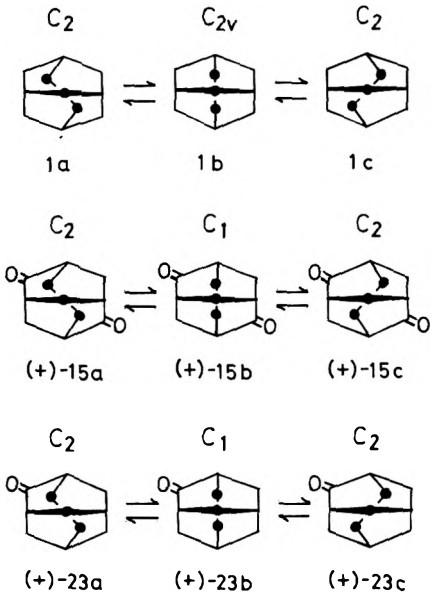
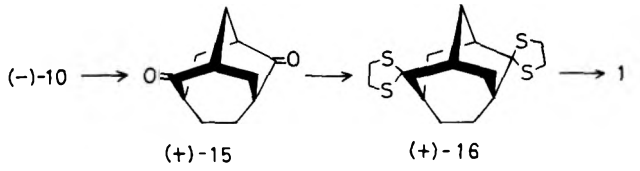
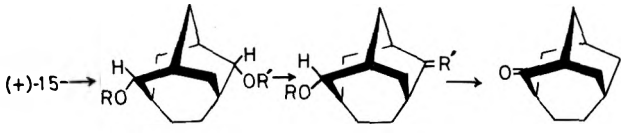


Figure 1. Conformational equilibria in homoadamantane derivatives. (The moleculars are viewed from the C_9 carbon atom in the direction of the C_2 axis of homoadamantane.)

Scheme IV



Scheme V



moved by the Hunsdiecker reaction of the silver salt of the carboxylic acid **13** followed by reduction of the resulting monobromide **14** with sodium in *tert*-butyl alcohol. Optically active protoadamantane **3** obtained by this sequence of reactions was levorotatory, $[\alpha]_D$ −118°, and melted at 174–177 °C.

These configurational correlations clearly indicate the (1*R*,3*S*,6*R*,8*R*) configuration to (−)-protoadamantane (tricyclo[4.3.1.0^{3,8}]decane) **3**, and the Wolff–Kishner reduction of (+)-protoadamantan-4-one (**9**) to (−)-protoadamantane **3** assigns the (1*S*,3*S*,6*R*,8*S*) configuration to this ketone **9** isolated from a culture solution containing the racemic ketone **9** as the substrate.[9]

Preparation of (+)-Homoadamantane-2,7-dione (15) and (+)-Homoadamantan-2-one (23). Successful bisdecarboxylation of the racemic dionedicarboxylic acid **10** demonstrated by Vogt[5b] provided (+)-(1*S*,3*R*,6*R*,8*S*)-homoadamantane-2,7-dione (**15**), mp 285–288 °C; $[\alpha]_D$ +49.4°, from the (−)-dionedicarboxylic acid **10**, $[\alpha]_D$ −35.7° (Scheme IV).

One of two homotopic carbonyl groups of (+)-dione **15** was removed via the (+)-diol **17**, prepared from the (+)-dione **15** by lithium aluminum hydride reduction. A sharp single acetyl

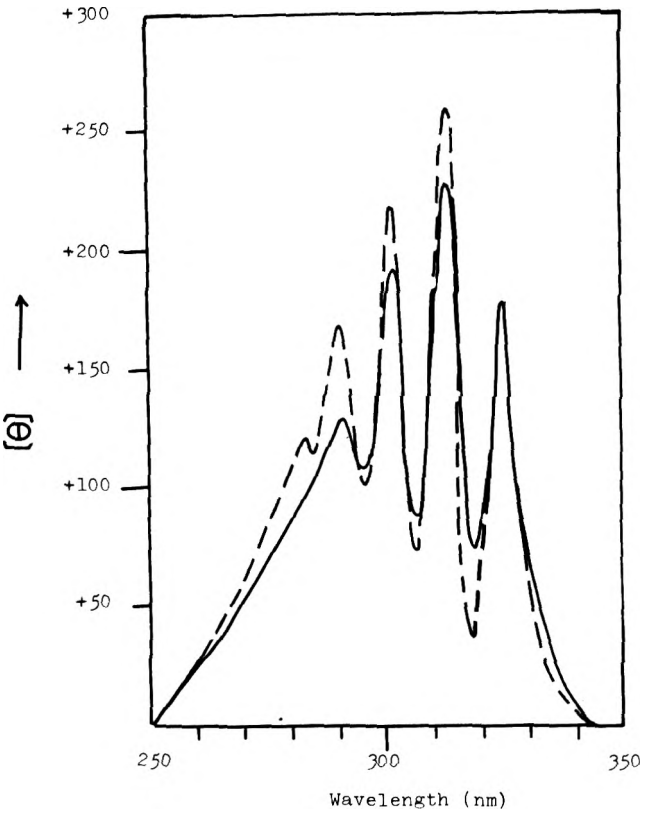


Figure 2. Temperature-dependent CD spectra of (+)-homoadamantan-2-one (**23**) (in methylcyclohexane–isopentane 75:15): (—) at 25 °C; (---) at − 68 °C.

peak (δ 2.08) observed in the NMR spectrum of the acetate **18** indicated stereochemical equivalence of the two hydroxyl groups, suggesting C_2 symmetry for the diol **17**. This, together with a plausible assumption of hydride attack from the less hindered methano bridge sides, suggested endo–cis configuration to the diol **17**, which was supported by the preparation of the endo alcohol **21** from the diol **17** (vide infra) (Scheme V).

Acetylation of the (+)-diol **17** with an equimolar amount of acetic anhydride in pyridine furnished the (+)-monoacetate **19** whose Jones' oxidation afforded the (+)-keto acetate **20**. The (+)-monoalcohol **21** obtained by the Wolff–Kishner reduction of the (+)-keto acetate **20** exhibited a double doublet for the methine proton at δ 3.88 in the NMR spectrum, and was found identical with the endo alcohol reported by Murray, Jr.,[10] supporting the endo–cis configuration previously assigned to the diol **17**.

Final oxidation with Jones' reagent completed the preparation of (+)-homoadamantan-2-one (**23**), $[\alpha]_D$ +32.8°, to which the configurational correlations illustrated in Schemes II, IV, and V assigned the (1*S*,3*R*,6*S*,8*S*) configuration.

Conformational Mobility in the Homoadamantane Framework. In the introductory part, a brief mention was made on the drastic change of conformational mobility brought by the mere one carbon atom ring expansion from rigid adamantane to flexible homoadamantane. Although Dreiding models, which are apt to mislead by overemphasizing angle strain, give a pair of enantiomeric conformational isomers **1a** and **1c** (C_2 symmetry) (Figure 1), Schleyer has favored the conformer **1b** with C_{2v} symmetry by his computor conformational analysis calculations[11] and temperature-dependent NMR study of homoadamantane.[12]

Desymmetrization of the homoadamantane framework by introducing carbonyl groups in the 2 or 2,7 positions changes the original pair of enantiomeric conformers **1a** ⇌ **1c** to the

pair of diastereomeric conformers (+)-**15a** ⇌ (+)**15c** and (+)-**23a** ⇌ (+)-**23c**, respectively (Figure 1).

Numerous examples[13] have confirmed the utility of the Cotton effect in detecting these subtle conformational changes, and we expected the temperature-dependent CD spectrum analysis of (+)-homoadamantan-2-one (**23**) and (+)-homoadamantane-2,7-dione (**15**) should furnish information on this homoadamantane conformational complexity.

If the molecules are twisted and the barriers between these diastereomeric conformers are large enough, the CD spectra should be temperature dependent. No such temperature dependence for (+)-**23** was observed in the range of +25 to −68 °C (Figure 2).

Although the CD spectrum of (+)-**15** (in EPA) showed a small bathochromic shift (5 mm) on going from −190 to 25 °C, almost no change of pattern and intensities was observed in this temperature range. These, together with the optical inactivity observed in a specimen of homoadamatane prepared from (+)-homoadamantane-2,7-dione via the (+)-bis(ethylene) ketal **16** (Scheme IV), appear to support Schleyer's view that the preferred conformation in homoadamantane (**1**) is essentially untwisted (1b in Figure 1) with C_{2v} symmetry.

Experimental Section

IR data were obtained from a Hitachi EPI-S2 spectrophotometer. NMR spectra were obtained from a JNM-MH-100 spectrometer. UV spectra were recorded on a Beckman DB spectrometer. Optical rotations were measured with a JASCO DIP-SL automatic polarimeter. Circular dichroism data were measured on a JASCO J-40 spectropolarimeter. Elemental analyses were determined on a Yanagimoto CHN-Corder Type II. All melting and boiling points are uncorrected.

(±)-Homoadamantane-2,7-dione-3,6-dicarboxylic Acid (10). Dimethyl bicyclo[3.3.1]nonane-2,6-dione-3,7-dicarboxylate[14] (32.4 g, 0.120 mol) was added slowly to a suspension of NaH (7.50 g, 0.312 mol) in dry 1,2-dimethoxyethane (120 mL). The mixture was stirred for 15 min at room temperature and then the solvent was distilled away. Ethylene bromide (204 g, 1.09 mol) was added and the mixture was stirred for 20 h at 118–120 °C. The cooled reaction mixture was poured onto ice, acidified with HCl, and extracted with $CHCl_3$, and the extract was washed with water and dried over $MgSO_4$. The solvent was removed, and the residue was dissolved in 80 mL of ether–benzene (9:1, v/v). Chilling overnight deposited 14.7 g of dimethyl homoadamantane-2,7-dione-3,6-dicarboxylate (41% yield). Recrystallization from benzene afforded an analytical sample, mp 196–197 °C (lit.[5b] mp 197–198 °C).

Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.05; H, 6.09.

A solution of this ester (14.0 g, 47.3 mmol) in acetic acid (210 mL) and 12 N HCl (150 mL) was refluxed for 3 h, poured into water (600 mL), and extracted for 3 days with ether. The extract was dried over $MgSO_4$ and the solvent was evaporated to give 8.40 g of **10** (66% yield), which was recrystallized from acetone–ether to give a pure sample: mp 287 °C (with gas evolution) (lit.[5b] mp 288–290 °C); IR (KBr) 1710, 1295, 1275, 1250, 1225, 945, and 720 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.58; H, 5.33.

Optical Resolution of Homoadamantane-2,7-dione-3,6-dicarboxylic Acid (10). To a solution of **10** (43.8 g, 0.165 mol) in 1 L of EtOH was added cinchonidine (95.0 g, 0.323 mol), and the mixture was refluxed for 5 h. After standing overnight at room temperature, the solution deposited 96.0 g of the cinchonidine salt: $[\alpha]^{15}_D$ −77.0° (*c* 0.374, EtOH). The filtrate was reserved for isolation of the enantiomer (−)-**10** (vide infra). Several times fractional recrystallization from EtOH afforded 56.5 g of the levorotatory salt: $[\alpha]^{14}_D$ −74.5° (*c* 0.430, EtOH), which was stirred for 6 h with 10% HCl (700 mL). The acidic solution was extracted for 7 days with ether. The extract was dried over $MgSO_4$ and the solvent was evaporated to give 14.7 g of (+)-**10**, $[\alpha]^{15}_D$ +30.0° (*c* 1.20, acetone), a part of which was recrystallized several times from acetone–ether (3:1, v/v) to give an analytical sample of (+)-**10**: $[\alpha]^{18}_D$ +41.1° (*c* 0.538, acetone); mp 266 °C (with gas evolution); IR (KBr) 1710, 1292 (sh), 1275, 1225 (sh), 945, and 710 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.43; H, 5.33.

The filtrate was concentrated to give 30.5 g of a viscous oily salt, which was treated with 10% HCl. The same workup described above afforded 6.40 g of (−)-**10**, $[\alpha]^{18}_D$ −36.2° (*c* 0.414, acetone), which was recrystallized several times from acetone–ether to yield 2.90 g of (−)-**10**, $[\alpha]^{18}_D$ −43.7° (*c* 0.529, acetone), mp 267 °C (with gas evolution).

Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.50; H, 5.32.

(+)-Twist-brendane-3,6-dicarboxylic Acid (7). A solution of (−)-**10** (2.66 g, 0.0100 mol), $[\alpha]^{18}_D$ −43.7°, in MeOH (20 mL) was neutralized with 1 N aqueous KOH and then made slightly acidic with diluted nitric acid. A solution of silver nitrate (3.40 g, 0.0200 mol) in MeOH (12 mL) and H_2O (6 mL) was added dropwise. After stirring for 30 min, disilver dicarboxylate was collected on a filter, washed with water and MeOH, and dried over phosphorus pentoxide at 70 °C (5 mm) for 5 days. When the disilver dicarboxylate (4.39 g, 9.14 mmol) was added to a solution of bromine (3.40 g, 21.5 mmol) in dry CCl_4 (10 mL), carbon dioxide evolved immediately. The mixture was stirred for 30 min at room temperature and then refluxed for 3 h. A solid was separated from the cooled reaction mixture and extracted with hot $CHCl_3$ for 6 days. The extract was concentrated and the residue was stirred with 5% $NaHCO_3$ solution for 2 h at room temperature to remove unreacted carboxylic acids. The insoluble dibromide **6** was collected to yield 1.70 g of **6** (50% yield), $[\alpha]^{17}_D$ +34.0° (*c* 0.356, $CHCl_3$), mp 288–290 °C, which was used for the following reaction without further purification.

A mixture of (+)-**6** (1.58 g, 4.70 mmol), KOH (3.53 g), EtOH (7 mL), and water (7 mL) was refluxed for 4 h. The chilled reaction mixture was made acidic with HCl and then concentrated under reduced pressure. To the residual solid was added acetone and the mixture was refluxed for 5 h. The insoluble solid was filtered off and the filtrate was treated with Norit. After filtration, the solvent was evaporated to yield 686 mg of (+)-**7** (82% yield): $[\alpha]^{20}_D$ +166° (*c* 0.634, MeOH); mp >300 °C; IR (KBr) 1690, 1415, 1305, and 1120 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.56; H, 6.62.

(+)-Twist-brendane 4. A solution of (+)-**7** (630 mg, 3.00 mmol) in MeOH (6 mL) was neutralized with 1 N aqueous KOH solution and then made slightly acidic with diluted nitric acid. A solution of silver nitrate (1.02 g, 6.00 mmol) in MeOH (4 mL) and water (2 mL) was added, and the mixture was stirred for 30 min. Disilver dicarboxylate was collected on a filter, washed with MeOH–H_2O, and dried over phosphorus pentoxide at 70 °C (5 mm) for 3 days. To a solution of bromine (1.60 g, 6.65 mmol) in dry CCl_4 (4 mL) was added the disilver dicarboxylate (1.20 g, 2.84 mmol). The mixture was stirred for 3 h at room temperature and then refluxed for additional 3 h. The cooled reaction mixture was filtered and the filtrate was washed with sodium thiosulfate solution, saturated $NaHCO_3$ solution, and water, and dried over $MgSO_4$. The solvent was removed to give 620 mg of **11**, $[\alpha]^{20}_D$ +163° (*c* 0.393, EtOH). The bromide **11** (570 mg) and dry *tert*-butyl alcohol (850 mg) were dissolved in dry THF (8.5 mL), and sodium (424 mg) was added. After the mixture was stirred for 30 min at room temperature, additional *tert*-butyl alcohol (1.5 g) was added. The mixture was refluxed for a further 3 h. To the chilled reaction mixture was added few milliliters of MeOH to destroy the excess sodium. The mixture was poured onto ice and extracted with pentane. The extract was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave 110 mg of twist-brendane (30% yield), which was sublimed at 40 °C (20 mm) to afford a pure sample: $[\alpha]^{20}_D$ +280° (*c* 0.393, EtOH) (98% optical purity[4a]); mp 163.5–164.5 °C (in a sealed tube). This was identified as twist-brendane **4** by comparison with an authentic sample[4a] (IR spectrum and VPC, TLC behaviors).

(−)-Protoadamantane-3-carboxylic Acid (13). The same procedure described for the (−)-enantiomer converted (+)-**10** (3.99 g, 15.0 mmol), $[\alpha]^{25}_D$ +30.0°, into (−)-**6** (1.81 g, 36% yield), $[\alpha]^{24}_D$ −24.0°. A mixture of (−)-**6** (1.76 g, 5.24 mmol), 10% $NaHCO_3$ solution (16 mL), and EtOH (16 mL) was refluxed for 1 h. The reaction mixture was extracted with $CHCl_3$ to remove neutral substances and then made acidic with HCl. The acidic solution was extracted with $CHCl_3$, and the extract was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave 1.01 g of **12** (71% yield), $[\alpha]^{25}_D$ −85.8° (*c* 0.410, $CHCl_3$). A mixture of (−)-**12** (930 mg, 3.41 mmol), zinc amalgam (4.0 g), and 12 N HCl (6 mL) was refluxed for 5 h and extracted with ether. The extract was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a semisolid, which was triturated with pentane to afford 150 mg of **13** (24% yield): $[\alpha]^{22}_D$ −119° (*c* 0.299, acetone); mp 85–88 °C; IR (KBr) 3400, 2600, 1690, and 1290 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.18; H, 8.88.

(−)-Protoadamantane 3. (−)-Protoadamantane-3-carboxylic acid

(13) (540 mg, 3.00 mmol) was converted into its silver carboxylate (715 mg, 83% yield) by the same procedure described above. When the silver carboxylate (715 mg, 2.49 mmol) was added to a solution of bromine (520 mg, 3.24 mmol) in dry CCl_4 (4 mL), carbon dioxide evolved immediately. The mixture was stirred for 3 h at room temperature and then refluxed for 3 h. After cooling, an inorganic solid was filtered off, and the filtrate was washed with sodium thiosulfate solution, $NaHCO_3$ solution, and water, and dried over $MgSO_4$. Evaporation of the solvent gave 290 mg of bromide **14**. Because of contamination with the corresponding chloride, a correct elemental analysis was not obtained.

To a mixture of the halide **14**, *tert*-butyl alcohol (280 mg), and dry THF (3 mL) was added sodium (140 mg). After the mixture was stirred for 3 h at room temperature, an additional amount of *tert*-butyl alcohol (0.55 g) was added, and the mixture was refluxed for a further 3 h. After the addition of a few drops of MeOH to the chilled reaction mixture, the mixture was poured onto ice and extracted with pentane. The extract was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a solid, which was sublimed at 50 °C (20 mm) to yield 102 mg of **3** (25% yield based on **13**): $[\alpha]^{26}_D$ −118° (*c* 0.177, EtOH); mp 212.5–214 °C (in a sealed tube) (lit.[5a] racemate, mp 215–216 °C); IR (KBr) 2850, 2790, 1460, 1350, 1335, 1320, 1305, 1100, 1070, 1008, 985, and 812 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 87.85; H, 11.70.

(+)-Homoadamantane-2,7-dione (15). (−)-Dicarboxylic acid **10** (6.18 g, 23.2 mmol), $[\alpha]^{15}_D$ −35.7°, was heated at 270–290 °C under reduced pressure (30 mm). A white solid was observed to condense on an inner wall of the condenser. After cooling, the solid was dissolved in ether, and the ethereal solution was washed with saturated $NaHCO_3$ solution and water and dried over $MgSO_4$. Evaporation of the solvent gave a solid, which was sublimed at 130–140 °C (5 mm) to yield 2.82 g of **15** (68% yield): $[\alpha]^{20}_D$ +49.4° (c 1.22, $CHCl_3$); mp 285–288 °C (in a sealed tube); IR (KBr) 1698, 1460, 1360, 1120, 1070, 1008, and 950 cm^{-1}; NMR ($CDCl_3$) δ 1.78–1.95 (m, 6 H), 2.08–2.35 (m, 4 H), 2.60–3.10 (m, 4 H); CD c 1.95×10^{-2} (isooctane, at 25 °C) [θ] (nm) 0 (244), $+8.72 \times 10^2$ (sh, 285), $+1.09 \times 10^3$ (292.7), $+1.33 \times 10^3$ (302.2), $+1.21 \times 10^3$ (312.7), $+6.21 \times 10^2$ (324.8), 0 (345); *c* 1.53×10^{-3} (EPA, at 25 °C) 0 (245), $+8.52 \times 10^2$ (294), $+1.04 \times 10^3$ (302), $+9.67 \times 10^2$ (311.5), $+4.97 \times 10^2$ (320), 0 (340); *c* 1.53×10^{-3} (EPA, at −68 °C) 0 (240), $+9.31 \times 10^2$ (292), $+1.12 \times 10^3$ (300.5), $+1.06 \times 10^3$ (310.5), $+5.23 \times 10^2$ (322), 0 (340); c 1.53×10^{-3} (EPA, at −190 °C) +89 (250), $+1.14 \times 10^3$ (288.5), $+1.28 \times 10^3$ (297), $+1.15 \times 10^3$ (308), $+5.50 \times 10^2$ (319), 0 (335).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.02; H, 7.89.

(+)- and (±)-Homoadamantane-2,7-diol (17). A solution of (+)-**15** (2.31 g, 13.0 mmol), $[\alpha]^{20}_D$ +49.4°, in dry ether (150 mL) was added to a suspension of $LiAlH_4$ (494 mg, 13.0 mmol) in dry ether (50 mL), and the mixture was refluxed for 4 h. Saturated NH_4Cl solution was added to the chilled reaction mixture and an inorganic solid was filtered off. The filtrate was dried over $MgSO_4$ and the solvent was evaporated to yield 2.07 g of **17** (88% yield): $[\alpha]^{20}_D$ +18.8° (*c* 0.680, $CHCl_3$); mp 326–328 °C (in a sealed tube); IR (KBr) 3350, 1080, 1048, 1022, 930, and 875 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.20; H, 9.97.

(±)-Homoadamantane-2,7-diol (**17**) was prepared from (±)-**15** by the same procedure described above; mp >330 °C.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.31; H, 9.99.

(±)-2,7-Diacetoxyhomoadamantane (18). Acetic anhydride (1 mL) was added to a cooled (0 °C) solution of (±)-**17** (153 mg, 0.841 mmol) in pyridine (5 mL). After standing overnight at room temperature, the reaction mixture was poured onto ice. A deposited solid was collected and washed with water and dried to give 181 mg of **18** (81% yield): mp 99.5–100 °C; NMR ($CDCl_3$) δ 1.2–2.1 (m, 12 H), 2.08 (s, 6 H), 2.2–2.5 (m, 2 H), 4.99 (dd, *J* = 6.6 and 6.3 Hz, 2 H); IR (KBr) 1735, 1365, 1255, and 1030 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.65; H, 8.32.

(+)-2-Acetoxyhomoadamantan-7-ol (19). Acetic anhydride (1.11 g, 10.9 mmol) was added to a cooled (0 °C) solution of (+)-**17** (1.98 g, 10.9 mmol) in dry pyridine (5 mL). The mixture was stirred for 4 h with ice cooling and then kept overnight at room temperature. It was poured onto ice and extracted with ether. The extract was washed with 10% HCl, saturated $NaHCO_3$ solution, and water, and dried over $MgSO_4$. After evaporation of the solvent, the residue (1.94 g) was chromatographed on silica gel. Fractions eluted with $CHCl_3$ gave 720 mg of impure (+)-**18** (25% yield), whose structure was confirmed by comparison with the racemic modification **18**. Fractions eluted with ether afforded 995 mg of **19** (41% yield): $[\alpha]^{27}_D$ +12.8° (*c* 0.665, $CHCl_3$); mp 108–111 °C; IR (KBr) 3480, 1710, 1270, and 1030 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.90; H, 8.96.

Final fractions with ether–MeOH (9:1, v/v) gave 150 mg of the starting material (**17**).

(+)-2-Acetoxyhomoadamantan-7-one (20). To a cooled (0 °C) solution of (+)-**19** (840 mg, 3.75 mmol) in acetone (5 mL) was added *excess of Jones' reagent. After stirring for 1 h at this temperature, the* reaction mixture was poured into ice water and extracted with ether. The extract was washed with saturated $NaHCO_3$ solution and water, dried ($MgSO_4$), and concentrated. The concentrated product on distillation gave 660 mg of **20** (79% yield), bp 130–140 °C (bath temperature) (5 mm), which solidified in the receiver: mp 69–72 °C; $[\alpha]^{27}_D$ +24.5° (*c* 0.868, $CHCl_3$); IR (KBr) 1725, 1700, 1370, 1245, and 1035 cm^{-1}; NMR ($CDCl_3$) δ 1.55–2.05 (m, 11 H), 2.09 (s, 3 H), 2.4–2.8 (m, 3 H), 5.09 (dd, *J* = 6.6 and 6.2 Hz, 1 H).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.97; H, 8.11.

(+)-Homoadamantan-2-ol (21). To a mixture of KOH (0.39 g), 100% hydrazine hydrate (0.4 mL), and triethylene glycol (4 mL) was added (+)-**20** (610 mg, 2.75 mmol). The mixture was heated for 1.5 h at 160 °C and then for additional 3 h at 190–200 °C. After cooling, a white solid condensed on an inner wall of the condenser was dissolved in ether. The chilled reaction mixture was diluted with water and extracted with ether. Combined ether solutions were washed with water and dried over $MgSO_4$. The solvent was evaporated to give a solid, which was sublimed at 100 °C (5 mm) to afford 380 mg of **21** (83% yield): $[\alpha]^{25}_D$ +7.4° (*c* 0.653, $CHCl_3$); mp 276–278 °C (in a sealed tube) (lit.[10] racemate, mp 283.5–285.5 °C); IR (KBr) 3300, 1450, 1065, and 1025 cm^{-1}; NMR ($CDCl_3$) δ 1.1–2.4 (m, 17 H), 3.88 (dd, *J* = 5.5 and 5.0 Hz, 1 H).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.63; H, 10.77.

(+)-2-Acetoxyhomoadamantane (22). To a solution of (+)-**21** (75 mg, 0.452 mmol) in dry pyridine (5 mL) was added acetic anhydride (200 mg, 1.96 mmol), and the mixture was stirred for 5 h at 0–5 °C. After standing overnight at room temperature, the mixture was poured onto ice and extracted with ether. The extract was washed with 10% HCl, saturated $NaHCO_3$ solution, and water, and dried (MSO_4). After removal of the solvent, the residue was chromatographed on silica gel. Fractions eluted with pentane–ether (1:1, v/v) gave an oily product, which was distilled to give 64 mg of (+)-**22** (68% yield): bp 110–120 °C (bath temperature) (5 mm); $[\alpha]^{21}_D$ +0.73° (*c* 0.480, $CHCl_3$); IR (neat film) 1735, 1250, 1240, 1040, and 1020 cm^{-1}; NMR ($CDCl_3$) δ 1.1–2.1 (m, 15 H), 2.08 (s, 3 H), 2.2–2.5 (br s, 1 H), 5.02 (dd, *J* = 6.4 and 6.1 Hz, 1 H).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.70; H, 9.59.

(+)-Homoadamantan-2-one (23). To a solution of (+)-**21** (300 mg, 1.81 mmol) in acetone (3 mL) was added excess of Jones' reagent with ice cooling, and the mixture was stirred for 1 h at this temperature. The reaction mixture was diluted with water and extracted with ether. The extract was washed with saturated $NaHCO_3$ solution and water and dried ($MgSO_4$). After removal of the solvent, a solid was sublimed at 100 °C (5 mm) to give 240 mg of **23** (80% yield): $[\alpha]^{25}_D$ +32.8° (c 0.629, $CHCl_3$); mp 262–263 °C (in a sealed tube); IR (KBr) 1698, 1450, 1113, 1068, 1000, and 960 cm^{-1}; CD *c* 2.61×10^{-2} (isooctane, at 25 °C) [θ] (nm) 0 (238), +84.3 (sh, 275), $+1.09 \times 10^2$ (282.5), $+1.34 \times 10^2$ (291.3), $+1.78 \times 10^2$ (301.2), $+2.32 \times 10^2$ (312.2), $+1.76 \times 10^2$ (324.5), 0 (340); *c* 4.81×10^{-3} [methylcyclohexane–isopentane (75:15), at 25 °C] 0 (250), $+1.30 \times 10^2$ (292), $+1.90 \times 10^2$ (302), $+2.30 \times 10^2$ (312.5), $+1.80 \times 10^2$ (325), 0 (340); *c* 4.81×10^{-3} [methylcyclohexane–isopentane (75:15), at −68 °C] 0 (250), $+1.20 \times 10^2$ (284), $+1.70 \times 10^2$ (291.5), $+2.20 \times 10^2$ (301.5), $+2.60 \times 10^2$ (312.5), $+1.80 \times 10^2$ (325), 0 (340).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.23; H, 9.73.

Homoadamantane (1). A mixture of (+)-**15** (400 mg, 2.25 mmol, $[\alpha]^{20}_D$ +49.4°), ethanedithiol (2.00 g, 21.2 mmol), and borontrifluoride etherate (2 mL) was stirred for 60 h at room temperature. The reaction mixture was poured onto ice and neturalized with Na_2CO_3. After extraction with $CHCl_3$, the extract was washed with water and dried ($MgSO_4$). The solvent was evaporated and the residue was triturated with pentane to give 500 mg of **16** (67% yield), $[\alpha]^{22}_D$ +25.7° (*c* 0.503, $CHCl_3$). To a solution of (+)-**16** (450 mg, 1.36 mmol) in EtOH (10 mL) was added Raney nickel (5 g), and the mixture was refluxed for 8 h. After Raney nickel was removed, the filtrate was concentrated to give

a solid, which was sublimed at 90 °C (30 mm) to yield 120 mg of 1 (58% yield): $[\alpha]^{24}D$ 0° (c 2.81, $CHCl_3$); mp 256–258 °C (in a sealed tube) (lit.[2] mp 258–259 °C).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 87.67; H, 12.04.

Acknowledgment. The authors thank Drs. Kaoru Kuriyama and Sanji Hagishita (Shionogi Research Laboratory) for performing the temperature-dependent CD measurements.

Registry No.—**1**, 281-46-0; (−)-**3**, 63902-00-1; (+)-**4**, 57287-49-7; (+)-**6**, 63903-40-2; (−)-**6**, 63902-01-2; (+)-**7**, 63902-02-3; (+)-**7** 2Ag, 63949-41-7; (±)-**10**, 63833-52-3; (+)-**10**, 63903-41-3; (+)-**10**, 63902-03-4; (−)-**10** cinchonidine salt, 63949-43-9; (−)-**10** 2Ag, 63949-44-0; (+)-**11**, 63833-53-4; (−)-**12**, 63902-04-5; (−)-**13**, 63902-05-6; (−)-**13** Ag salt, 63949-45-1; **14**, 63833-54-5; (±)-**15**, 63833-55-6; (+)-**15**, 63902-06-7; (+)-**16**, 63833-56-7; (±)-**17**, 63833-57-8; (+)-**17**, 63902-07-8; (±)-**18**, 63833-58-9; (+)-**19**, 63833-59-0; (+)-**20**, 63833-60-3; (+)-**21**, 63902-08-9; (+)-**22**, 63902-09-0; (+)-**23**, 63902-10-3; (±)-dimethyl bicyclo[3.3.1]nonane-2,6-dione-3,7-dicarboxylate, 54696-28-5; ethylene bromide, 106-93-4; (±)-dimethyl homoadamantanedione-3,6-dicarboxylate, 63833-61-4; cinchonidine, 485-71-2.

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Stereochemistry and Total Synthesis of (±)-Ivangulin

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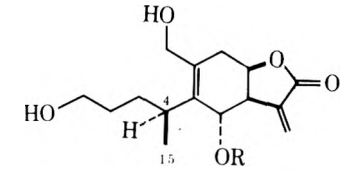
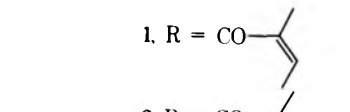
The stereochemistry and total synthesis of the novel secoeudesmanolide ivangulin (**3**) is reported. The introduction of the β-oriented C-15 methyl group involves acid-catalyzed opening of cyclopropyl ketal **4** and equilibration to the more stable β position (**4** → **5**). The establishment of the β-oriented γ-lactone functionality is facilitated by the presence of the angular α-methyl group in diene **6**. Cleavage of ring A in compound **10** via a Baeyer–Villiger oxidation completes the construction of the side chain.

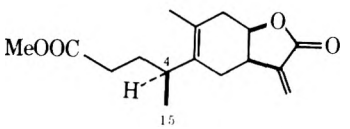
The isolation and structure elucidation of two novel highly oxygenated secoeudesmanolides, eriolangin (**1**) and eriolanin (**2**), from the chloroform extracts of *Eriophyllum lanatum*



1, R = CO



2, R = CO

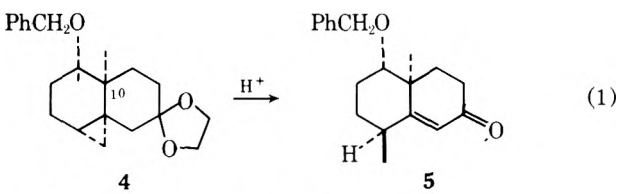


3

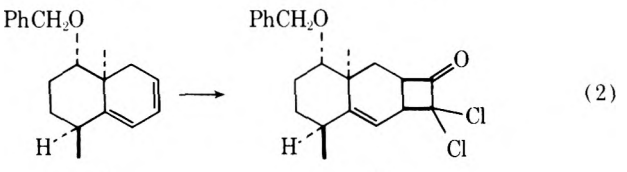
Forbes (Compositae) has been reported by Kupchan.[1] The significant in vivo tumor-inhibitory activity associated with both **1** and **2** can be attributed to the presence within each molecule of two α,β-unsaturated carbonyl functions.[2] In 1967, Herz and co-workers isolated, as a result of examining several collections of *Iva angustifolia* Natl. (section *Linearbractea*) found in Texas and Oklahoma, the only other 1,10-seconeudesmanolide, ivangulin (**3**), whose structure was based on IR, NMR, and chemical degradative data.[3] However, no information regarding the stereochemistry at C-4 was provided.

In conjunction with our efforts to synthesize eriolangin and eriolanin, we have examined several model systems and report herein our preliminary findings which have resulted in the successful synthesis of **3** whose NMR and IR were identical with the spectra of natural ivangulin, thus establishing the stereochemistry at C-4.[4]

Of prime importance to any synthesis of ivangulin and its

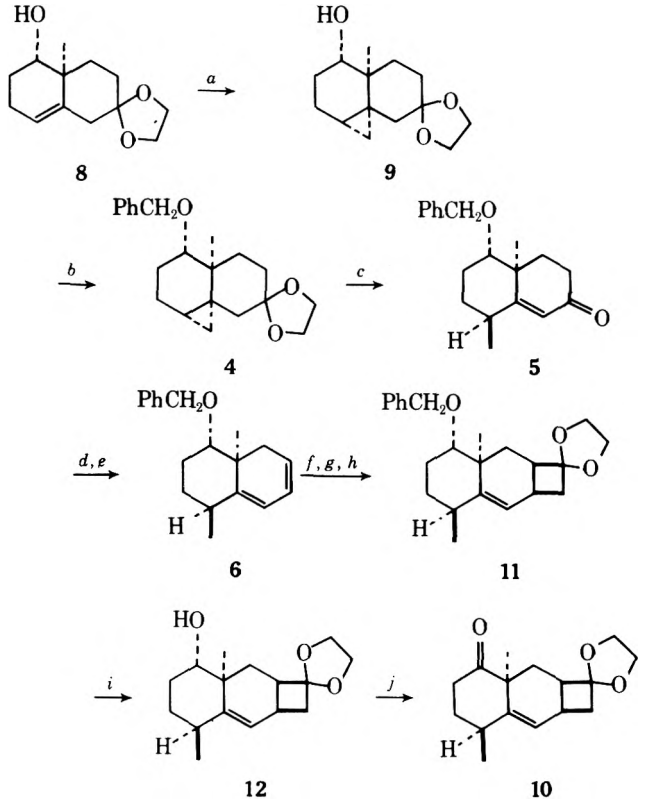


4 **5** (1)



6 **7** (2)

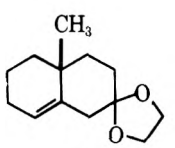
Chart I



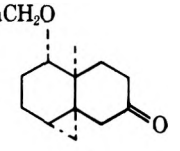
[a] Zn–Cu/CH_2I_2/Et_2O. [b] NaH/Me_2SO/$PhCH_2Br$. [c] MeOH/H_2SO_4. [d] p-$CH_3C_6H_4SO_2NHNH_2$/PhH/BF_3·Et_2O. [e] LDA/THF/−78 → 0 °C. [f] $Cl_2CHCOCl$/Et_3N/hexanes. [g] HOAc/Zn. [h] $HOCH_2CH_2OH$/PhH/TsOH. [i] Li/NH_3. [j] CrO_3·2Py/CH_2Cl_2.

more highly oxygenated derivatives is the introduction of the C-4 methyl group with the proper stereochemical relationship to the α-methylene-γ-butyrolactone functionality. One of the key steps in our synthesis was the introduction of the β-oriented methyl group on the acyclic side chain. As illustrated in eq 1, acid-catalyzed opening of cyclopropyl ketal **4** was accompanied by equilibration to the more stable equatorial position (vide infra). This approach is dependent upon successful cleavage of the C-1, C-10 carbon–carbon bond at some point in the synthesis. The proper stereochemical relationship between the C-4 methyl group and the eventual γ-lactone moiety was facilitated by the presence of the C-10 α-oriented methyl group in diene **6** which directed the addition of dichloroketene from the β-face of the molecule (eq 2). Preparation of cyclopropyl ketal **4** along with its conversion to the tricyclic keto ketal **10** is detailed in Chart I.

The known ketal olefin **8**[5] was efficiently cyclopropanated in high yield employing the LeGoff modification[6] of the Simmon–Smith reaction[7] in which the zinc–copper couple is readily prepared by treating zinc dust with a hot acetic acid solution of cupric acetate monohydrate. It is of interest to note that in the absence of the α-oriented hydroxyl function at C-1 no cyclopropanation occurred. For example, we were unable to cyclopropanate olefin I employing several procedures. The



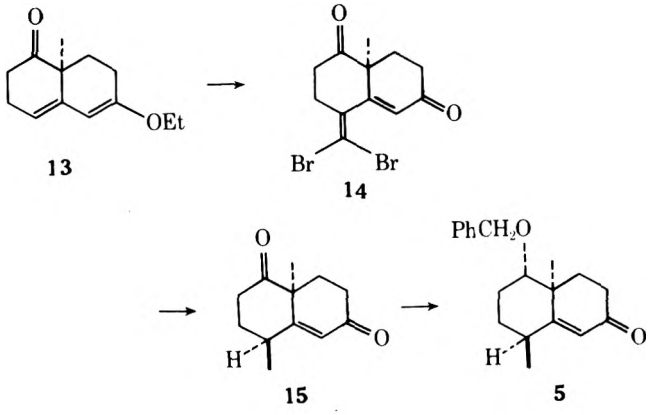
I



II

above results were not completely unexpected in view of Winstein's observation some years ago that the hydroxyl group of 3-cyclopenten-1-ol controls methylene transfer.[8]

Chart II



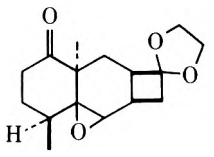
Prior to cyclopropane ring opening and equilibration, the free hydroxyl was protected as its benzyl ether. Exposure of ketal **4** to concentrated sulfuric acid in methanol at 80–85 °C for 30 min led to opening of the cyclopropane ring with equilibration to the β position. The major product, albeit in only overall yields of between 40 and 50%, was clearly an α,β-unsaturated ketone as evidenced by infrared bands at 1680 and 1614 cm^{-1} and a one-proton doublet (J = 1.8 Hz) in the NMR spectrum located at δ 5.62. In addition, a three-proton doublet (J = 7 Hz) centered at δ 1.07 for the C-4 methyl group was evident. The initial stereochemical assignment at C-4 in compound **5** was based on an observation reported some years ago that in 6-substituted Δ^4-3-keto steroids the stereochemistry at C-6 can be deduced from the multiplicity of the olefinic proton at C-4 which appears as a singlet (W_H = 1.5–1.8 Hz) in the C-6 β-substituted series and as a doublet (J = 1.6–1.8 Hz) in the C-6 α-substituted series.[9] Attempts to open the cyclopropane ring via treatment of cyclopropyl ketone **II** with base (e.g., potassium *tert*-butoxide, 1,5-diazabicyclo[5.4.0]undec-5-ene) gave discouragingly low yields (<10%) of desired enone **5**.

Unequivocal confirmation of the structure assigned to compound **5** was arrived at by the synthetic route outlined in Chart II. Reaction of dienol ether **13** with carbon tetrabromide in pyridine provided the dibromomethylene compound **14** (~50%) which when subjected to hydrogenation using Pd/$SrCO_3$ and equilibration provided the known enedione **15** (38%).[10] Reduction of the unconjugated carbonyl with sodium borohydride in absolute ethanol (0 °C) generated the desired alcohol which was converted to its sodium alkoxide in tetrahydrofuran and treated with benzyl bromide in the presence of tetrabutylammonium iodide.[11] The benzyl ether generated by this procedure was identical in all respects with the sample of compound **5** prepared above.

Introduction of the 1,3-conjugated diene system was carried out on the tosylhydrazone of enone **5** employing a modification of the original procedure of Dauben and Shapiro.[12,13] Use of excess lithium diisopropylamide in tetrahydrofuran gave reproducibly in >90% yield the sensitive diene **6**. The in situ cycloaddition of dichloroketene generated from dichloroacetyl chloride and triethylamine in hexane[14] to diene **6** gave predominantly adduct **7** resulting from β attack.[15] Approximately 10–15% of the α adduct could be detected. Dechlorination of **7** with zinc in glacial acetic acid followed by ketalization gave the crystalline tricyclic ketal **11**, mp 96–97 °C, in an overall yield ranging from 50 to 70%. Debenzylation (lithium, liquid ammonia, tetrahydrofuran, *tert*-butyl alcohol) and oxidation with Collins reagent provided in 90% overall yield the tricyclic ketone **10**.

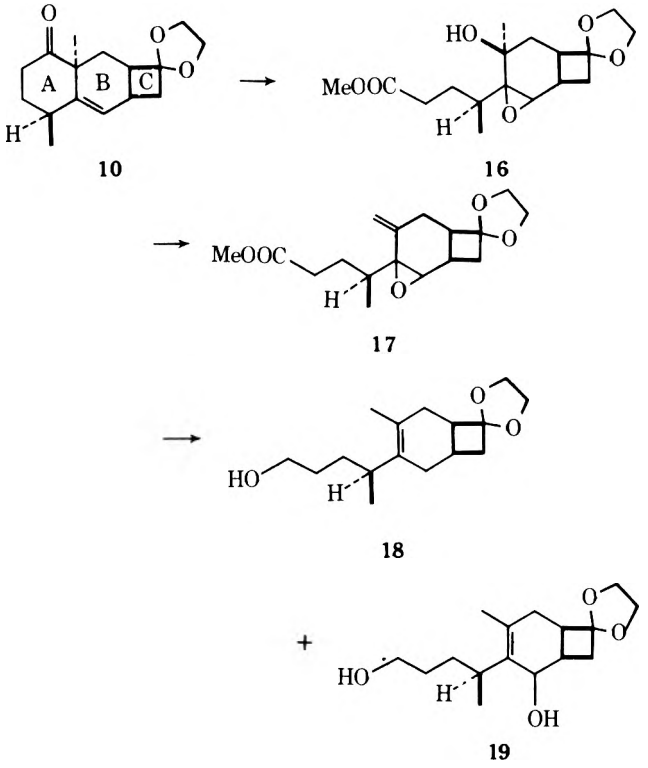
With compound **10** in hand, we turned our attention to the cleavage of ring A. Treatment of ketone **10** with 1 equiv of *m*-chloroperbenzoic acid methylene chloride containing so-

dium bicarbonate gave rapid epoxidation of the double bond with no evidence of Baeyer–Villiger product. Under a variety of conditions, formation of compound **20** was faster than



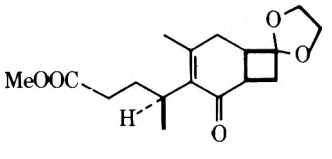
20

lactone formation. Use of 2.0 equiv of *m*-chloroperbenzoic acid followed by treatment with potassium carbonate in methanol gave the hydroxy ester **16** as a crystalline compound, mp



10 **16** **17** **18** **19**

65.5–66.5 °C, in 84% overall yield. Mesylation of alcohol **16** with methanesulfonyl chloride in methylene chloride in the presence of triethylamine at −5 °C gave not the expected mesylate but the sensitive epoxy olefin **17** in 70% yield after purification on florisil. The NMR and infrared spectra of compound **17** were in accord with the assigned structure of the purified compound. The NMR spectrum of compound **17** revealed two new singlets (1 H each) located at δ 5.08 and 5.16, and the infrared spectrum displayed new absorptions at 3100 and 1644 cm^{-1}. It is of interest to note that compound **17** represents a potential intermediate for the synthesis of eriolangin and eriolanin. During an attempted purification on silica gel, compound **17** underwent a smooth high-yield transformation to the undesired α,β-unsaturated enone **21**.

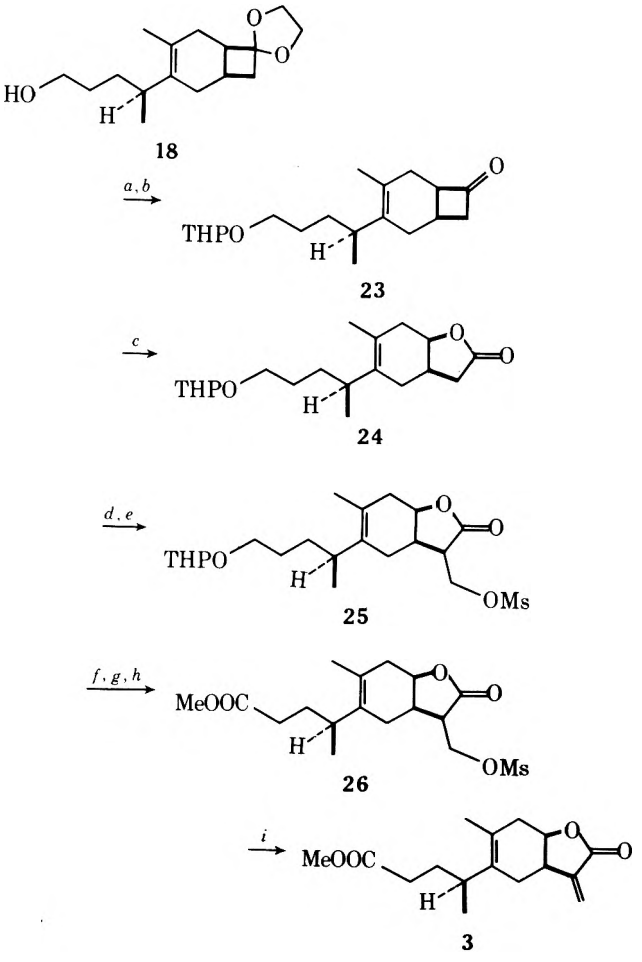


21

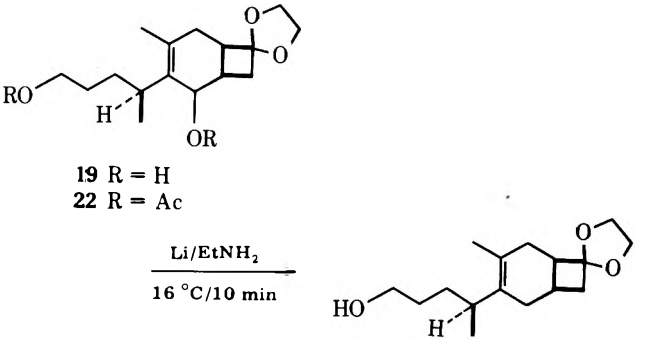
Once again, the NMR and IR spectra allowed ready assignment of the unwanted product. The NMR spectrum exhibited a new three-proton singlet attributed to the olefinic methyl group, and the infrared spectrum showed new bands at 1650 and 1620 cm^{-1}.

Treatment of the sensitive epoxy olefin **17** with lithium in liquid ammonia–tetrahydrofuran containing *tert*-butyl alcohol gave after chromatographic separation two products, A (35%) and B (46%), which were identified as the monoalcohol **18** and the diol **19**, respectively. Conversion of diol **19** to its diacetate **22** (94%), mp 59–60 °C, with acetic anhydride and triethylamine in ether containing *p*-dimethylaminopyridine[16] followed by reduction with lithium in ethylamine gave a 91% yield of pure alcohol **18**. In the absence of *p*-dimethylaminopyridine, the conversion of **19** to **22** required approximately 5 days.

Chart III



[a] THF/10% aq HCl/25 °C. [b] DHP/CH_2Cl_2/TsOH. [c] *t*-BuOOH/10% aq NaOH/THF/0 °C. [d] LDA/THF/−25 °C/HCHO. [e] MsCl/Py/CH_2Cl_2. [f] MeOH/TsOH. [g] Jones/0 °C. [h] CH_2N_2/Et_2O. [i] DBU/PhH/rt.



19 R = H
22 R = Ac

$Li/EtNH_2$, 16 °C/10 min

18

Transformation of compound **18** to ivangulin was carried out as indicated in Chart III. Hydrolysis of ketal **18** with 10% hydrochloric acid followed by tetrahydropyranylation in methylene chloride containing *p*-toluenesulfonic acid gave in near quantitative yield cyclobutanone **23**. Baeyer–Villiger

oxidation of **23** with *m*-chloroperbenzoic acid led only to disappointingly low yields of lactone **24**. Similarly, use of basic hydrogen peroxide in tetrahydrofuran led to only a 32% yield of lactone **24**.[17] However, utilization of *tert*-butyl hydroperoxide in tetrahydrofuran containing 10% aqueous sodium hydroxide gave a 76% yield of the desired γ-lactone. Substitution of triton B for sodium hydroxide in the *tert*-butyl hydroperoxide reaction gave a 54% yield of **24**.

Hydroxymethylation[18] of the lactone enolate prepared from lactone **24** with lithium diisopropylamide in tetrahydrofuran at −78 °C proceeded smoothly in 92% yield. Mesylation of the resulting adduct in methylene chloride containing pyridine generated the corresponding mesylate **25** in high yield. Cleavage of the tetrahydropyranyl ether, Jones oxidation of the resulting alcohol, and esterification of the corresponding carboxylic acid function all proceeded in near quantitative yield despite the presence of the potentially sensitive β-mesyloxy lactone moiety. Conversion of **26** to ivangulin was accomplished in 97% yield with 1,5-diazabicyclo[5.4.0]undec-5-ene in benzene at room temperature. Crystalline ivangulin, mp 66.0–66.5 °C, was identical with natural ivangulin by comparison of spectral properties (NMR, IR), thus establishing the stereochemistry at C-4.[4]

Experimental Section

Melting points were determined on a Fisher-Johns hot-stage melting-point apparatus. All melting and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 247 grating infrared spectrometer, and nuclear magnetic resonance (NMR) spectra were recorded at either 60 (Varian A-60A or T-60 spectrometer) or at 250 MHz as indicated. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ_{Me_4Si} = 0.0 ppm) as an internal standard. Low-resolution mass spectra were recorded on an LKB-9000 spectrometer. High-resolution spectra were recorded on a Varian MAT CH-5DF instrument. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Reactions were run under an atmosphere of nitrogen. "Dry" solvents were dried immediately before use. Tetrahydrofuran and dimethoxyethane were distilled from lithium aluminum hydride; dimethylformamide (DMF), hexamethylphosphoramide (HMPA), dimethyl sulfoxide (Me_2SO), and pyridine were distilled from calcium hydride. Diethyl ether and dioxane were distilled from sodium. Methylene chloride was passed through a column of alumina prior to use.

***cis*-10α-Methyl-7,7-ethylenedioxy-4α,5α-methano-1α-decalol (9).** To a solution of 128.6 g of diiodomethane in 500 mL of anhydrous ether was added 62 g of zinc–copper couple (freshly prepared via the LeGoff modification[6]). The heterogeneous mixture was refluxed under nitrogen. After 30 min, 15.9 g (71 mmol) of octalol **8** in 300 mL of anhydrous ether was added dropwise over 30 min with the aid of a dropping funnel. The reaction was refluxed for 2 h. The cooled reaction mixture was filtered and the filtrate was poured into 200 mL of cold saturated aqueous ammonium chloride solution. The organic layer was separated, washed with saturated sodium bicarbonate solution and saturated brine solution, and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo provided 39 g of crude product. Chromatography on 800 g of silica gel employing ether–hexanes, 1:2, gave 12.8 g (76%) of pure **9** as an oil: IR ($CHCl_3$) 3620, 3475, 3065, 3000, 2960, 2935, 2880, 1465, 1455, 1431, 1385, 1363, 1355, 1320, 1280, 1234, 1178, 1123, 1100, 1076, 1046, 1030, 971, 950, 915, 900, 881, 868, 830 cm^{-1}; NMR ($CDCl_3$) δ 3.91 (s, 4 H), 3.42 (m, 1 H), 1.2–1.3 (m, 10 H), 1.12 (s, 3 H), 0.1–1.0 (m, 3 H). An analytical sample was prepared by distillation [85 °C (bath temperature)/0.8 mmHg].

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.71; H, 9.46.

***cis*-10α-Methyl-7,7-ethylenedioxy-4α,5α-methano-1α-benzyloxydecalin (4).** To a suspension of 5.28 g (109 mmol) of sodium hydride (50% oil dispersion) in 160 mL of dry benzene was added 18.6 g (78 mmol) of decalol **9** in 8 mL of dry dimethyl sulfoxide. After the mixture was refluxed for 1 h, 13.1 mL (110 mmol) of benzyl bromide was added over 10 min. After an hour at reflux, an additional 3.74 g (78 mmol) of sodium hydride was added followed by 0.27 mL (78 mmol) of benzyl bromide after 30 min. After 50 min, TLC analysis indicated the presence of starting material. An additional 2.62 g (54.6 mmol) of sodium hydride and 6.48 g (54.6 mmol) of benzyl bromide were added. After 40 min, TLC analysis (hexanes–ether, 2:1) indicated no starting alcohol present. The product was isolated by extraction with ether.[19] There was obtained 51 g of crude product which was chromatographed on 800 g of silica gel. Elution with hexanes–ether, 6:1, afforded 23.9 g (93%) of pure benzyl ether **4** as an oil: IR (CCl_4) 3070, 3035, 2960, 2940, 2880, 1500, 1465, 1455, 1431, 1383, 1370, 1360, 1349, 1325, 1304, 1280, 1260, 1246, 1220, 1195, 1134, 1118, 1100, 1078, 1060, 1035, 1015, 967, 951, 918, 905 cm^{-1}; NMR (CCl_4) δ 7.20 (s, 5 H), 4.33 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 16 Hz), 3.78 (s, 4 H), 2.96 (m, 1 H), 1.13 (s, 3 H), 0.3–1.0 (m, 3 H). An analytical sample was prepared by distillation [110 °C (bath temperature)/1.5 mmHg].

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 77.08; H, 8.77.

1α-Benzyloxy-4β-methyl-10α-methyl-Δ$^{5(6)}$-octal-7-one (5). To a solution of 11.95 g (36.4 mmol) of cyclopropyl ketal **4** in 237 mL of methanol cooled to 0 °C was added dropwise over 10 min 91 mL of concentrated sulfuric acid. The mixture was heated to ca. 85 °C for 30 min. The reaction was quenched by pouring onto ice. Isolation of the product by extraction with benzene[19] gave 19 g of crude material. Chromatography on 800 g of silica gel [elution with hexanes–ether, 7:1] gave 4.5 g of crystalline product. Recrystallization from hexanes gave 4.2 g (40%) of pure crystalline octalone (**5**): mp 74–75 °C; IR ($CHCl_3$) 3090, 3055, 3040, 2975, 2940, 2910, 2855, 1680, 1615, 1500, 1462, 1457, 1420, 1375, 1360, 1348, 1331, 1295, 1272, 1238, 1218, 1205, 1178, 1145, 1100, 1075, 1031, 1017, 959, 937, 914, 880 cm^{-1}; NMR (CCl_4) δ 7.30 (s, 5 H), 5.62 (d, J = 1.8 Hz, 1 H), 4.51 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 13.4 Hz), 3.10 (m, 1 H), 1.4–2.6 (m, 9 H), 1.21 (s, 3 H), 1.07 (d, 3 H, J = 6.5 Hz).

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.50; H, 8.49.

Preparation of Conjugated Diene 6. To a suspension of 8.0 g (28 mmol) of octalone **5** and 5.8 g (31 (mmol) of *p*-toluenesulfonylhydrazide in 80 mL of anhydrous benzene was added 16 drops of boron trifluoride etherate. The mixture gradually became homogeneous. After 40 min, the solvent was removed on a rotary evaporator under reduced pressure. The residue was redissolved in 50 mL of benzene and evaporated to dryness to remove traces of moisture. This process was repeated again. The resulting tosylhydrazone was dried at 0.1 mmHg for 1 h.

The above tosylhydrazone in 70 mL of anhydrous tetrahydrofuran cooled to −78 °C was treated dropwise with a precooled (−78 °C) solution of lithium diisopropylamide [prepared from 19.7 mL (141 mmol) of diisopropylamine and 88.1 mL of 1.6 M *n*-butyllithium (in hexane) in 180 mL of dry tetrahydrofuran at −78 °C]. The mixture was warmed to 0 °C where stirring was continued for 2 h. After 2 h at room temperature, the reaction was quenched at 0 °C with water. The solvent was removed under reduced pressure. The product was isolated by extraction with hexanes.[19] There was obtained 7.43 g (98% overall) of pure sensitive diene **6** as an oil: IR (CCl_4) 3100, 3050, 2980, 2945, 2880, 2870, 1610, 1590, 1501, 1458, 1446, 1432, 1398, 1375, 1365, 1346, 1325, 1310, 1261, 1247, 1220, 1210, 1171, 1148, 1110, 1100, 1075, 1035, 1005, 996, 926, 909, 881 cm^{-1}; NMR (CCl_4) δ 7.26 (s, 5 H), 5.64 (m, 3 H), 4.53 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 16 Hz), 3.22 (dd, 1 H, J = 4 and 11 Hz), 1.2–2.7 (m, 7 H), 1.05 (d, 3 H, J = 7 Hz), 1.00 (s, 3 H).

Preparation of Tricyclic Ketal 11. To a solution of 7.43 g (27.7 mmol) of diene **6** in 100 mL of hexanes was added simultaneously over a period of 1.5 h via two syringe pumps 7.18 mL (74.8 mmol) of dichloroacetyl chloride in 40 mL of hexanes and 10.7 mL (77.6 mmol) of triethylamine in 40 mL of hexanes. Approximately 30 min after addition was complete, the precipitate was removed by filtration and the solvent was removed under reduced pressure. The crude dichlorocyclobutanone [IR (CCl_4) 1810 cm^{-1}] was dissolved in 100 mL of glacial acetic acid and treated cautiously with 10.9 g of zinc dust. Cooling is necessary during the addition. After all the zinc was added, the heterogeneous reaction mixture was heated at 55 °C for 1.5 h. The reaction mixture was filtered and the solvent was removed under reduced pressure on a rotary evaporator. The residue was diluted with a 1:1 mixture of ether and benezene. The organic solution was washed several times with saturated sodium bicarbonate solution and brine and dried over anhydrous magnesium sulfate. Filtration followed by removal of the solvent in vacuo gave 9.98 g of crude cyclobutanone [IR (CCl_4) 1770 cm^{-1}] which was directly dissolved in 150 mL of benzene containing 34.4 g (55.4 mmol) of ethylene glycol and 80 mg of *p*-toluenesulfonic acid. The reaction mixture was refluxed with azeotropic removal of water using a Dean–Stark apparatus. The benzene solution of the crude product was washed with saturated sodium bicarbonate solution and brine and was dried over anhydrous sodium sulfate. Filtration and removal of the solvent under reduced pressure left 11.2 g of crude ketal **11**. Chromatography on 500 g of silica

gel using hexanes–ether, 10:1, provided 4.8 g (50% overall) of pure crystalline ketal **8**: mp 91.5–92.5 °C; IR (CCl_4) 3098, 3075, 3045, 2975, 2945, 2880, 1501, 1460, 1430, 1400, 1380, 1360, 1315, 1295, 1220, 1205, 1185, 1100, 1079, 1030, 1020, 970, 955, 920 cm^{-1}; NMR (CCl_4) δ 7.20 (s, 5 H), 5.31 (br s, 1 H), 4.50 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 9 Hz), 3.80 (m, 4 H), 2.98 (dd, 1 H, J = 4 and 10 Hz), 0.99 (s, 3 H), 0.98 (d, 3 H, J = 6.5 Hz).

Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 78.11; H, 8.62.

Debenzylation of Benzyl Ether 11. To a refluxing solution of 1.2 g of lithium metal in 700 mL of anhydrous liquid ammonia was added dropwise 2.82 g (7.96 mmol) of benzyl ether **11** in 15 mL of anhydrous tetrahydrofuran. After 2 h at −33 °C, the excess lithium was destroyed by the addition of ammonium chloride. Evaporation of the ammonia followed by isolation of the product by ether extraction[19] gave 2.2 g of crude alcohol **12**. Purification on 100 g of silica gel using hexanes–ether, 2:1, afforded 1.99 g of crystalline product. Recrystallization from ether–hexanes provided pure **12**: mp 97–98 °C; IR (CCl_4) 3610, 3475, 3015, 2950, 2910, 2850, 2840, 1450, 1435, 1415, 1365, 1339, 1300, 1280, 1190, 1160, 1124, 1110, 1090, 1060, 1020, 1010, 985, 953, 938, 905, 890 cm^{-1}; NMR (CCl_4) δ 5.40 (br s, 1 H), 3.81 (br s, 4 H), 3.25 (m, 1 H), 0.98 (d, 3 H, J = 6.5 Hz), 0.92 (s, 3 H).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C= 72/3[: H, 9.03.

Preparation of Octalone 10. Chromium trioxide (4.2 g, 42 mmol) was carefully added to 6.8 mL of dry pyridine in 100 mL of methylene chloride. After approximately 30 min, 1.85 g (7 mmol) of alcohol **12** in 7 mL of methylene chloride was added in one portion. After 15 min, the reaction mixture was filtered through Celite. The pad of Celite was washed thoroughly with ether. The filtrate and combined washings were evaporated under reduced pressure. The residue was dissolved in ether and once again passed through Celite. Removal of the solvent afforded 1.66 g (90%) of pure ketone **10** as an oil: IR (CCl_4) 3040, 2970, 2940, 2880, 1710, 1658, 1458, 1425, 1380, 1370, 1357, 1340, 1333, 1320, 1310, 1288, 1258, 1240, 1218, 1170, 1118, 1085, 1068, 1041, 1020, 945, 908 cm^{-1}; NMR (CCl_4) δ 5.42 (br s, 1 H), 3.80 (s, 4 H), 1.12 (d, 3 H, J = 6.5 Hz), 1.10 (s, 3 H).

Anal. Calcd for $C_{16}H_{22}O_3$: m/e 262.1568. Found: m/e 262.1566.

Baeyer–Villiger Oxidation of Octalone 10. To 1.66 g (6.33 mmol) of octalone **10** in 50 mL of methylene chloride containing 1.33 g (15.8 mmol) of suspended sodium bicarbonate at 0 °C was added 3.21 g of *m*-chloroperbenzoic acid. After approximately 30 h at 25 °C, the reaction was cooled and filtered. The filtrate was evaporated in vacuo and the residue was dissolved in 70 mL of methanol. Potassium carbonate (1.8 g) was added and the reaction was stirred for 25 min at room temperature. After the addition of 70 mL of benzene, the solid material in the flask was filtered. The solvent was removed under reduced pressure and the product was isolated by extraction with ether–benzene, 1:1.[19] There was obtained 2.30 g of crude product which was chromatographed on 140 g of silica gel. Elution with ether–hexanes, 1:1, gave 1.65 g (80%) of pure crystalline hydroxy ester **16**: mp 65.5–66.5 °C; IR (CCl_4) 3610, 3500, 2990, 2950, 2885, 1741, 1460, 1450, 1440, 1390, 1365, 1345, 1340, 1291, 1220, 1190, 1175, 1135, 1118, 1100, 1065, 1025, 946, 930 cm^{-1}; NMR (CCl_4) δ 3.81 (br s, 4 H), 3.63 (s, 3 H), 3.03 (d, 1 H, J = 2.4 Hz), 1.18 (s, 3 H), 0.95 (d, 3 H, J = 7 Hz).

Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.43; H, 7.98.

Preparation of Epoxy Olefin 17. To a solution of 1.25 g (3.83 mmol) of **16** in 6 mL of methylene chloride at −10 °C was added 2.13 mL (15.3 mmol) of triethylamine in 9 mL of methylene chloride and 1.19 mL (15.3 mmol) of methanesulfonyl chloride in 5 mL of methylene chloride simultaneously over 15 min. After approximately 2 h at −5 °C, the product was isolated by ether extraction.[19] Purification of the crude product (1.58 g) on 50 g of Florisil using hexanes–ether, 2:1, gave 826 mg (70%) of pure sensitive epoxy olefin **17**: IR (CCl_4) 3100, 2975, 2950, 2880, 1740, 1641, 1460, 1440, 1385, 1360, 1280, 1180, 1021, 905 cm^{-1}; NMR δ (CCl_4) 5.15 (s, 1 H), 5.07 (s, 1 H), 3.77 (br s, 4 H), 3.62 (s, 3 H), 3.08 (d, 1 H, J = 2 Hz), 0.93 (d, 3 H, J = 7 Hz).

Metal–Ammonia Reduction of Epoxy Olefin 17. A solution of 99 mg (0.32 mmol) of epoxide **17** in 1.5 mL of dry tetrahydrofuran containing 1.5 mL of *tert*-butyl alcohol was added to a solution of lithium metal (66 mg) in 12 mL of liquid ammonia cooled to −78 °C. After approximately 10 min, the blue color disappeared and the ammonia was evaporated. The product was isolated by ether extraction.[19] Purification of the crude product (87 mg) on silica gel gave upon elution with ether–benzene, 1:2, 30 mg (35%) of alcohol **18**: IR (CCl_4) 3640, 3480, 2935, 2870, 1455, 1415, 1375, 1341, 1305, 1266, 1225, 1060, 1021, 950 cm^{-1}; NMR (CCl_4) δ 3.77 (s, 4 H), 3.50 (t, 2 H, J = 6 Hz), 1.73 (s, 3 H), 0.90 (d, 3 H, J = 7 Hz).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.01; H, 9.79.

Continued elution with ethyl acetate provided 42 mg (46%) of pure **19** as an oil: IR (CCl_4) 3380, 2945, 2860, 1660, 1455, 1415, 1379, 1355, 1309, 1270, 1230, 1190, 1140, 1091, 1058, 1019, 966, 946, 930, 890 cm^{-1}; NMR (CCl_4) δ 4.22 (m, 1 H), 3.82 (s, 4 H), 3.0–3.7 (m, 4 H), 1.73 (s, 3 H), 0.92 (d, 3 H, J = 7 Hz).

Diacetate 22. To a solution of 108 mg (0.382 mmol) of diol **19** in 200 μL of absolute ether containing 4 mg of *p*-dimethylaminopyridine was added 160 μL (1.15 mmol) of triethylamine and 152 μL (1.60 mmol) of acetic anhydride. After 2 h at room temperature, the product was isolated by ether extraction.[19] Chromatography of the crude product (140 mg) on 4.0 g of silica gel (ether–benzene, 1:1) gave 131 mg (94%) of crystalline **22**: IR (CCl_4) 2952, 2875, 1735, 1651, 1450, 1370, 1305, 1240, 1190, 1160, 1135, 1105, 1050, 1020, 965, 945, 932, 905 cm^{-1}; NMR δ 5.52 (d, 1 H, J = 5 Hz), 3.6–4.2 (m, 2 H), 2.80 (s, 4 H), 2.00 (s, 3 H), 1.98 (s, 3 H), 1.80 (s, 3 H), 0.95 (d, 3 H, J = 7 Hz). An analytical sample was prepared by recrystallization from hexanes, mp 55–56 °C.

Anal. Calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.46; H, 8.26.

Conversion of Diacetate 22 to Alcohol 18. To a solution of 30 mg (0.08 mmol) of diacetate **22** in 2.0 mL of anhydrous ethylamine cooled to 0 °C was added 18 mg of lithium metal. After ca. 10 min, excess lithium was destroyed by addition of ammonium chloride. Isolation of the product by ether extraction[19] left 23 mg of crude product. Purification on 12 g of silica gel (elution with ether–benzene, 1:1) gave 20 mg (91%) of pure alcohol **18** which was identical by TLC, IR, and NMR with a sample prepared above.

Preparation of Cyclobutanone 23. A solution of ketal alcohol **18** (50 mg, 0.19 mmol) in a mixture of 2 mL of tetrahydrofuran and 0.5 mL of 10% aqueous hydrochloric acid was stirred for 3 h at room temperature. The product was isolated by extraction with benzene.[19] The crude product (44 mg) [IR (CCl_4) 3640, 3450, 1782 cm^{-1}; NMR (CCl_4) δ 1.71 (s, 3 H), 0.95 (d, 3 H, J = 7 Hz)] was dissolved in 1.5 mL of a precooled (0 °C) methylene chloride solution containing 1.5 mL of dihydropyran and 6.0 mg of *p*-toluenesulfonic acid. Stirring was continued for 2 h at 0 °C. After standard workup, the crude product was purified on 6.0 g of silica gel. Elution with hexanes–ether, 4:1, gave 58 mg (99%) of **23** as a colorless oil: IR (CCl_4) 2960, 2945, 2930, 2880, 1782, 1455, 1445, 1390, 1370, 1355, 1345, 1325, 1308, 1290, 1278, 1262, 1208, 1189, 1141, 1121, 1080, 1052, 986 cm^{-1}; NMR (CCl_4) δ 4.53 (br s, 1 H), 1.74 (s, 3 H), 0.95 (d, 3 H, J = 7 Hz).

Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87; Found: C, 74.28; H, 9.79.

Baeyer–Villiger Oxidation of Ketone 23. A mixture of 66 mg (0.22 mmol) of ketone **23**, 65 μL (0.66 mmol) of *tert*-butyl hydroperoxide, and 103 μL (0.26 mmol) of 10% aqueous sodium hydroxide in 2.3 mL of tetrahydrofuran cooled to 0 °C was stirred for 30 min. The reaction mixture was taken up in 50 mL of benzene–ether (1:1) and was washed with 2 mL of water and two 2-mL portions of brine. The organic layer was dried over magnesium sulfate and the solvent was evaporated in vacuo leaving 60 mg of crude γ-lactone. Purification of 5 g of silica gel (elution with ether–benzene, 2:3) afforded 53 mg (76%) of pure lactone **24** as an oil: IR (CCl_4) 2955, 2945, 2880, 1784, 1555, 1455, 1445, 1422, 1390, 1359, 1350, 1330, 1290, 1255, 1220, 1210, 1190, 1145, 1124, 1085, 1039, 998, 990, 940, 915, 868 cm^{-1}; NMR (CCl_4) δ 4.68 (m, 1 H), 4.53 (br s, 1 H), 1.78 (s, 3 H), 0.95 (d, 3 H, J = 7 Hz).

Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.70; H, 9.35.

Hydroxymethylation of Lactone 24. To a solution of diisopropylamine (26 μL, 0.18 mmol) in 1.6 mL of dry tetrahydrofuran cooled to −78 °C was added 116 μL of a 1.6 M solution of *n*-butyllithium in hexane. After 15 min, a solution of 30 mg (0.09 mmol) of lactone **24** in 1.6 mL of dry tetrahydrofuran was added dropwise over a period of 1 min. After 30 min at −78 °C, the reaction was warmed to −25 °C and formaldehyde, generated from 30 mg of paraformaldehyde at 150 °C, was passed into the reaction mixture with the aid of a stream of nitrogen. After complete depolymerization, the reaction mixture was stirred for an additional 30 min at −25 °C. The reaction was quenched by the addition of a saturated ammonium chloride solution. The product was purified on 12 g of silica gel. Elution with ether–benzene, 1:1, gave 30 mg (92%) of pure hydroxymethylated lactone: IR ($CHCl_3$) 3600, 3450, 1755 cm^{-1}; NMR (CCl_4) δ 4.4–4.8 (m, 2 H), 1.73 (s, 3 H), 0.95 (d, 3 H, J = 7 Hz). A solution of the above alcohol (29 mg) in 3.0 mL of methylene chloride containing 20 μL of methanesulfonyl chloride and 20 μL of pyridine was allowed to stir for 4 h at room temperature. Purification of the reaction mixture on 12 g of SilicAR CC-7 (Mallinckrodt) using ether–benzene, 1:2, gave 30 mg (85%) of

mesylate **25**: IR ($CHCl_3$) 1770 cm^{-1}; NMR ($CDCl_3$) δ 3.07 (s, 3 H), 0.96 (d, 3 H, J = 7 Hz).

Preparation of Intermediate 26. A solution of the above tetrahydropyranyl ether **25** (30 mg, 0.07 mmol) in 2.0 mL of absolute methanol containing 7 mg of *p*-toluenesulfonic acid was allowed to stir for 30 min at 0 °C. After an additional 45 min at room temperature, the solvent was evaporated under reduced pressure. The crude alcohol was purified on 12 g of SilicAR CC-7 using ether–benzene, 2:1. There was obtained 27 mg (99%) of alcohol [IR ($CHCl_3$) 3530, 2765 cm^{-1}; NMR ($CDCl_3$) δ 4.86 (m, 1 H), 4.45 (d, . 2 H, J = 4 Hz), 3.62 (br s, 2 H), 3.05 (s, 3 H), 1.75 (s, 3 H), 0.95 (d, 3 H, J = 7 Hz)] which was used directly in the next reaction.

A mixture of the above alcohol (18 mg, 0.05 mmol) and 222 μL of 0.7 M Jones reagent in 1.2 mL of acetone was allowed to stir at 0 °C for 1.5 h. The reaction was quenched by the addition of 2-propanol. After evaporation of the solvent in vacuo, the residue was taken up in ethyl acetate.[19] The resulting crude carboxylic acid was esterified with an ethereal solution of diazomethane. Chromatography of the crude ester on SilicAR CC-7 using ether–benzene, 1:2, provided 20 mg (100%) of pure **26**: IR (CCl_4) 1740, 1778 cm^{-1}; NMR (CCl_4) δ 4.68 (m, 1 H), 4.38 (d, 2 H, J = 4 Hz), 3.62 (s, 3 H), 2.98 (s, 3 H), 1.74 (s, 3 H), 0.97 (d, 3 H, J = 7 Hz).

(±)-Ivangulin (3). A solution of 17 mg (0.04 mmol) of mesylate **26** in 1.0 mL of dry benzene containing 20 μL of 1,5-diazabicyclo-[5.4.0]undec-5-ene was allowed to stir at room temperature for 30 min. The reaction mixture was purified directly on 6.0 g of silica gel. Elution with ether–hexanes (1:2) gave 12.5 mg (99%) of crystalline (±)-ivangulin, mp 66–66.5 °C [IR($CHCl_3$) 3020, 2960, 2925, 2875, 2845, 1738, 1730, 1660, 1620, 1460, 1438, 1405, 1382, 1368, 1355, 1328, 1272, 1175, 1145, 1110, 1080, 1038, 1005, 989, 970, 948, 905, 865, 815 cm^{-1}; NMR ($CDCl_3$) δ 6.27 (d, 1 H, J = 3 Hz), 5.68 (d, 1 H, J = 3 Hz), 4.87 (q, 1 H, J = 5 Hz), 3.64 (s, 3 H), 3.25 (m, 1 H), 1.70 (s, 3 H), 0.94 (d, 3 H, J = 7 Hz)] whose NMR and IR spectra were in complete accord with spectra provided by Professor W. Herz.

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Registry No.—**3**, 63640-50-6; **4**, 63600-03-3; **5**, 63600-04-4; **5** tosylhydrazone, 63600-05-5; **6**, 63600-06-6; **7**, 63600-07-7; **8**, 63600-08-8; **9**, 63600-09-9; **10**, 63600-10-2; **11**, 63600-11-3; **11** free ketone, 63600-12-4; **12**, 63600-13-5; **16**, 63600-14-6; **17**, 63600-15-7; **18**, 63600-16-8; **19**, 63600-17-9; **22**, 63609-71-2; **23**, 63600-18-0; **23** free alcohol, 63600-19-1; **24**, 63600-20-4; **24** hydroxymethylated product, 63600-21-5; **25**, 63600-22-6; **25** ditetrahydropyran analogue, 63600-23-7; **26**, 63600-24-8; **26** free acid, 63600-25-9; benzyl bromide, 100-39-0.

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Natural Products of Marine Sponges. 7. The Constitution of Weakly Basic Guanidine Compounds, Dibromophakellin and Monobromophakellin

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The isolation and elucidation of the structure of dibromophakellin and monobromophakellin are reported. Although these molecules contain a guanidine moiety in their skeleton, they do not exhibit the high basicity expected from the presence of this functionality. A theoretically plausible explanation for the anomaly in the base strength of these compounds is discussed.

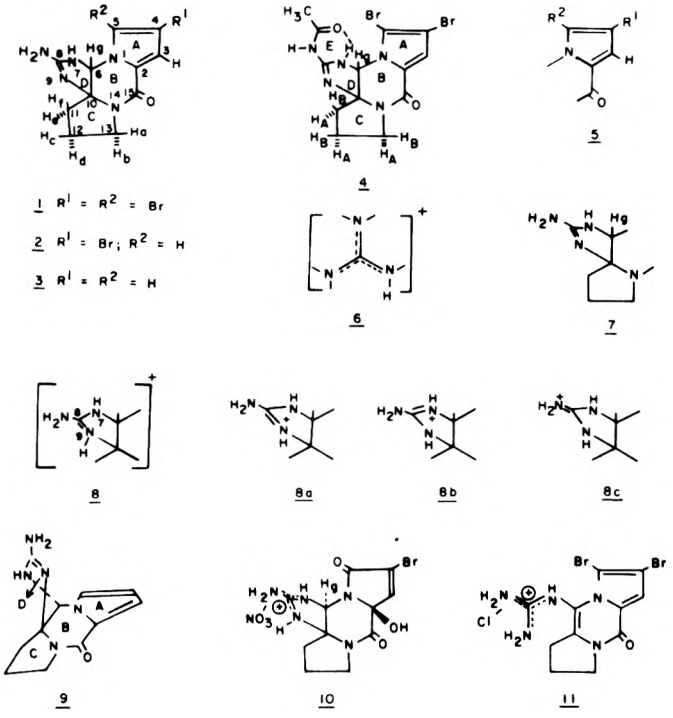
A few years ago we isolated two guanidine derivatives, dibromophakellin and monobromophakellin, from the marine sponge *Phakellia flabellata*.[2] These compounds showed pKa values of <8 which were rather low when compared with the pKa values of >13.4 reported for other guanidines. This paper describes in detail the isolation and characterization of bromophakellins and discusses the factors which make these compounds behave as weak bases.[3]

Dibromophakellin and monobromophakellin occur as hydrochlorides in the sponge *P. flabellata*. The hydrochlorides exhibit a very mild antibacterial action against *B. subtilis* and *E. coli*. The strong antibacterial activity of the methanol extract of the sponge is due to the presence of some other substance(s) which could not be isolated in pure form.

The sponge showed considerable seasonal variations in the production of monobromophakellin, dibromophakellin, and

the antibacterial substance. The material collected during the summer showed very weak antibacterial activity, and systematic fractionation of these specimens gave only monobromophakellin hydrochloride. In contrast, the specimens collected during the winter were found to be very rich in natural products, and from this material dibromophakellin hydrochloride, a fraction containing a strong antibacterial substance, and several other compounds were isolated.[4] Some specimens collected during the winter were found to contain both dibromophakellin hydrochloride and monobromophakellin hydrochloride.

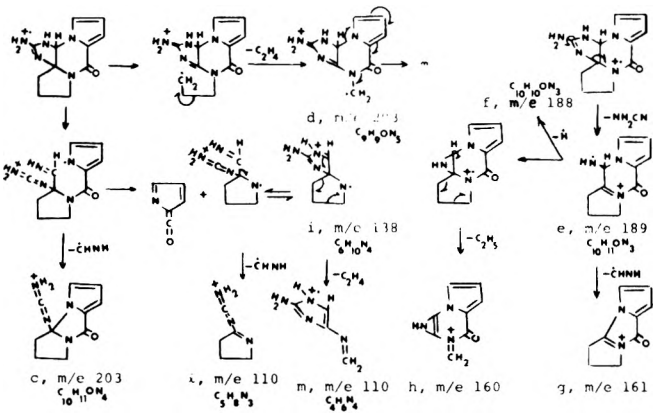
Addition of concentrated ammonia to the aqueous solutions of dibromophakellin hydrochloride ($C_{11}H_{11}N_5OBr_2$·HCl, $[\alpha]^{25}_D$ −203) and monobromophakellin hydrochloride ($C_{11}H_{12}N_5OBr$·HCl, $[\alpha]^{25}_D$ −123) gave the corresponding free bases **1** and **2**. Catalytic hydrogenation of **1** and **2** gave phakellin **3** ($C_{11}H_{13}N_5O$). The UV spectra of the three phakellins showed absorbtion maxima around 233 and 281 nm which were suggestive of the presence of a pyrrole ring having a carbonyl function at the 2 position.[5] The infrared spectra of **1**, **2**, and **3** revealed the presence of amino groups, methylenes, an amide function, and a C=N unit, and provided further support for the presence of a pyrrole ring.



The ^{1}H NMR spectrum of **3** revealed the presence of a $-CH_2CH_2CH_2NCO-$ unit, a highly deshielded methine proton Hg, a 1,2-disubstituted pyrrole ring, and three D_2O-exchangeable protons in the structural framework of phakellins. A comparison of the NMR spectra of **1** and **3** suggested that the two bromine atoms in **1** are present at the 4 and 5 positions of the pyrrole ring. The single bromine atom in **2** was placed at the 4 position because in the NMR spectrum of this compound the two heteroaromatic protons showed doublets (J = 1.8 Hz).[6]

Although both dibromophakellin and monobromophakellin are levorotatory, their molecular rotations differed by more than 400 units and their long-wavelength UV bands showed Cotton effects of the opposite sign. These compounds were shown to possess the same configuration at the asymmetric centers by reacting monobromophakellin with 1 mol equiv of bromine and establishing the identity of the resulting product with dibromophakellin. Since addition of substituents to the pyrrole ring produces vast changes in chiroptic properties of

Scheme I



phakellins, it was concluded that this ring is directly linked to one of the two chiral centers of these molecules.

The mass spectra of **1**, **2**, and **3** were notable for the presence of fragment ion peaks produced by the expulsion of NH_3, HCNH, CH_2=CH_2, NH_2CN, and the pyrrole ring from M^+. The mechanisms of some of the fragmentation processes are proposed in Scheme I. The peaks at m/e 138 and 110 (doublet) shift cleanly to m/e 141, 113, and 112 in the spectrum of phakellin-d_3.[7] The elemental composition of all ions indicated in Scheme I were established by high-resolution mass measurements. The main significance of mass spectral data is that it provides strong evidence for the presence of a guanidine moiety and structural unit **7** in phakellins.

Partial structures **5** and **7** account for all the atoms of phakellins. These structural units were combined to form a tetracyclic skeleton, and dibromophakellin, monobromophakellin, and phakellin were considered to possess structures **1**, **2**, and **3**, respectively. In these structures, the guanidine double bond was placed at the endocyclic 8,9 position to explain the deshielding of the pyrrolidine proton H_a upon conversion of phakellins to their hydrochlorides. With the double bond at this position, **1**, **2**, and **3** will protonate at N(9). The deshielding of H_a in phakellin hydrochlorides may then be attributed to the reduction in the long-range shielding effect of the lone pair associated with N(9).

The ^{13}C NMR spectrum of monobromophakellin hydrochloride, determined in Me_2SO-d_6, was consistent with the general structure proposed for phakellins. The spectrum showed peaks at δ 156.21 [C(15)], 154.5 [C(8)], 123.81 [C(4)], 122.31 [C(3)], 113.51 [C(5)], 98.29 [C(2)], 82.19 [C(10)], 68.23 [C(6)], 45.24 [C(13)], 37.73 [C(11)], and 19.51 [C(12)]. The chemical shift of C(6) is consistent with the view that this carbon atom is directly linked to two electron-withdrawing groups, the guanidine moiety and the pyrrole nitrogen.

Confirmatory evidence for the tetracyclic skeleton of phakellins was provided by the single crystal x-ray analysis of monoacetyldibromophakellin **4**.[8] The structure was solved by conventional heavy-atom methods. The ORTEP diagram of one molecule of **4** as viewed along the y axis is shown in Figure 1. The coordinates and temperature factors of all atoms found in the electron-density maps, together with their estimated standard deviations (except for the temperature factors in hydrogens), are listed in Table I (Supplementary Material). The bond distances and bond angles derived from this study are compiled in Table II (Supplementary Material). The distances have an esd of the order of 0.01 Å, and the angles of about 0.5°. The equations for the least-squares planes of important structural moieties are given in Table III (Supplementary Material).

The skeleton of phakellins as revealed by the x-ray analysis of **4** is in complete accord with the one proposed on the basis of spectroscopic data and chemical studies. The crystallographic data indicate that the atoms defining the pyrrole ring

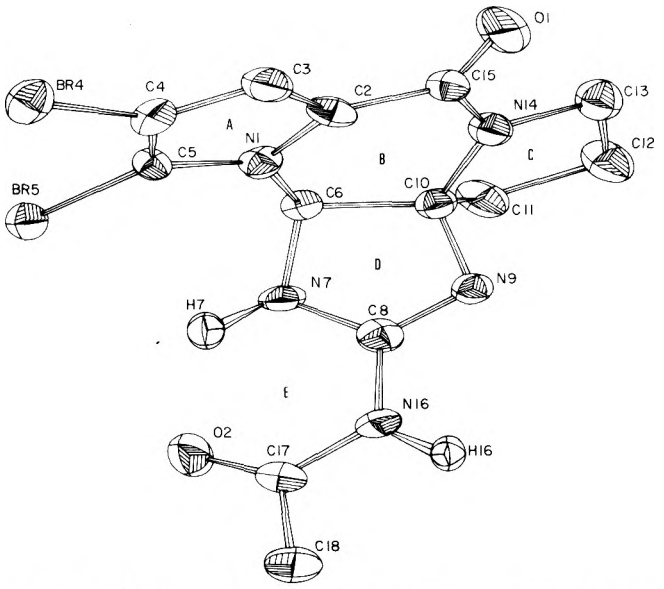


Figure 1. Perspective ORTEP diagram of monoacetyldibromophakellin. The thermal vibration ellipsoids are shown on a 50% probability scale. All hydrogens except H(7) were omitted. The inclusion of H(7) illustrates the hydrogen bonding resulting in the formation of ring E.

of phakellins are coplanar with maximum deviation from the least-squares plane of 0.008 Å. The six-membered ring B is markedly nonplanar as is the pyrrolidine ring C (Table III, Supplementary Material). In general, bond distances and bond angles of these rings agree very well with the accepted values.

The acetylaminoimidazoline ring D has a twisted conformation. An appreciation of the extent of twist can be obtained by examining the displacements of the five atoms of the ring from the least-squares plane. Whereas atoms N(7) and C(10) are located at a distance of 0.140 and 0.152 Å below the ring plane, the atoms C(6), C(8) and N(9) lie above the average plane and are displaced from it by 0.175, 0.037, and 0.079 Å, respectively. The guanidine moiety of ring D is planar; only the central carbon atom of the CN_3 skeleton deviates slightly (0.018 Å) from the least-squares plane (Table III, Supplementary Material). The bonds linking the guanidine moiety to ring B make a dihedral angle of about 29° with each other.

The C(8)–N(9) bond distance of the imidazoline ring is 1.287 Å, which is in close agreement with C=N distance of 1.27 Å reported in the literature.[9] The C(8)–N(7) and C(8)–N(16) bond lengths of 1.368 and 1.39 Å are within the range expected for a carbon–nitrogen single bond adjacent to a double bond.[9] These parameters suggest that in **4** the guanidine double bond is present at the 8,9 position. It is significant to note that phakellins are the only cyclic guanidines which have a double bond at the endocyclic position and which, upon treatment with acetic anhydride, give derivatives of the endocyclic acetylamino type. All other cyclic guanidines have been found to retain the double bond at the exocyclic position and their acetyl derivatives exist in the exocyclic acetylamino form.[10]

In the acetamide group (CH_3COHN) of **4** the N(16)–C(17) and C(17)–O bond lengths are 1.38 and 1.21 Å. These values are similar to those found in acetamide and *N*-methylacetamide.[9] It seems, therefore, that in the acetylaminoguanidine system of **4** the normal amide resonance which imparts a considerable amount of double-bond character to CN bonds and a single-bond character to CO bonds is not suppressed by the opposite mesomeric effect in the imine group.[11]

The crystal structure of **4** revealed the presence of only two hydrogen bonds, one intramolecular and the other intermolecular. The intramolecular hydrogen bond is between the oxygen atom of the acetyl carbonyl and the NH at position 7 (Figure 1; see also structure **4**). Because of this internal H bond, the hydrogen atom H(7) finds itself a member of the planar six-membered ring E. The intermolecular hydrogen bond is between the carbonyl oxygen of ring B and N(16)–H. The atoms participating in the intermolecular hydrogen bond are 2.6-Å apart and the N(16)–H. . .0 angle is 160°. Apart from this, there are no other short contacts in the crystal structure of **4**.

With the availability of a complete x-ray analysis of **4**, the structures assigned to phakellins may be considered to have been fully established. However, an explanation for the low basicity of the guanidine group of these molecules is needed.

In order to explain the anomaly in the base strength of phakellins, it is essential to first consider the reason for the high basicity of guanidines. Guanidines are strong bases because they protonate at the imine nitrogen to give cations which have a resonance-stabilized structure **6**.[12] The extra resonance stabilization of the ions has been estimated to be of the magnitude of 6–8 kcal/mol which would increase the base strength of guanidines very greatly. Resonance in the guanidinium ion has been confirmed by IR spectroscopy, Raman spectroscopy, and x-ray crystallography.[13]

The evidence presented below suggests that phakellins also protonate at the imine nitrogen [N(9)] of the guanidine moiety, but resonance in the resulting cations (hereafter called phakellinium cations) is inhibited. The inhibition of resonance will reduce the tendency of the imine nitrogen of the guanidine groups of **1**, **2**, and **3** to add a proton and in consequence these compounds would behave as weak bases.

Information on the site of protonation of phakellins was obtained by analyzing the NMR spectra of phakellinium cations produced by dissolving **1**, **2**, and **3** in trifluoroacetic acid. In these spectra the guanidinium protons exhibit three singlets in the 7–8.7-ppm region. From low to high field the singlets integrate for 1 H, 1 H and 2 H, respectively. This spectral data is consistent with the protonation of phakellins at N(9) to give cation **8**. The lowest field singlet is assigned to N(7)–H because this resonance is shielded by the anisotropy of the bromine atom present at the 5 position of 4,5-dibromophakellinium cation. It is noteworthy that the vicinal protons of the system H–N(7)–C(6)–Hg do not exhibit spin–spin interactions which is consistent with the dihedral angle of ~90° between N(7)–H and C(6)–Hg bonds. If protonation of phakellins had taken place at N(7), then the dihedral angle between C(6)–Hg and N(7)–H′ [H′ is the second proton on N(7)] would be about 10°. In this case, the resonances of Hg and N(7)–H′ should appear as doublets. Since none of the resonances assigned to the guanidinium protons and Hg showed this feature, phakellins were considered not to protonate at N(7). The degree of charge delocalization in the guanidinium system of phakellinium cations was determined by comparing the IR spectra of guanidine hydrochlorides with those of phakellin hydrochlorides and by studying the exchange of the guanidinium protons in phakellin hydrochlorides with D_2O.

The IR spectra of several guanidine hydrochlorides have been reported in the literature.[14] The data reveal that when a guanidino group protonates the characteristic C=N absorbtion vanishes (due to resonance) and is replaced by two bands in the 1700–1580 cm^{-1} region, which correspond to the antisymmetrical vibrations of the carbon–nitrogen bonds within the guanidinium group. The positive charge on the nitrogen atoms of a resonance-stabilized guanidinium cation is appreciably smaller than in ammonium ions. Consequently,

the NH-stretching modes in the IR spectra of guanidine hydrochlorides occur above 3200 cm^{-1} (i.e. in the region of free amines) rather than below 3200 cm^{-1} where typical amine hydrochlorides normally absorb.

The IR spectra of phakellin hydrochlorides displayed a broad band stretching from 3500 to 2900 cm^{-1} (Figure 2), indicating that in cations the positive charge is not evenly distributed over all the atoms of the CN_3 skeleton. The 1700–1580-cm^{-1} region of the spectra showed one band around 1650 cm^{-1} and a second around 1695 cm^{-1}. The former band is due to the absorption by the amide carbonyl. Since there is no absorption around 1595 cm^{-1}, the band at 1695 cm^{-1} is assigned to the absorption by the C=N group which apparently does not vanish when phakellins are protonated. In the IR spectra of phakellins, the C=N absorption occurs around 1670 cm^{-1}. The increase in C=N stretching frequency upon passing from phakelline to phakellin hydrochlorides suggests that in cations most of the positive charge resides on the imine nitrogen.

In the NMR spectrum of dibromophakellin hydrochloride, the guanidinium protons give two broad bands centered at δ 9.8 [2 H, C=NH and N(7)-H] and 8.2 (2 H, C-NH_2). When the spectrum was recorded immediately after the addition of 1 equiv of D_2O, the 9.8-ppm band was found to have broadened considerably and partially merged with the 8.2-ppm band. The combined intensity of the two bands corresponded to three protons. Addition of 2 equiv of D_2O made the 9.8-ppm band disappear completely within 10 min. The 8.2-ppm band did not start broadening and diminishing in intensity until a total of 6 equiv of D_2O had been added. In fact, 10 equiv of D_2O was needed to make this band disappear completely in 20 min. Assuming exchange rates of protons reflect charge distribution in the CN_3 skeleton, then the NH_2 group of the cations may be considered to bear little, if any, positive charge. This conclusion appears to be valid when it is realized that the in the phakellinium skeleton the NH_2 group is least hindered, but its protons exchange last upon titration with D_2O.

Although the acetyl carbonyl of **4** can conjugate strongly with an exocyclic double bond, this compound could not be converted to the acetylimino form by reacting with an acid or a base. This observation also suggests that the guanidino group of phakellins has very little tendency to develop a C=N^+ character at the 8,16 position.

The evidence for the presence of some positive charge on N(7) of cations is provided by the large downfield shift (0.5–0.6 ppm) of Hg upon protonation of **1**, **2**, and **3**. If during protonation the guanidinium double had entirely shifted to the 7,8 position, then the resonance of Hg would have been deshielded by 1.5–1.8 ppm (1–1.3 ppm for the double bond plus 0.5 ppm for the positive charge). Based on this assumption, a downfield shift of 0.5 ppm in the resonance of Hg should correspond to about 35% imminium character at the 7,8 position of phakellinium cations.

The data presented above suggests that the phakellinium cations should be represented by a structure to which the three canonical forms **8a**, **8b**, and **8c** make contributions in the following order: **8a** > **8b** ≫ **8c**. Hence, resonance in phakellinium cations is inhibited. Since the guanidine moiety of phakellins is planar, the inhibition of resonance in cations will have to be attributed to some other structural features of the phakellinium skeleton.

It was pointed out earlier that the imidazoline ring (ring D) of phakellins has a twisted conformation, because it is fused to the chair-shaped ring B via two bonds which are skew (see structure **9**). Inspection of the molecular models indicated that ring D cannot be made planar without introducing severe conformational strains in ring B. It may then be argued that perhaps it is the twisted shape of the imidazoline ring which inhibits resonance in phakellinium cations. The mechanism

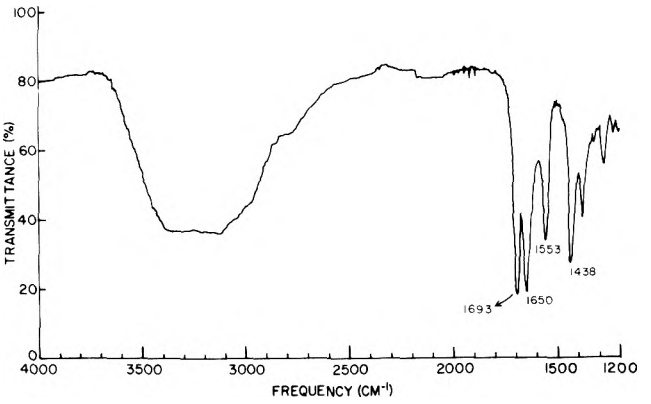


Figure 2. The 4000–1200-cm^{-1} region of the IR spectrum of dibromophakellin hydrochloride determined in KBr.

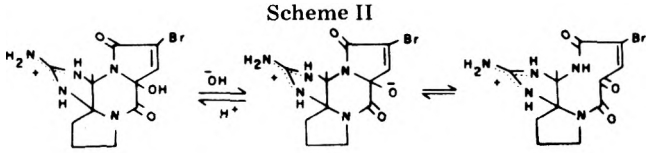
by which the resonance could have been inhibited may be visualized by considering the formation of the guanidinium cation in terms of molecular orbital description. Protonation of the imine nitrogen of a guanidino group first gives a cation which has a positive charge localized on the carbon atom, and the three nitrogen atoms exhibit pyramidal arrangement of valencies.[13] In this species,[13,14] the axis of the p-type lone pairs on the nitrogen atoms would be oriented in a direction not parallel to the vacant orbital of the carbon atom considered as C^+. For resonance to take place, each nitrogen atom of this ion will have to change from pyramidal arrangement of valencies to the planar ones. In the case of phakellinium cations, a simultaneous change in the hybridization of all three nitrogen atoms followed by equal interaction of the three lone pairs of electrons with the vacant p orbital of the central carbon atom may require the imidazoline ring to be planar. Since this ring cannot become planar, the sequence of events leading to resonance will be suppressed and the imine nitrogen of phakellins will exhibit reduced tendency to add a proton. One way to test this hypothesis would be to convert the tetracyclic skeleton of phakellins into a structure in which the imidazoline ring is planar. If the explanation offered for the inhibition of resonance in phakellinium cations is correct, then the guanidine moiety of the transformation product should be highly basic, and upon protonation this functionality should give a resonance-stabilized cation.

Oxidation of dibromophakellin with dilute nitric acid gave a compound ($C_{11}H_{12}N_5O_3Br \cdot HNO_3 \cdot H_2O$) to which structure **10** was assigned on the basis of spectroscopic data and single crystal x-ray analysis.[18] Molecular models revealed that in **10** the six-membered ring is a boat with a planar imidazoline ring strainlessly fused to the eclipsed bonds at the side of the boat. Thus, structure **10** has all the features needed for verifying the explanation offered for the inhibition of resonance in phakellinium cations.

In the IR spectrum of **10** the NH-stretching frequencies occurred above 3200 cm^{-1}, and the 1700–1580-cm^{-1} region contained two bonds (1695 and 1600 cm^{-1}) due to the antisymmetric vibrations of the CN bonds of a resonance-stabilized disubstituted guanidium cation. Thus, unlike the guanidinium group of phakellinium cations, the guanidinium group of **10** has a resonance-stabilized structure.

Potentiometric titrations of **10** revealed that this compound is a monoacidic base of pK_a 7.9. If this pK_a is due to the deprotonation of a guanidinium group, then upon treatment of **10** with sodium hydroxide the corresponding free base should be liberated. When 0.01 N NaOH was added to the aqueous suspension of **10**, a clear solution was obtained. Lyophilization of the solution gave a product which was crystallized from a 90% methanol–water mixture. The results of several combustion analyses indicated that the crystallized material is a

Scheme II



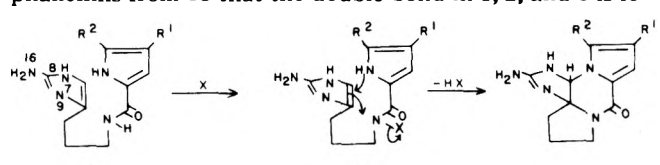
12

free base ($C_{11}H_{12}N_5O_3Br \cdot 2\text{-}3H_2O$) which retains variable amounts of moisture very tenaciously. The 1740–1630-cm^{-1} region of the IR spectrum of the free base showed a broad band with shoulders at 1720, 1690, 1665, and 1640 cm^{-1}. In addition, the spectrum showed peaks at 1600 and 1570 cm^{-1}. The most significant point which emerges from this data is that those bands in the IR spectrum of **10** which must be associated with the guanidinium system appear unchanged in the free base. This observation suggests that the deprotonation of **10** upon treatment with a base takes place at a site other than the guanidinium group. It is proposed that the pKa value of **10** as determined by potentiometric titrations represents the deprotonation of the hydroxyl group and formation of ionic species shown in Scheme II.

Reactions of **10** or **12** with dimethyl sulfate or methyl iodide failed to give the corresponding O-methyl derivative. Consequently, the normal basic function of **10** could not be masked to determine the exact pKa value of the guanidinium group. Nevertheless, the indirect evidence presented above clearly suggests that the guanidinium group of **10** is highly basic and this group upon protonation gives a resonance-stabilized cation. From this the conclusion would follow that once the imidazoline ring of phakellins is made planar then the guanidine moiety of this ring behaves like normal guanidine derivatives. The explanation offered for the low basicities of phakellins, therefore, appears to be correct.

Reaction of dibromophakellin with dilute HCl (10–20%) at 100 °C for 1 h gave a mixture which could not be resolved into its components by chromatography over Sephadex G-10. Repeated crystallization of the mixture from water gave a product which showed a single spot on silica gel plates in a variety of solvent systems. Microanalysis and mass spectrometry (M^+ at 387, 389, and 391; $C_{11}H_{11}N_5OBr_2$) indicated that this compound is a hydrochloride of an organic base isomeric with dibromophakellin. Structure **11** is assigned to this compound on the basis of IR, UV, and NMR spectral data. The reaction of dibromophakellin with hydrochloric acid proceeds in the direction of **11** because cleavage of the N(9)–C(10) bond removes conformational strains in the phakellinium cation.

Dihydrooroidin **13** and phakellins appear to be biogenetically related.[21] Perhaps it is because of the biosynthesis of phakellins from **13** that the double bond in **1**, **2**, and **3** is located at the 8,9 position. Once the tetracyclic skeleton has been formed then migration of the double bond to the exocyclic position will involve a transition state which requires the imidazoline ring to be planar. Since this ring cannot become planar, the guanidine double bond in phakellins and their derivatives is forever locked at the 8,9 position.



13 14

X = Leaving group

In conclusion, it may be stated that the low basicities of phakellins are explainable in terms of I-strain concepts.[15] Theoretically, the basicity of a cyclic guanidine derivative will fall off rapidly as the four atoms of the CN_3 skeleton depart from planarity and/or as the conformational strains in the ring inhibit the nitrogen atoms of the CN_3 skeleton to change from the pyramidal configuration of valencies to planar ones. Since in phakellins the CN_3 skeleton is planar, the lowering of the pKa value of the guanidine group of these molecules by as much as 6 pKa units may be solely due to the twisted conformation of the imidazoline ring. A rigorous test of the adequacy of this view would require synthesis of the O-methyl derivative of **10** and determination of the exact pKa of the guanidinium group. Until this is accomplished, the explanation offered for the low basicities of phakellins may be considered to be only partially substantiated. This is especially so when it is realized that a certain amount of hindrance to the protonation of phakellins may also come from the unfavorable interaction between the hydrogen atom C(11)–H_f and the proton to be attached to N(9). If the pKa of the guanidinium group of **10** turns out to be greater than that of phakellins but less than that of other guanidine derivatives, then the repulsion term arising from the nonbonded interaction between the hydrogen atoms identified above may also have to be considered.[22]

Experimental Section

Melting points are corrected. Elemental analyses were done by Alfred Bernhardt Microanalytical Laboratories, West Germany. The UV spectra were recorded with a Beckman Model DK-2A ratio recording spectrophotometer. The IR spectra were recorded on a Perkin-Elmer 337 spectrometer. The NMR spectra were recorded on a Varian HR 220-MHz NMR spectrometer.

Dibromophakellin Hydrochloride. The wet sponge (1 kg) and methanol (3 L) were homogenized in a blender to give a fine slurry. After keeping for 48 h at room temperature, the slurry was filtered and the residue extracted twice more with methanol. The methanol from the combined extracts was removed under reduced pressure and the residue was stirred with 400 mL of water for 1 h. The suspension was filtered and the aqueous filtrate was first extracted with three 200-mL portions of ethyl acetate and then four times with water-saturated n-butanol, using 200 mL of the solvent each time. The butanol extracts were combined and concentrated under reduced pressure to yield a yellow residue (~12 g). A portion (1.0 g) of this residue was dissolved in a minimum amount of water, and the clear solution (filtered if necessary) was chromatographed on 100 g of Sephadex G-10, packed in a 1 in. i.d. column. By eluting the column with water, 20 25-mL fractions were collected. The fractions (12–15) having an absorbtion maxima at 270–280 and 230–240 nm were combined and lyophilized. The lyophilized material (100 mg) was rechromatographed on 100 g of Sephadex G-10. Elution with water gave fractions which showed UV maxima at 278 and 233 nm. These fractions were combined and freeze-dried to give 85 mg of dibromophakellin hydrochloride. Crystallization from methanol or water gave needles: mp 220–221 °C; $[\alpha]^{25}_D$ −205 (c 2.875, MeOH); IR (KBr) 3400–3100, 3100–2600, 1693, 1650, 1553, 1438, 1375, 970 and 740 cm^{-1}; UV (MeOH) 282 (ϵ 9138) and 234 (ϵ 9333). The CD curve showed maxima at 283 ($\Delta\epsilon$ −3.61) and 2 nm ($\Delta\epsilon$ −8.03) and the onset of a third much stronger negative cotton effect with maxima below 210 nm ($\Delta\epsilon$ at 210 nm = 16.06): NMR (Me_2SO-d_6) δ 9.9 (2 H, br, NH and C=NH^+), 8.37 (2 H, br, NH_2), 7.0 (1 H, s, H-3), 6.34 (1 H, s, Hg), 3.65 (1 H, q, H_a, J = 18 and 9.5 Hz), 3.43 (1 H, q, H_b, J = 18 and 9.5 Hz), 2.13–2.47 (2 H, m, H_c and H_d), 2.06 (2 H, br, H_e and H_f). In F_3AcOH, the guanidinium protons gave three singlets at δ 8.29 (1 H, NH), 8.18 (1 H, C = NH^+) and 7.11 (2 H, NH_2).

Anal. Calcd for $C_{11}H_{11}N_5OBr_2 \cdot HCl$: C, 31.02; H, 2.82; N, 16.45; Br, 37.60; Cl, 8.34. Found: C, 31.05; H, 2.84; N, 16.24; Br, 37.40; Cl, 8.28.

Dibromophakellin (1). Addition of concentrated ammonia to the aqueous solution of dibromophakellin hydrochloride gave a white precipitate which was crystallized from methanol to give pure dibromophakellin as a methanol solvate ($C_{11}H_{11}N_5OBr_2 \cdot CH_3OH$): mp 237–245 °C (dec); pKa 7.7; IR (KBr) 3400 (br), 2875, 2950, 1675, 1635, 1587, 1550, 1490, 1437, 972 and 741 cm^{-1}; UV (MeOH) 281 (ϵ 8813) and 233 nm (ϵ 8877); mass spectrum M^+ m/e 387, 389, and 391, and fragmentation patterns shown in Scheme I. The CD spectrum displayed maxima at 285 ($\Delta\epsilon$ −4.58) and 239 nm ($\Delta\epsilon$ −12.43) and the onset of another negative cotton effect with maxima below 210 nm ($\Delta\epsilon$ at 210 nm = 26.18): NMR (Me_2SO-d_6) δ 6.81 (1 H, s, H-3), 5.76 (1 H, s, Hg), 4.2 (3 H, br, NH and NH_2), 3.5 (2 H, br, 13-CH_2), 1.85–2.27 (4 H, br m, 11-CH_2 and 12-CH_2).

Anal. Calcd for $C_{11}H_{11}N_5OBr_2 \cdot CH_3OH$: C, 34.43; H, 3.2; N, 16.55;

Br, 40.54. Found: C, 34.29; H, 3.23; N, 16.68; Br, 40.40.

Monobromophakellin Hydrochloride. Monobromophakellin hydrochloride (350 mg) was isolated from the specimens of *P. flabellata* (1 kg) collected during the summer. The isolation procedure was the same as described for dibromophakellin hydrochloride. Monobromophakellin hydrochloride was crystallized from water to give white needles having mp 215–220 °C; $[\alpha]^{25}_D$ −123 (c 3.015, MeOH); IR (KBr) 3100 (br), 1695, 1550, 1475, 930, and 740 cm^{-1}; UV (MeOH) 277 nm (ϵ 5535) and 227 nm (ϵ 7135); CD (MeOH) 275 nm ($\Delta\epsilon$ +2.25), 236 nm ($\Delta\epsilon$ −10.58) and the onset of another negative Cotton effect with maxima below 210 nm ($\Delta\epsilon$ at 210 nm 16.87); NMR (Me_2SO-d_6) δ 9.87 (2 H, br, NH and C =NH^+), 8.52 (2 H, br, NH_2), 7.46 (1 H, d, H-5, $J_{5,3}$ = 1.8 Hz), 6.8 (1 H, d, H-3, $J_{3,5}$ = 1.8 Hz), 6.08 (1 H, s, Hg), 6.35 (1 H, m, H_a, J = 18 and 9.5 Hz), 3.5 (1 H, m, H_b, J = 18 and 9.5 Hz), 2.13–2.5 (2 H, m, H_c and H_d) 2.06 (2 H, br m, H_e and H_f). In TFA the guanidinium protons give three singlets at δ 8.63 (1 H, NH), 7.97 (1 H, C=NH^+) and 7.12 (2 H, NH_2).

Anal. Calcd for $C_{11}H_{12}N_5OBr$·HCl: C, 38.09; H, 3.46; N, 20.20; Br, 23.08; Cl, 10.24. Found: C, 38.23; H, 3.48; N, 19.89; Br, 23.51; Cl, 9.95.

Monobromophakellin (2). Monobromophakellin was obtained by treating the aqueous solution of the hydrochloride with concentrated ammonia. The base was crystallized from methanol to give **2** having mp 260–270 °C (dec): p*K*a 7.6; UV (MeOH) 275 (ϵ 6111) and 228 nm (ϵ 7777); IR (KBr) 3300 (br), 1650, 1620, 1590, 1550, 1480, 1420, 1117, 932, 830, 750 and 618 cm^{-1}; mass spectrum showed M^+ at *m/e* 309 and 311 and fragmentation patterns shown in Scheme I; NMR (Me_2SO-d_6) δ 7.01 (1 H, d, H-5, $J_{5,3}$ = 1.8 Hz), 6.8 (3 H, br, NH and NH_2), 6.6 (1 H, d, H-3, $J_{3,5}$ = 1.8 Hz), 5.52 (1 H, s, Hg), 3.49 (2 H, br t, 13-CH_2), 1.8–2.13 (4 H, br m, 11-CH_2 and 12-CH_2).

Bromination of 2. A solution of monobromophakellin hydrochloride (172 mg) and sodium acetate (82 mg) in glacial acetic acid (5 mL) was reacted at room temperature with 0.5 M bromine solution (1.0 mL) prepared in the same solvent. After stirring for 0.5 h, the solvent was removed under reduced pressure and the residue was dissolved in 2 mL of water. Addition of concentrated ammonia to the solution gave a white precipitate (200 mg) which was identical with **1** in all respects.

Phakellin (3). A solution of diboromophakellin hydrochloride (150 mg) and sodium acetate (100 mg) in methanol was hydrogenated at room temperature and atmospheric pressure over 10% Pd-C catalyst. After the consumption of hydrogen had ceased (1 h), the catalyst was removed by filtration and the filtrate was evaporated under nitrogen to give a white solid. This solid was dissolved in a minimum amount of water and chromatographed over a Rexyn 203 (weak base organic anion exchanger) column in the OH form. Phakellin was eluted by washing the column with water. The water was freeze-dried, and the lyophilized material (57 mg) was crystallized from water to give pure **3**: mp 280 °C (dec); UV (MeOH) 275 and 225 nm; p*K*a 8; IR (KBr), 3440, 1650, 1610, 1590, and 1550 cm^{-1}; mass spectrum M^+ at *m/e* 231.11264 calculated for $C_{11}H_{13}ON_5$ 231.11199; NMR (Me_2SO-d_6) δ 7.01 (1 H, dd, H-5, $J_{5,4}$ = 3, $J_{5,3}$ = 1.8 Hz), 6.56 (1 H, dd, H-3, $J_{3,4}$ = 4 Hz, $J_{3,5}$ = 1.8 Hz), 6.19 (1 H, dd, H-4, $J_{4,3}$ = 4, $J_{4,5}$ = 3 Hz), 5.56 (1 H, s, Hg), 4.1 (3 H, br, NH and NH_2), 3.5 (2 H, br t, 13-CH_2), 1.96 (4 H, m, 11-CH_2 and 12-CH_2). The NMR spectrum of phakellin hydrochloride in Me_2SO-d_6 showed bands at δ 8.62 (2 H, br, NH and C=NH^+), 8.03 (2 H, br, NH_2), 7.38 (H-5), 6.38 (H-4), 6.77 (H-3), 6.12 (1 H, s, Hg), 3.70 (1 H, q, H_a, *J* = 18 and 8 Hz), 3.51 (1 H, q, H_b, *J* = 18 and 8 Hz), 2.5–2.15 (2 H, m, H_c and H_d), 2.1 (2 H, br q, H_e and H_f). In F_3AcOH the guanidinium protons showed three singlets at δ 8.65 (1 NH), 8.13 (1, C=NH^+) and 7.18 (2 NH_2).

Monoacetyldibromophakellin (4). The compound was prepared by reacting **1** in pyridine with 1–3 mol of acetic anhydride for 3 h at room temperature. Normal workup followed by crystallization from methanol gave **4**: mp 245 °C (dec); $[\alpha]^{27}_D$ −221 (*c*, 3.15, methylcellosolve); UV (MeOH)[20] 282 (ϵ 8328) and 231 nm (ϵ 18 072); CD (MeOH) 285 ($\Delta\epsilon$ −4.18), 240 ($\Delta\epsilon$ −12.97), and 210 nm ($\Delta\epsilon$ −11.72); IR (KBr) 3360, 3225, 2975, 1710, 1640 (br), 1590 and 1550 cm^{-1}; mass spectrum *m/e* at 429, 431, and 433 M^+; NMR (Me_2SO-d_6) δ 6.86 (1 H, s, H-3), 5.96 (1 H, s, Hg), 4–6 (2 H, br, NH and CH_3CONH), 3.56 (2 H, br, 13-CH_2), 2.02 (7 H, 11-CH_2, 12-CH_2, and CH_3CO). Hydrochloride of **4** in MeOH-d_4 showed bands at δ 7.37 (1 H, s, H-3), 6.47 (1 H, s, Hg), 4.0 (1 H, m, H_a), 3.72 (1 H, m, H_b), 2.6 (2 H, m, H_c and H_d), 2.25 (5 H, H_e, H_f and CH_3CO–).

Anal. Calcd for $C_{13}H_{13}N_5O_2Br_2$: C, 36.13; H, 3.01; N, 16.20; Br, 37.04. Found: C, 36.33; H, 3.09, Br, 37.26.

Transformation of 1 to 10. Dilute nitric acid was prepared by adding 5 mL of water to 2 mL of 70% nitric acid. A solution of 50.0 mg of dibromophakellin in 1.5 mL of dilute nitric acid was heated at 70–75 °C for 5–10 min when evolution of NO_2 started and a white product crystallized out of solution. The white product was collected by suction and crystallized from water to give pure **10** as white needles (25 mg): mp above 300 °C; UV (H_2O) no well defined maxima above 210 nm, ϵ values at 220 and 235 nm are 16 513 and 7339, respectively; IR (KBr) 3250, 1740, 1700, 1648, 1600, and 1564 cm^{-1}; NMR (Me_2SO-d_6) δ 9.42 (br, 2 H, D_2O exchangeable), 8.0 (br, 3 H, D_2O exchangeable), 7.66 (s, 1 H, C(3)–H) 5.80 [s, 1 H, C(6)–H] 3.52–3.09 (two closely spaced multiplets, 2 H, 13-CH_2), 2.1 (br, 2 H, 11- or 12-CH_2) and 1.9 (br, 2 H, 11- or 12-CH_2). In some NMR spectra the five D_2O-exchangeable protons of **10** were found to give four singlets at δ 9.62 [1 H, N(7)–H], 9.3 [1 H, N(9)–H], 8.98 [2 H, C(8)–NH_2], and 7.88 [1 H, OH].

Anal. Calcd for $C_{11}H_{12}N_5O_3Br$·HNO_3H_2O: C, 31.20; H, 3.54; N, 19.90; Br, 18.91. Found: C, 31.23; H, 3.21; N, 20.00; Br, 19.0.

Transformation of 1 to 11. Eight milliliters of water was added to 2 mL of concentrated HCl to prepare dilute hydrochloric acid. Dibromophakellin, 100 mg, was dissolved in 5 mL of dilute HCl. The solution was heated on a boiling water bath until in the UV spectrum of an aliquot the ratio of the intensities of the 237- and 285-nm bands was 3.5 (1 h). Concentration of the reaction mixture under reduced pressure gave a solid which showed four spots on silica gel plates using methanol/acetone/diethylamine (5:5:1) as solvent. Repeated crystallization of this solid from water gave **11** as an amorphous material (16 mg): mp 155–175 °C (dec); R_f 0.21; IR (KBr) 3500–3300 (three bands), 2970, 1700, 1640 and 1590 cm^{-1}; UV (MeOH) 285 (ϵ 3872) and 237 nm (ϵ 16 266); the CD spectrum showed no maxima above 210 nm; NMR (60 MHz) 2.2 (br, 2 H), 2.9 (br q, 2 H), 4.05 (m, 2 H), 7.4 (s, 1H) and 7.9 (br, 4 H, D_2O exchangeable); mass spectrum *m/e* at 387, 389, and 391 (weak, M^+), 370, 372, and 374 (M − NH_3), 345, 347, and 349 (M − NH_2CN), 308 and 310 (M − Br), and 266 and 268 (loss of NH_2CH from M − Br).

Anal. Calcd for $C_{11}H_{11}N_5OBr_2$·HCl: C, 31.02; H, 2.82, N, 16.45; Br, 37.60; Cl, 8.34. Found: C, 30.82; H, 2.56; N, 16.38; Br, 37.52; Cl, 8.12.

Potentiometric Titrations. Analytically pure phakellins (~5 mg) were dissolved in 1.0 mL of carbon dioxide free 40% methylcellosolve–water mixture. The p*K*a values were determined by titrating the magnetically stirred solutions at room temperature with 0.01 N HCl using a Copenhagen pH meter (SDR type made in Denmark) equipped with a glass electrode, a calomel electrode, and a buret capable of delivering 0.025 mL of the titrant accurately. Dibromophakellin gave approximately the same p*K*a value in 80, 60, and 40% methylcellosolve–water mixtures. The p*K*a of **10** was determined in water by titrating with 0.011 N NaOH using a Mettler Automatic Titrator.[19]

X-Ray Crystallography of 4. The precession and Weissenberg photographs showed that the crystals of **4** are orthorhombic and belong to the space group $P2_12_12_1$ as indicated by the systematic absence of reflections *h*00 with *h* odd, 0*k*0 with *k* odd, and 00*l* with *l* odd. A crystal with dimensions 0.26 × 0.35 × 0.30 mm was mounted on a Picker four-circle automatic diffractometer with the *b* axis parallel to the θ axis of the diffractometer. The 2θ values for a number of reflections were measured; the unit cell parameters obtained from least-squares analysis of these measurements are: *a* = 15.336, *b* = 12.728, and *c* = 7.767 Å. The density calculated by assuming that there are four molecules of monoacetyldibromophakellin in the unit cell is 1.872 g cm^{-3}; the density measured by flotation in 1.885 g cm^{-3}.

The three-dimensional intensity data were collected with nickel-filtered Cu radiation using a $\theta - 2\theta$ scanning technique. Measurements were made for 1339 independent reflections in the range $4° \leq 2\theta \leq 100°$. Two standard reflections were measured after every 50 reflections to check the stability of the instrument and the stability of the crystal. The fluctuations in the intensity of standard reflections were less than 1%. Background counts of 20 s were taken at each end of the scan. The intensities were corrected for Lorenz and polarization factors and were placed on an approximate absolute scale by a constant obtained from a Wilson plot. All reflections were used including unobservable ones.[16] Corrections for absorption effects were applied because the magnitude of the linear absorption coefficient (μ = 68.18 cm^{-1}) was high.

A three-dimensional $E^2 - 1$ Patterson synthesis was computed to locate the two bromine atoms. The map showed seven peaks of sufficient densities to be Br–Br vectors. The peaks at 0.0 and ½ (intramolecular Br–Br vectors) and 0.276, 0.375, and 0.0 [vectors between Br(4) and Br(5) of molecules related by screw axis operations along *z*] suggested that the two heavy atoms have the same *x*, *y* coordinates and that these atoms are separated by ½ along *z* axis. This interpretation was consistent with the presence of remaining Br–Br vector peaks in the Patterson map.

The *x* and *y* coordinates of Br(4) and Br(5) were deduced from the

peak located at $w = 1/2$. The four peaks in the planes $\mu = 1/2$ and $v = 1/2$ gave two values for the z coordinates of Br(4). A choice between these values could not be made at this stage of the analysis because it was not possible to decide which two of the four peaks represent vectors between symmetry-related bromine atoms. The second bromine atom, Br(5), was assigned the z coordinate of $1/2$ + the z value of Br(4). The two sets of coordinates thus obtained for Br(4) and Br(5) are listed as follows; set I: Br(4) 0.1160, 0.1875, −0.1625; Br(5) 0.1160, 0.1875, 0.3375; set II: Br(4) 0.1160, 0.1875, −0.090; Br(5) 0.1160, 0.1875, 0.410.

Although calculation of structure factors with the atomic positions listed in sets I and II gave the same value (0.50) for the residual index ($R = \sum||F_o| - |F_c||/\sum|F_o|$), the electron-density maps computed from these sets of coordinates were quite different. Only the electron-density map derived from the atomic coordinates listed in set I showed features of a chemically meaningful structure. In this first three-dimensional Fourier map, the six-membered ring B, the five-membered ring D, and the four atoms of the pyrrole ring A of structure **4** were clearly discernible. Eight of the best-defined atoms were chosen as the basis of second Fourier in which all 22 nonhydrogen atoms belonging to **4** appeared distinctly. A third Fourier based on all 22 atoms gave a structure in which all atoms were well defined and no false peaks were present. The atomic coordinates were now refined and used as a basis for fourth Fourier which gave $R = 0.30$. The R was reduced to 0.13 through least-squares refinement on isotropic thermal parameters and coordinates. In these refinements the nitrogens were treated as carbons because the identity of these atoms could not be inferred from the electron-density maps. The oxygen and bromine atoms were clearly distinguishable from F_o synthesis.

The nitrogen atoms were identified as follows: All atoms, except oxygens and bromines, were assigned an atomic scattering factor of carbon and temperature factor of $B = 3.0$ Å.[2] Least-squares refinement on temperature factors showed five atoms had a value of $B \simeq 1/2$ of that of other atoms (Table IV, Supplementary Material). This suggests that the number of electrons assigned to these atoms are insufficient. Consequently, these five atoms were considered to be nitrogens. A second least-squares refinement on isotropic temperature factors and positional parameters, using the correct structure factors for C, N, O, and Br atoms, gave reasonable values of B for all atoms (Table IV) and a residual index of 0.09. changing isotropic to anisotropic temperature factors lowered the residual index to 0.056.

A difference electron-density map revealed the positions of 11 of the 13 hydrogen atoms. The H(11B) and H(12B) were not observed. Placement of 11 hydrogens and inclusion of anomalous scattering factor contributions for two bromine atoms followed by still further least-squares refinements lowered the reliability index to the current value of 0.040 for the structure. The residual index for the mirror image was 0.048. This statistically significant difference suggests[17] that the structure and not its mirror image is the correct absolute configuration. The structure of monoacetyldibromophakellin as presented in Figure 1 was now considered to be correct, and it may well be presumed that the parent alkaloid, dibromophakellin, has structure **1**.

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Supplementary Material Available. A complete listing of coordinates and structure factor amplitudes of all atoms (Table I) and the bond distances and bond angles (Table II). The least-squares planes and deviation of individual atoms from these planes (Table III) and the temperature factor refinement for the identification of nitrogen atoms (Table IV). Ordering information is given on any current masthead page.

Registry No.—**1**, 31954-96-8; **1** HCl, 63700-27-6; **2**, 31955-05-2; **2** HCl, 63700-28-7; **3**, 33051-47-7; **3** HCl, 31955-03-0; **4**, 31955-04-1; **4** HCl, 63700-29-8; **10**, 63626-31-3; **11**, 63626-32-4.

References and Notes

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(19) We express our gratitude to Mr. G. P. McTernan of Lederle Laboratories, Pearl River, N.Y. 10965, for measuring the pKa value of **10**. Mr. McTernan also determined the pKa values of **2** and **3**, using a Model E-436 Metrohm Potentiograph. His results and ours were in agreement within experimental errors.
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Disproportionation of Tetrakis(anilinomethyl)phosphonium Chloride in Ethanol

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The product of the disproportionation of tetrakis(anilinomethyl)phosphonium chloride (1) or tris(anilinomethyl)phosphine (3) in ethanol has been identified as 1,1′-diphenyl-1,1′-diaza-3,3′-biphosphetidine (2). The proton NMR spectrum of 2 exhibits an ABX_2 splitting pattern with some unusual features.

The reactions of tetrakis(hydroxymethyl)phosphonium chloride (Thpc) with primary or secondary amines are of interest because they provide an insight into the chemistry of flame-retardant cotton finishes prepared from Thpc and polyfunctional nitrogen compounds such as ammonia, urea, or melamine.[2] The title compound (1), a product of the reaction of Thpc and aniline,[3] is a white, crystalline solid, mp 129–130 °C. With care, it can be recrystallized from organic solvents such as methanol, acetic acid, tetrahydrofuran, or chloroform, but upon attempted recrystallization from ethanol the product that separates is a high-melting white, crystalline solid (2), mp 170–171 °C. Recrystallization from methanol, if not performed rapidly, also yields 2 instead of 1. The isolation and characterization of 2 is the subject of this paper.

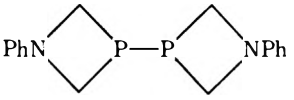
Elemental analysis of 2 establishes its empirical formula as C_8H_9NP. The IR spectrum shows aromatic C=C absorption but no NH. The proton NMR spectrum shows a well-separated pair of multiplets in the Ph and CH_2 regions in a ratio of 5 to 4. Together, these data suggest the composition $PhN(CH_2)_2P$.

The mass spectrum of 2 shows the fragmentation pattern characteristic of methyleneaniline derivatives,[4,5] with *m/e* 91 (PhN^+), 93 ($PhNH_2^{\cdot+}$), 104 ($PhN{=}CH^+$), and 105 ($PhN{=}CH_2^{\cdot+}$) as abundant ions. In addition, strong lines appear at 119 [$PhN(CH_2)_2^+$], 120 [$PhNH(CH_2)_2^+$], and 300 {$[PhN(CH_2)_2P]_2^{\cdot+}$}. The strong parent ion at 300, coupled with a correct (P + 1)/P ratio,[6] establishes the compound to be a dimer of molecular formula $C_{16}H_{18}N_2P_2$ and probable composition $[PhN(CH_2)_2P]_2$.

The methylene multiplet in the 60-MHz NMR spectrum of 2 has the appearance of a singlet superimposed on an ABX octet (Figure 1). The singlet, however, shifts upfield toward the center of the multiplet when the field strength is increased from 60 to 100 MHz and is consequently not independent of the octet. By inspection, the separation of the singlet from the downfield AB quartet is found to be identical with the separation of the two AB quartets (7.25 Hz). The ratio of the intensities of the three subspectra approaches 1:2:1. These spacings and relative intensities are characteristic of ABX_2 spectra[7] and, in fact, analysis of the data using the appropriate equations for the ABX_2 system,[8] treating the singlet as an AB quartet of 0:2:2:0 intensity, provides a line spectrum that shows a good fit to the observed spectrum (Figure 1).

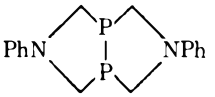
For confirmation, the NMR spectrum of 2 was examined at 100 MHz. This is a deceptively simple spectrum of five or possibly six lines (Figures 2 and 3). Calculation of the transition energies and relative intensities, using the 60-MHz data, provides a theoretical line spectrum that shows a good fit to the observed spectrum. The chemical shifts derived from this analysis are $\delta_A = 3.74$ and $\delta_B = 3.53$ ppm, and the coupling constants are $J_{AB} = 12.5$, $J_{AX} = 0.8$, and $J_{BX} = 13.7$ Hz. Details of the analysis are given in the supplementary section of this paper.

There are three possible structures that satisfy the composition $[PhN(CH_2)_2P]_2$. The first is 1,1′-diphenyl-1,1′-diaza-3,3′-biphosphetidine, consisting of two four-membered rings linked through the phosphorus atoms.



Tetramethylbiphosphine, a related acyclic compound, exhibits an A_3XX' spectrum whose parameters are $^2J_{PH} = 2.90$, $^3J_{PH} = 11.25$, and $J_{PP} = -179.7$ Hz.[9] 1,1′-Biphospholane is known[10] but not its NMR parameters. Assuming rapid nitrogen inversion and ring puckering but slow phosphorus inversion (assumptions valid for related six-membered ring systems),[3,11] the ring structure of the biphosphetidine imposes a constraint on the molecule such that the four outer-face hydrogen atoms are shielded constantly by the lone-pair electrons of the adjacent phosphorus atom. The four inner-face hydrogen atoms, owing to free rotation about the P–P bond, are shielded intermittently by the lone-pair electrons of the other phosphorus atom. The four outer-face hydrogen atoms (and, likewise, the four inner-face hydrogen atoms) are magnetically equivalent, since each has a counterpart in the other ring that is either identical to it or is a mirror image that is indistinguishable from it by NMR. A priori, the spectrum should exhibit an ABXX′ splitting pattern, where A and B are the outer- and inner-face hydrogen atoms, respectively, and X and X′ are the phosphorus atoms. The phosphorus atoms, though chemically equivalent, are not magnetically equivalent unless they are equally coupled to A and B.

The other two possible structures are the cis and trans isomers of 2,5-diphenyl-2,5-diaza-3a,6a-diphosphabicyclo[3.3.0]octane, consisting of two five-membered rings fused either cis or trans through the phosphorus atoms.



Very few ring systems of this type are known. Bicyclo[3.3.0]-octane itself exists in both cis and trans forms, the latter showing evidence of substantial strain.[12] Models of the two phosphorus compounds show severe distortion owing to the unequal P–P, P–C, and C–N bond lengths. It seems unlikely that either would possess sufficient symmetry to exhibit a simple ABXX′ splitting pattern.

This leaves the biphosphetidine structure as the only option. The criteria for obtaining ABX_2 spectra from compounds that contain nonequivalent X groups have been discussed by Riggs.[13] If the X groups have the same chemical shift as in the ABXX′ case, they need not be equally coupled to A and B provided that the sums of the coupling constants are identical.[14] In our case, this means that $^2J_{PH_A}$ and $^2J_{PH_B}$ are not necessarily equal to $^3J_{PH_A}$ and $^3J_{PH_B}$, respectively, provided that the sums are related as follows:

$$^2J_{PH_A} + {}^2J_{PH_B} = {}^3J_{PH_A} + {}^3J_{PH_B} = 14.50 \text{ Hz}$$

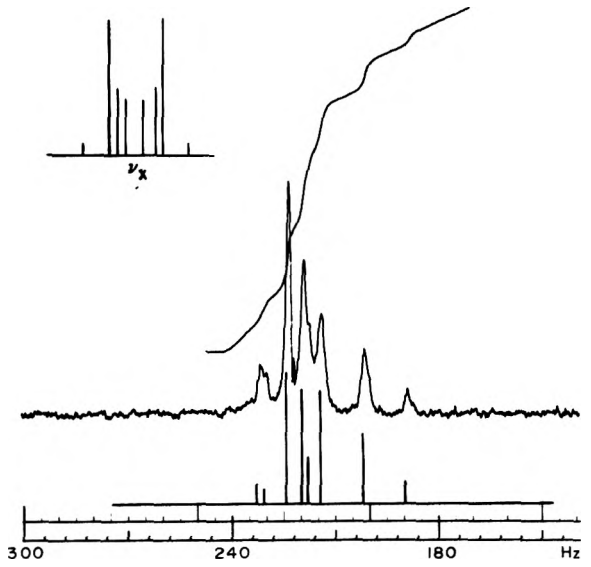


Figure 1. Methylene segment of the 60-MHz proton-NMR spectrum of **2** in $CDCl_3$. Scale: 1 cm = 10 Hz (h) or 0.80 H (v). Inset: Predicted ^{31}P-NMR spectrum.

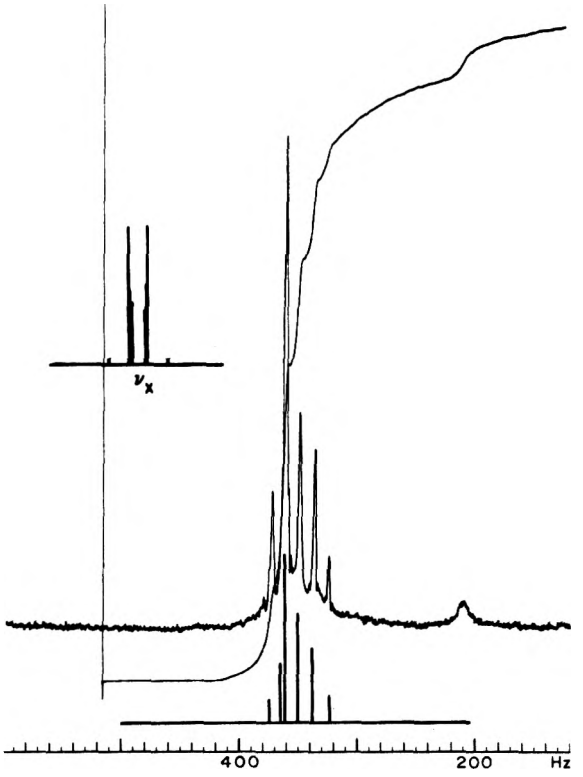


Figure 2. Methylene segment of the 100-MHz proton-NMR spectrum of **2** in $CDCl_3$. Scale: 1 cm = 30 Hz (h) or 0.46 H (v). Inset: Predicted ^{31}P-NMR spectrum.

The biphosphetidine structure is therefore compatible with the NMR spectrum of **2**, even though the phosphorus atoms do not appear to be magnetically equivalent.

The biphosphetidine **2** can also be prepared from tris(anilinomethyl)phosphine (**3**) but not from its methylene-bridged derivative, 5-anilinomethyl-1,3-diphenyl-1,3,5-diazaphosphorinane (**4**). Forcing conditions are required for **3**, and the yields are lower. Attempts to prepare oxide or sulfide derivatives of **2** were unsuccessful.

The disproportionation of **1** and **3** to substances richer and poorer in NH seems to be related to the disproportionation of *N,N'*-diphenylmethanediamine to aniline and hexahydro-1,3,5-triphenyl-*s*-triazine,[15] though obviously more deep-seated changes are involved. Equations 1 and 2, which satisfy the stoichiometry of the disproportionation, suggest that *N*-methylaniline and the triazine precursor, *N*-methyleneaniline, are formed in addition to **2** and aniline.

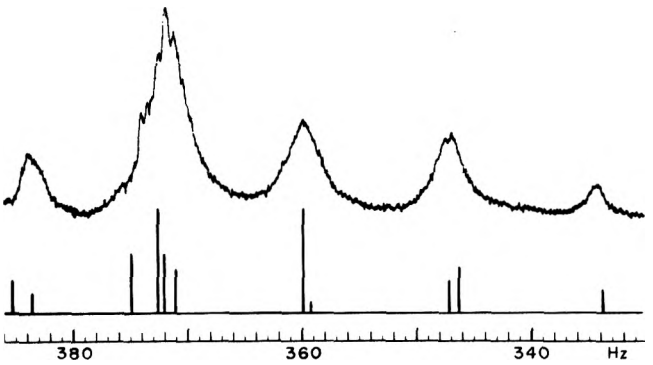
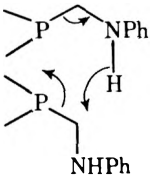


Figure 3. Methylene segment of Figure 2 expanded tenfold. Scale: 1 cm = 3 Hz (h) or 0.46 H (v).

$$2(PhNHCH_2)_4PCl \rightarrow [PhN(CH_2)_2P]_2$$
1 **2**
$$+ 3PhN{=}CH_2 + PhNHCH_3 + 2PhNH_2{\cdot}HCl \quad (1)$$

$$2(PhNHCH_2)_3P \rightarrow [PhN(CH_2)_2P]_2$$
3 **2**
$$+ PhN{=}CH_2 + PhNHCH_3 + 2PhNH_2 \quad (2)$$

These by-products could be formed as follows:



Further investigation is needed to identify the by-products and to determine to what extent, if any, the solvent participates in the disproportionation.

Experimental Section

Melting points are corrected. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.[16] Infrared spectra (IR) were taken on a Perkin-Elmer 137B spectrophotometer with NaCl optics. Nuclear magnetic resonance spectra (^1H NMR) were taken on a Varian A-60 spectrometer at 60 MHz or a JEOLCO MH-100 spectrometer at 100 MHz, with tetramethylsilane as an internal standard. Mass spectra were taken on a CEC 21-110B spectrometer at 70 eV by direct probe insertion.

1,1'-Diphenyl-1,1'-diaza-3,3'-biphosphetidine (2). A. From 1. The phosphonium salt **1**[3] (2.00 g, 4.07 mmol) was slurried in ethanol (20 mL) and heated at reflux until it dissolved. The solution was allowed to cool and was filtered, giving 0.25 g (41.0%) of **2**, mp 167–168 °C. After stripping, the filtrate yielded 1.35 g of pale yellow oil: $n^{20}D$ 1.6618; IR (neat) 3400 (vs, NH) cm^{-1}. One recrystallization of the solid from ethanol afforded pure **2**: mp 170–171 °C; IR (Nujol) 682 (s, Ph), 719 (w), 740 (m, sh), 749 (vs, Ph), 777 (w), 857 (m), 913 (w), 956 (w), 989 (w), 1030 (w), 1130 (w), 1165 (w), 1195 (s), 1250 (m, CN_{arom}), 1300 (vs, CN_{arom}), 1435 (vs), 1495 (vs, $C{=}C_{arom}$), 1560 (w), 1600 (vs, $C{=}C_{arom}$) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.1–3.8 (m, 4 H, CH_2) and 6.7–7.3 (m, 5 H, Ph); mass spectrum *m/e* (% rel abundance, ion fragment) 301 (10, P + 1), 300 (55, P), 223 (3), 208 (5), 207 (7), 195 (8, P − $PhN{=}CH_2$), 194 (9), 181 (3), 180 (4), 179 (3), 162 (8), 150 (5), 133 (7), 132 (16), 125 (4), 121 (10), 120 (83, $PhNH(CH_2)_2^+$), 119 (55, $PhN(CH_2)_2^+$), 118 (7), 107 (7), 106 (20, $PhNH{=}CH_2^+$), 105 (39, $PhN{=}CH_2^+$), 104 (31, $PhN{\equiv}CH^+$), 94 (4), 93 (56, $PhNH_2^+$), 92 (13, $PhNH^+$), 91 (100, PhN^+), 78 (7), 77 (37, Ph^+), 66 (13, $C_5H_6^+$), 65 (12, $C_5H_5^+$), 51 (15, $C_4H_3^+$). Anal. Calcd for C_8H_9NP: C, 64.00; H, 6.04; N, 9.33; P, 20.63; mol wt, 300 (dimer). Found: C, 63.99; H, 5.85; N, 9.02; P, 20.50; mol wt (osmometric, in $CHCl_3$), 346.

The biphosphetidine **2** is soluble in chloroform and acetone and insoluble in water. It dissolves in carbon disulfide without giving the

red color characteristic of tertiary phosphines[17] but decolorizes iodine instantly[18].

If the solvent for recrystallization is methanol, the outcome depends on the severity of the treatment. When the phosphonium salt 1 (10.00 g) was gently warmed with methanol (50 mL) until the solid just dissolved and the solution was cooled rapidly and filtered, part of 1 (3.20 g, 32.0%) was recovered unchanged (mp, IR). The filtrate, concentrated to half its volume, yielded 0.16 g (5.2%) of 2. When 1 (3.00 g) was recrystallized from hot methanol (25 mL) as described above for ethanol, the first product to separate was 2 (0.15 g, 16.4%), none of 1 being recovered. When a solution of 1 in methanol was heated for 30 min at reflux prior to workup, neither substance could be isolated from the gummy mass that resulted.

B. From 3. The tertiary phosphine 3 (2.000 g, 5.15 mmol)[3] was heated in ethanol (50 mL) at reflux for 4 h under nitrogen. At first the 3 dissolved, but within 30 min white solids started to separate and were removed from time to time as the reaction proceeded, giving fractions of mp 95–97 °C dec (0.200 g), 128–148 °C (0.114 g), and 160–163 °C (0.058 g). The third fraction was identified (IR, NMR) as 2 (7.5%). The residue was a pale yellow oil: 1.260 g; $n^{20}D$ 1.6387; IR (neat) 3400 (vs, NH) cm^{-1}.

Pure 2, free of solid by-products, was obtained in 2.1% yield by stirring a slurry of 3 (0.500 g, 1.29 mmol) in ethanol (20 mL) in a stoppered flask for 16 h at 25 °C. The yield of 2 was improved to 17.2% when the reaction was carried out in the presence of 0.039 g (1.29 mmol) of dissolved paraformaldehyde in an abortive attempt to prepare the methylene-bridged derivative 4.

Acknowledgments. We thank Mr. Gordon J. Boudreaux and Mr. James B. Stanley, both of this Center, for the NMR and mass spectra.

Registry No.—1, 34885-67-1; 2, 63731-20-4; 3, 34885-71-7; ethanol, 64-17-5.

Supplementary Material Available: The ABX_2 analysis (5 pages). Ordering information is given on any current masthead page.

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Photosensitized Dimerization of Methylcytosine Derivatives

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Irradiation of cytosine and its 1-methyl, 4-methyl, 1,4-dimethyl, 4,4-dimethyl, and 1,4,4-trimethyl derivatives in acetone or acetone–water solutions with 313-nm light produces the corresponding derivatives of cyclobutyldicytosine (cytosine dimer, Cyt<>Cyt) with yields ranging from 14 to 86%. Under mild acid conditions, Cyt<>Cyt derivatives can be converted to the corresponding isomers of uracil dimer (Ura<>Ura) by deamination. This allows the stereoconfigurations of various Cyt<>Cyt to be determined by comparing with the corresponding isomers of Ura<>Ura and Me^1Ura<>Me^1Ura. Except for Cyt, which forms (t,a) Cyt<>Cyt in addition to the (t,s) isomer, the others yield only the (t,s) isomer. In F_3CCOOH, (t,a) Cyt<>Cyt is decomposed to Cyt, while syn dimers are stable. These Cyt<>Cyt derivatives display the AB or AA'BB' patterns in the NMR spectra, determined in F_3CCOOD at −2 °C. The mass spectra of these dimers resemble those of the corresponding monomer. N^4-unsubstituted dimers (U), Cyt<>Cyt and Me^1Cyt<>Me^1Cyt, have λ_{max} ~245 nm and ϵ_{max} ~10 000; N^4-monosubstituted dimers (M), Me^4Cyt<>Me^4Cyt and $Me_2^{1,4}$Cyt<>$Me_2^{1,4}$Cyt, have λ_{max} ~250 nm and ϵ_{max} ~15 000, and N^4-disubstituted dimers (D), $Me_2^{4,4}$Cyt<>$Me_2^{4,4}$Cyt and $Me_3^{1,4,4}$Cyt<>$Me_3^{1,4,4}$Cyt, have λ_{max} ~260 nm and ϵ_{max} ~20 000. These batho- and hyperchromic shifts indicate that the amino form is predominant in D and the imino form in U. In M both forms may be more evenly distributed. This assumption is further verified by the spectral characteristics of $Me_2^{1,3}$Cyt<>$Me_2^{1,3}$Cyt, which was synthesized because it could exist only in the imino form. IR and deuterated IR spectra were also studied (ν_{NH}/ν_{ND} = 1.33) in order to gather additional evidence for a possible amino–imino tautomerization for these Cyt<>Cyt derivatives in polar and nonpolar solvents. This information should be of importance to the photochemistry and photobiology of nucleic acids.

There is evidence to show that cyclobutane dipyrimidines containing cytosine [such as cytosine dimer (Cyt<>Cyt) or cytosine–thymine dimer (Cyt<>Thy)] are produced as photoproducts in DNA or polynucleotides by 280-nm irradiation[1] or possibly by photosensitized dimerization.[2] These Cyt-containing hetero- and homodimers were found[1] to be monomerized by shorter wavelength irradiation more easily than their corresponding Ura and Thy dimers and DNA

Table I. Preparation and Properties of N-Methylated Cyt<>Cyt

Cyt derivative	Registry no.	Acetone–water, %	Temp, °C	Irrad period, h	Derivative of Cyt<>Cyt Yield, %	mp, °C	R_f a	R_f b	R_f c
Cyt	71-30-7	67–33	3	50	18	>280	0.00	0.02	0.07
1-Me	1122-47-0	85–15	3	168	20	>280	0.02	0.06	0.21
N^4-Me	6220-47-9	85–15	3	96	42	>280	0.02	0.03	0.23
$1,N^4$-Me_2	6220-49-1	100–0	20	65	36	>280	0.03	0.15	0.23
$N^{4,4}$-Me_2	6220-48-0	95–5	3	168	86	275–278	0.07	0.44	0.50
$1,N^{4,4}$-Me_3	2228-27-5	100–0	20	72	14	260–268	0.13	0.55	0.46

[a] Silica gel with eluent B. [b] Cellulose with eluent B. [c] Cellulose with eluent A.

photolyase in the presence of visible light (photoreactivation), to inhibit in vitro nuclease activity and affect DNA synthesis like Thy<>Thy, and to be excised from the DNA of radiation-resistant bacteria at the same rate as Thy<>Thy. Despite the biological implications of these Cyt<>Cyt derivatives, their nature has not been fully characterized due to the fact that these compounds are exceedingly labile under general experimental conditions.[3-5] In order to clarify the detailed nature of various Cyt<>Cyt derivatives and this dimerization process, studies have been carried out with *N*-methylcytosine derivatives[6] and the cytosine nucleosides.[7] Due to the apparent stability of these *N*-methyl Cyt<>Cyt, it is possible to gain insight into the chemical characteristics of these dimers, and such knowledge can serve as a basis for a better understanding of Cyt dimers of nucleic acid components (in preparation).

Experimental Section

Syntheses of *N*-Methylcytosine Derivatives. Preparation of 4-Thiouracil (Sra). The compound was prepared according to the procedure of Ueda and Fox.[8]

***S*-Methyl-4-Thiouracil (Me^4Sra) and N^1,*S*-Dimethyl-4-Thiouracil ($Me_2^{1,4}$Sra).** These compounds were prepared according to the methods of Wheeler and Johnson.[9]

Preparations of Various N^4-Methylcytosine Derivatives. Me^4Cyt, $Me_2^{1,4}$Cyt, $Me_2^{4,4}$Cyt, and $Me_3^{1,4,4}$Cyt were prepared according to the methods reported in references 10–13, respectively.

Preparation of 1-Methylcytosine. Me^1Cyt was prepared according to the method of Fox and Shugar.[14]

Preparations of N^3-Methylcytosine Derivatives. Me^3Cyt was prepared according to the method of Brooks and Lawley.[15]

Irradiation of *N*-Methyl Derivatives of Cytosine. Irradiation Apparatus. These irradiators have been described previously[16] and are equipped with a bank of seven Sylvania fluorescent lamps F15T8/BL.

Irradiation Experiments. In Table I, the specific conditions are presented. The following is the general procedure. The compound was dissolved in acetone or acetone–water to give a 20 mM solution. This solution was transferred to quartz tubes and was flushed with argon for 30 min before irradiation. The tubes were sealed with paraffin films, and the irradiation was carried out either at ambient or cold room temperature. The dimer formed was deposited during the irradiation. It was collected by filtration and washed with acetone. The filtrate and acetone washes were combined. After concentration at reduced pressure, the residue was applied on preparative TLC plates (silica gel, 60F-254, Merck or 13254 cellulose, 6065, Eastman) and the eluents were (A) *n*-PrOH–water (10:3) and (B) chloroform–methanol–water (4:2:1) + 5% of methanol to the organic phase. The R_f values are listed in Table I.

Determination of Stereochemistry of Dimers. Deamination of *N*-Methylated Cytosine Dimers. Acid-catalyzed deamination of dimers was carried out with 5 mg of the dimers dissolved in 1 mL of 0.1 N HCl. The resulting solution was allowed to stand at room temperature for 48 h. The deposited crystals were collected. Its identification was established by spectral comparison with known stereoisomers of derivatives of Ura<>Ura.

C and N Methylation of Me^1Ura<>Me^1Ura to Form $Me_2^{1,3}$Thy<>$Me_2^{1,3}$Thy. This synthesis was accomplished with a novel procedure reported by Taguchi and Wang.[17]

Spectral Determinations. Ultraviolet and infrared (KBr pellets) absorption spectra were recorded on a Beckman Model DK-1 and a Perkin-Elmer Model 21 recording spectrophotometer, respectively. Nuclear magnetic resonance spectra were obtained on a Varian 220-MHz spectrometer. $(CD_3)_2SO$ was used as solvent at 22 °C; however, at −2 °C, CF_3COOD was used instead. $(CH_3)_4Si$ was the internal standard. Mass spectra were obtained on a CEC-21-110 mass spectrometer at 70 eV ionizing voltage and a source temperature of 250 °C.

Results and Discussion

It is well known that facile deamination occurs with dihydrocytosine (hCyt) derivatives.[18] Because of the instability, studies involving hCyt compounds are, in general, perplexing. In photochemical studies, photohydration of Cyt derivatives has proved to be problematic in the isolation of the product, a ho^6hCyt derivative.[19] This predicament again has impeded the progress in the studies of photodimerization of Cyt derivatives. In order to gain a satisfactory understanding of the nature of Cyt dimers (Cyt<>Cyt), acetone-sensitized photodimerization studies of *N*-methyl-substituted Cyt derivatives have been carried out. The advantage of selecting these derivatives is twofold. First, N^1-methyl derivatives are analogues of biologically active compounds, Cyd, dCyd, or CMP; and, second, N^4-methyl derivatives may afford information concerning an important issue, i.e., the nature of amino–imino tautomerism of the C^4–NH_2 moiety in the Cyt<>Cyt and possibly hCyt derivatives in general.

Photosensitized dimerization of the Cyt derivatives in the presence of acetone with mainly 313-nm light gave cyclobutyl dicytosines (cytosine dimers, Cyt<>Cyt) as expected. Unexpectedly, we often found that crystals of a pure stereoisomer deposited directly from reaction solutions. This is indeed an added advantage in using these MeCyt derivatives as model compounds and has facilitated our study. The product yields of these various dimers and their respective R_f values are given in Table I.

Determinations of the stereoconfigurations of these Cyt dimers required an approach that is outlined below. This

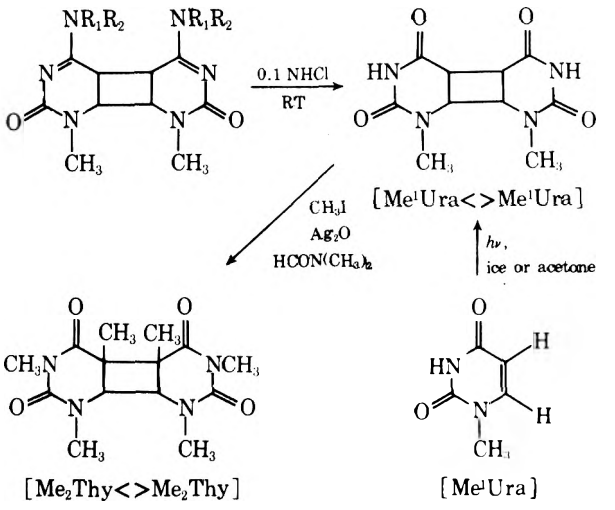


Table II. Acid-Catalyzed Deamination and Splitting of Various Cyt<>Cyt and Related Dimers

Dimer	Product	Stereoconfiguration	Yield, % In 0.1 N HCl	Yield, % In F_3CCOOH
Cyt<>Cyt	Ura<>Ura	(t,s),(t,a)	33, 53[a]	31 (45% Cyt)[b]
Me^1Cyt<>Me^1Cyt	Me^1Ura<>Me^1Ura	(t,s)	57	
Me^4Cyt<>Me^4Cyt	Ura<>Ura	(t,s)	70	70
$Me_2^{1,4}$Cyt<>$Me_2^{1,4}$Cyt	Me^1Ura<>Me^1Ura	(t,s)	75	60
$Me_2^{4,4}$Cyt<>$Me_2^{4,4}$Cyt	Ura<>Ura	(t,s)	62	
$Me_3^{1,4,4}$Cyt<>$Me_3^{1,4,4}$Cyt	Me^1Ura<>Me^1Ura	(t,s)	72	82
Me^1Ura<>Me^1Ura	No change	All four		
Ura<>Ura	No change	All four		

[a] Estimated from IR spectral data. [b] Anti dimers decompose in strong acid media to the monomer.

Table III. Chemical Shifts of N-Methylated Cyt<>Cyt

Dimer	Chemical shifts (δ, ppm from Me_4Si) N^1CH_3 (s)	N^4CH_3 (s)	C^5H (d) [J][b]	C^6H (d) [J]
Cyt<>Cyt			4.57 (dd)[c]	5.12 (dd)[c]
			4.76 [7]	4.85 [7]
Me^1Cyt<>Me^1Cyt				
Me^4Cyt<>Me^4Cyt		3.44	4.73 [7]	4.88 [7]
$Me_2^{1,4}$Cyt<>$Me_2^{1,4}$Cyt	3.30	3.42	4.64 [7]	4.86 [7]
$Me_2^{4,4}$Cyt<>$Me_2^{4,4}$Cyt		3.65, 3.69	4.50 [6]	5.32 [6]
$Me_3^{1,4,4}$Cyt<>$Me_3^{1,4,4}$Cyt	3.29	3.60, 3.64	4.50 [6]	5.36 [6]
	3.00[a]	2.83[a]	3.74 [6][a]	4.03 [6][a]

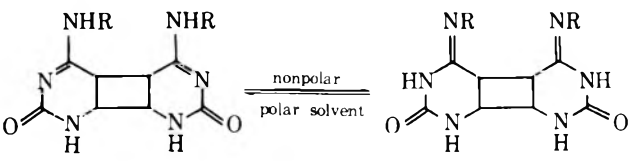
[a] These values were estimated at 22 °C in $(CD_3)_2SO$ and the other values were determined at −2 °C in F_3CCOOH. [b] Coupling constants are given in brackets and in Hz. [c] These chemical shifts are for the (t,a) isomer, but all the others are for the (t,s) isomer.

approach necessitated the study of Me^1Ura photodimerization (Taguchi and Wang, in preparation) and the development of a new method of C-alkylation of Pyr<>Pyr.[17] Alternatively, structural elucidation by means of x-ray diffraction analysis of a single crystal can be used.[20] In pursuing this chemical approach, several interesting findings were also noted and are being reported elsewhere. Apparently, under the mild conditions for deamination (Table II), Cyt<>Cyt were converted to the corresponding Ura<>Ura in fair yields and, at the same time, we found that all four isomers of Ura<>Ura and of Me^1Ura<>Me^1Ura were not affected. On the other hand, with trifluoroacetic acid similar results were obtained for the syn isomers of Cyt<>Cyt, but anti isomers were split quantitatively to the corresponding monomers. Except Cyt<>Cyt, only the (t,s) isomer was obtained for all five N-methylated Cyt<>Cyt. This finding agrees with that observed in photosensitized dimerization of Me^6Ura.[21] Such (t,s) isomer formation was shown not to be influenced by the solvent dipole moments. Therefore, the possibility that a $^3\pi^*,\pi$ complex or a collision complex having a head to head or syn arrangement precedes the formation of the dimers and determines their configurations should be considered. This suggestion was made[22] for cyclic enones; however, it seems not only applicable to Me^6Ura but also for Cyt derivatives having a somewhat different ground-state electronic configuration.

The NMR spectra of these dimers are given in Table III. These dimeric molecules have at least one symmetry axis; therefore, the AB or AA′BB′ patterns displayed are those expected. Because of the low solubility of the dimers in $(CH_3)_2SO$, F_3CCOOD had to be used for NMR determinations. In order to avoid acid-catalyzed splitting of these dimers at room temperature, −2 °C was maintained during the study. However, (t,s) isomers were proved to be the only photoproduct in these reactions and this precaution was, in effect, not imperative. As expected, there was considerable upfield shift for these signals in neutral solvent as seen in $Me_3^{1,4,4}$Cyt<>$Me_3^{1,4,4}$Cyt which has sufficient solubility in $(CH_3)_2SO$.

The mass spectra of these dimers resembled those of the corresponding monomers. Apparently, cleavage across the cyclobutane ring of the dimers generates abundant ions, and subsequent fragmentation of which are equivalent to the respective ionized monomers.[23]

The UV spectral data of these dimers are listed in Table IV. Both the solvent and pH effects have been studied. Two features are apparent: one is the ~5-nm bathochromic or red shift of λ_{max} for each N^4CH_3 group and the other is the ~5000 hyperchromic effect of ϵ_{max} also for each N^4CH_3 substituent. Therefore, these dimers were divided into three categories: N^4 unsubstituted (U), N^4 monosubstituted (M), and N^4 disubstituted (D) for our consideration. The reported values of λ_{max} and ϵ_{max} of hCyt (239 nm, 11.3×10^3) and Me^1hCyt (243 nm, 10.5×10^3)[24] may serve as the basis. Because U can be considered as derivatives of hCyt with substituents on C^5 and C^6, one would expect slight bathochromic shifts as have been observed. However, the *molar* extinction coefficient (ϵ_{max}) for U should double that of the monomeric hCyt because each dimeric molecule contains two identical chromophores. Yet, the ϵ_{max} values estimated were only ~10 000 for U rather than ~20 000 as expected. For M, λ_{max} are shifted as anticipated and ϵ_{max} at ~15 000 are again lower than those expected. Distinctively, in the cases of D, both ϵ_{max} and λ_{max} observed are as anticipated. This suggests that only D may possess the same chromophore as the monomeric hCyt and Me^1hCyt. One obvious possibility is the amino–imino tautomeric equilibrium, as shown, which could occur with U and M but not with



amino form imino form

D. This possibility was considered in the cases of hCyt and Me^1hCyt monomers.[24] From the pK_a value of Me^1hCyt in aqueous solution, these authors estimated the amino–imino

Table IV. UV Spectra of N-Methylated Cyt<>Cyt

Dimer	Registry no.	Concn (mM)	λ_{max} (nm)	$\epsilon_{max} \times 10^{-3}$	Solvent [pH]
		N^4 unsubstituted (U)			
Cyt<>Cyt	64161-45-1	0.073	*243*[a]	10.4	H_2O [9.01]
			243	10.3	H_2O [7.02]
			(219)[b]	(8.65)	H_2O [2.03]
					CH_3OH
Me^1Cyt<>Me^1Cyt	64103-42-0	0.064	*246*	9.56	H_2O [9.03]
			246	8.85	H_2O [7.05]
			(219)	(8.42)	H_2O [2.02]
			end absorption		CH_3OH
		N^4 monosubstituted (M)			
Me^4Cyt<>Me^4Cyt	64082-05-9	0.069	248	15.1	H_2O [9.04]
			235	13.4	
		0.033	*248*	14.1	CH_3OH
			234	15.0	
$Me_2^{1,4}$Cyt<>$Me_2^{1,4}$Cyt	64082-06-0	0.088	253	14.8	H_2O [9.01]
			236	12.5	
		0.076	*252*	14.4	CH_3OH
			234	14.6	
		0.038	*249*	9.67	CH_3CN
			233	14.1	
		N^4 disubstituted (D)			
$Me_2^{4,4}$Cyt<>$Me_2^{4,4}$Cyt	64082-08-2	0.052	258	19.1	H_2O [9.00]
		0.039	257	20.0	CH_3OH
		0.054	253	19.5	CH_3CN
$Me_3^{1,4,4}$Cyt<>$Me_3^{1,4,4}$Cyt	64082-07-1	0.031	263	18.8	H_2O [9.01]
		0.045	261	19.8	CH_3OH
		0.030	255	19.8	CH_3CN

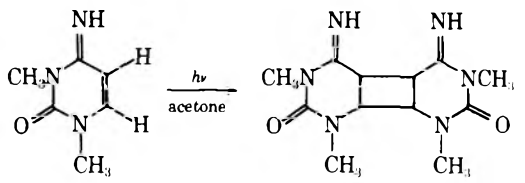
[a] λ_{max} in italics indicates a shoulder in the spectra. [b] The values given in parentheses are approximate because acid-catalyzed deamination is likely to occur.

tautomeric constants to be approximately 25, greatly in favor of the amino form.

Consequently, one may conclude that hCyt moieties in dimers are likely to have λ_{max} >240 nm with ϵ_{max} ~20 000, if they should exist in the amino form. On the other hand, if both are present in the imino form these dimers should have λ_{max} <230 nm with ϵ_{max} ~10 000. Thus, in aqueous media, it is probable that the amino form is predominant in D and the imino form exists largely in U. In M, both forms may be more evenly distributed.

In less polar solvents, CH_3OH and CH_3CN, an hypochromic effect in the 250-nm region for U and M is apparent. The effect results in the appearance of only end absorption or a decrease in ϵ_{max}. On the contrary, little change in ϵ_{max}'s was observed for D, although there is certain blue or hypsochromic shift. This shift is a trend expected for a $\pi\pi^*$ band in less polar solvents.[25] Any decrease in ϵ in the 250-nm region with a concomitant increase in the <230-nm region may be interpreted as evidence of a shift of equilibrium from an amino to an imino form. Thus, we may assume that the contribution of the imino form in the dimers would increase with decreasing polarity of the media.

For verification of this assumption, photosensitized dimerization of $Me_2^{1,3}$Cyt was carried out. With the N^3–CH_3 group, this monomeric compound could exist only in the imino form, as shown. Although $Me_2^{1,3}$Cyt in an ethanolic solution



gives rise to a UV spectrum with λ_{max} at 223 and 273 nm and ϵ_{max} of 10 000 and 8500, respectively, its reduced product $Me_2^{1,3}$hCyt in an aqueous solution has λ_{max} 227 nm with ϵ_{max} 12 000. As expected, $Me_2^{1,3}$Cyt<>$Me_2^{1,3}$Cyt, which could exist only in the imino form, has an ϵ_{max} of 9000 at 228 nm in water. In both CH_3OH and CH_3CN, this dimer shows only end absorption. This observation corroborates our interpretation of UV spectra of these dimers.

A study of the infrared spectra of these dimers was also undertaken to gather additional evidence for this amino–imino tautomerization. In principle, on deuteration of an imino–NH band, it would shift to a lower frequency with an isotopic ratio, ν_{NH}/ν_{ND}, of 1.375.[26] This method has been used for the study of such a tautomerization in heterocyclic systems.[27] For Cyt derivatives, the isotopic ratios of this shift were found to be in the range of 1.30–1.36.[26] For Me^3Cyt<>Me^3Cyt, a shift with a ratio of 1.33 was observed for the $=N^4H$ stretching band (2976 cm^{-1} in $CDCl_3$; 2960 cm^{-1} in a KBr pellet) and the corresponding $=N^4D$ band (2242; 2222 cm^{-1}). Similar shifts are evident in the spectra of Cyt<>Cyt (3021 to 2255 cm^{-1}) and of Me^1Cyt<>Me^1Cyt (2976 to 2252 cm^{-1} in Nujol).

In summary, a number of rather "stable" Cyt<>Cyt derivatives have been prepared, thus permitting the study of their UV absorption spectra. Interestingly, the observation that solvent polarity changes cause a change in the tautomeric equilibrium is unusual, as is the finding that an imino form in heterocyclic compounds is capable of a tautomeric shift to an amino form.[28] However, since the tautomeric constant for 5,6-saturated Cyt derivatives is relatively small,[28] the observed shift can be appreciated. In addition, IR, mass, and NMR spectra have also been examined. Such knowledge was not available previously with Cyt<>Cyt derivatives and affords further information concerning the characteristics of these compounds. Specifically, the possible amino–imino tautomerization of these dimers is of interest not only to chemical studies but also to biological considerations. If such a tautomerization should take place in the biological microenvironment, it could result in miscoding or in facile deamination

causing the conversion of Cyt to Ura even after enzymatic repair. Furthermore, the configuration of these dimers was determined to be trans with the trans–syn isomer as the only or the predominant product. If a cis–syn isomer should form as reported,[4,5] in the study of Cyd and dCyd, its acid-catalyzed deamination product, cis–syn Ura<>Ura, should be extremely stable and easily identifiable. The information concerning the stereoconfiguration of these dimers is of particular importance when related to the photochemistry of nucleic acids.[29–33]

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Diterpenoid Total Synthesis, an A → B → C Approach. 12. Aromatic C Rings without Alkyl Substituents. Model Systems for Podocarpic Acid and Diterpenoid Alkaloids[1]

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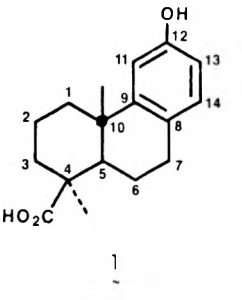
Examination of the general sequence **2** → **7** for addition of a 13-unsubstituted phenolic C ring[2] to decalones **2a–e** is described. Condensation of the decalones with HCO_2Et is uniformly efficient, but the rates and yields for conversion of the 8-hydroxymethylene derivatives to 8-formyl-Δ^8-7-octalones by reaction with DDQ vary remarkably. Addition of the sodium enolate of $MeCOCH_2CO_2$-*t*-Bu to α-formyl enones **4a–d** and acid-catalyzed cyclization of the adducts **5a–c** to tricyclic enediones **6a–c** proceed normally and in high yield. Aromatization of **6a–c** by $pyHBr_3$ affords not only 7-keto-12-phenols (**7**), the sole products from their 13-alkyl analogues, but also 13-bromo-7-keto-12-phenols and, at least in the case of **6a**, 13-bromo-Δ^{13}-7,12-enediones (**9**). Dehydrohalogenation of **9a** by collidine produces **7a**, a podocarpic acid model. Hydrogenolysis of the 12-(2′-benzoxazolyloxy) derivative of **7b** provides tetracyclic amide **19**, which has been formally converted to several diterpenoid alkaloids.[15]

Total syntheses of several C-aromatic perhydrophenanthrene diterpenoids have demonstrated the efficiency of the general sequence **2** → **7** (Scheme I) for constructing a substituted aromatic ring at carbons 8 and 9 of a *trans*-7-decalone.[1a,2–4] A C-13 alkyl substituent (R^4) has been an important component of all the natural products we have previously prepared by this route, and we consider that one of the significant advantages of this synthetic procedure is its ability to include introduction of that group as an integral part of the annulation process. However, certain diterpenoids such as podocarpic acid (**1**) are devoid of such C-ring substitution, and this might also be true of other structures for which use of this ring elaboration plan would be desirable. Investigations reported here show that the synthesis is equally applicable to structures in which R^4 = H, but that modifications of the sequence may be necessary. They also reveal some unexpected effects of structure on the reaction of an α-hydroxymethylene ketone with DDQ (**3** → **4**). These conclusions result primarily from research into the synthesis of model compounds in the podocarpic acid and diterpenoid alkaloid series.



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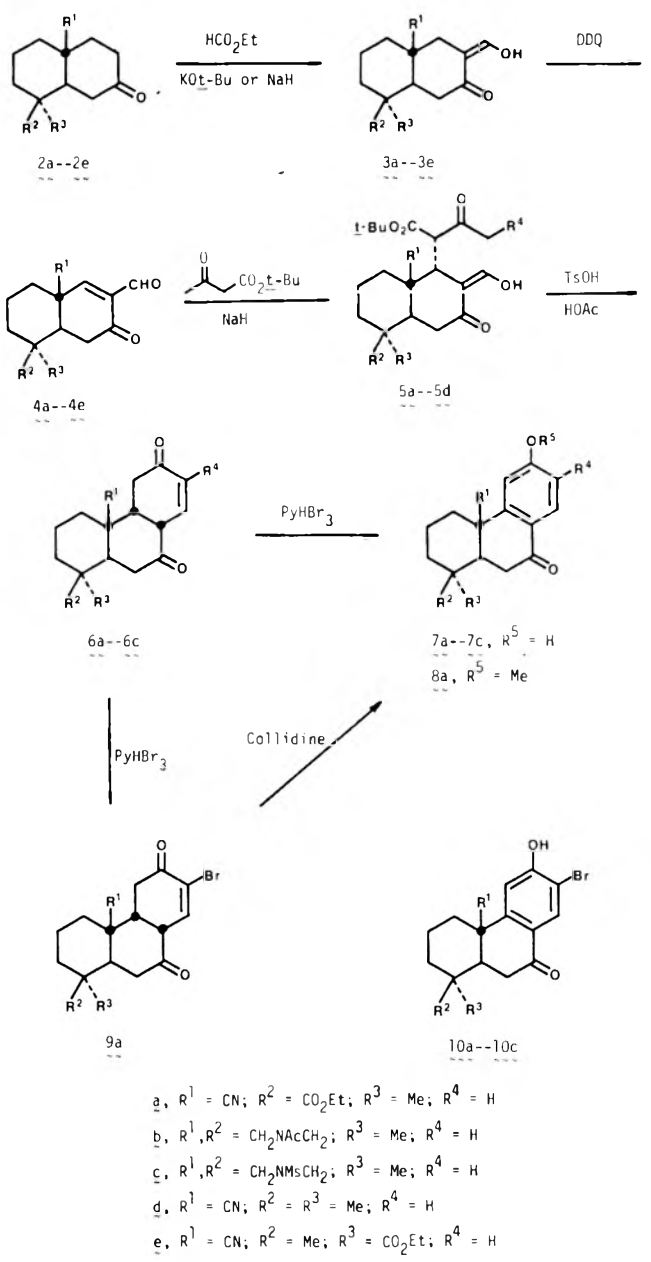
The decalones which were used in this work, **2a–e**, have been reported earlier,[5,6] and their condensation with ethyl formate is unexceptional. However, dehydrogenation of these hydroxymethylene ketones by DDQ under conditions which have given 75–95% yields of α-formyl enones **4** in other

Scheme I



a, R^1 = CN; R^2 = CO_2Et; R^3 = Me; R^4 = H

b, R^1,R^2 = CH_2NAcCH_2; R^3 = Me; R^4 = H

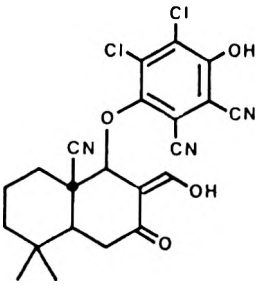
c, R^1,R^2 = CH_2NMsCH_2; R^3 = Me; R^4 = H

d, R^1 = CN; R^2 = R^3 = Me; R^4 = H

e, R^1 = CN; R^2 = Me; R^3 = CO_2Et; R^4 = H

series[1a,3,4] is not uniformly successful. The 4β-carbethoxy-10-cyano and *N*-acetylimino derivatives **3a** and **3b** react normally to afford the corresponding aldehydes **4a** and **4b** in 75–85% yield after 5 min at room temperature in dioxane containing acetic acid.[4] The 10-cyano-4,4-dimethyl compound **3d** also reacts rapidly under these conditions, but aldehyde **4d** is obtained in only 28% yield and is unaccompanied by residual **3d.** The remainder of the material from the latter reaction has not been isolated or identified, but it seems to be lost during bicarbonate treatment of the crude product to remove dichlorodicyanohydroquinone and this suggests the possible formation of a substance such as **11.** Analogous species have occasionally been encountered in other reactions of DDQ,[7] although conjugate addition of the hydroquinone to an α-formyl enone has not been a problem during oxidation of the other hydroxymethylene decalones we have examined. Reasons for this peculiar behavior of **3d** are not clear. However, we hesitate to ascribe it solely to an influence of the angular cyano group in view of the fact that **3a** and the $\Delta^{5,6}$ analogue of **3d**[5] react normally, and they both contain a similarly proximate nitrile.

Hydroxymethylene ketones **3c** and **3e** are dehydrogenated by DDQ in dioxane far more slowly than are their counterparts



11

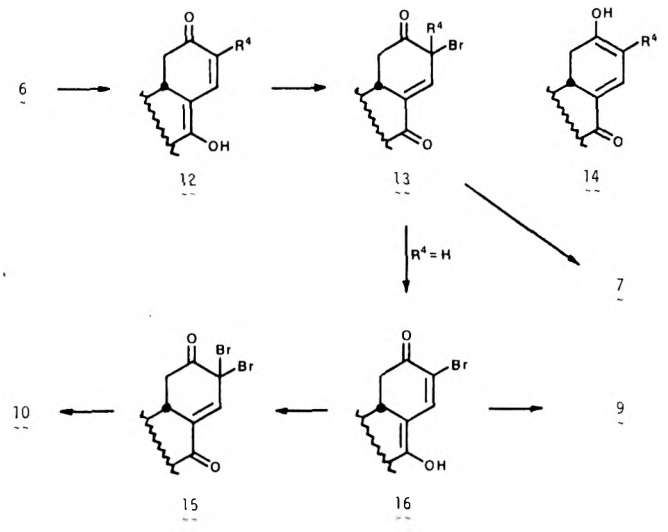
3a, 3b, etc. In fact, these reactions are so slow that 50% or more of the hydroxymethylene ketone remains after up to 18 h even in the presence of excess DDQ. The sulfonamido compound **3c** can be converted to its formyl enone **4c** in excellent yield (89%) by treatment with DDQ for 18 h in refluxing benzene,[8] but even these conditions do not substantially improve matters with **3e.** These differences in the rates of dehydrogenation of hydroxymethylene ketones by DDQ are particularly perplexing when they are brought about by structural changes as slight as the nature of a remote substituent on nitrogen (**3b** vs. **3c**) or the configuration at a remote center (**3a** vs. **3e**). The main comment we can presently make regarding the synthetic utility of this reaction is that it is surprisingly sensitive to subtle structural effects, and if the usual procedure is not effective with a particular compound a search for alternate reaction conditions may be fruitful.[9]

Addition of the sodium enolate of *tert*-butyl acetoacetate to α-formyl enones **4a–d** proceeds normally.[3-5,10] Acid-catalyzed conversion of the adducts to *trans-syn-cis*-$\Delta^{13,14}$-enediones **6a–c**[10] also occurs without incident,[11,12] but these enediones are more sensitive than are their 13-alkyl counterparts. In most cases the crude products appear to be substantially free of contaminants (^{1}H NMR), but attempted purification leads to considerable losses. Nonetheless, the crude materials suffice for further use, so the general sequence **2** → **6** is quite acceptable for synthesis of these compounds in overall yields of 50–60% from the decalones.

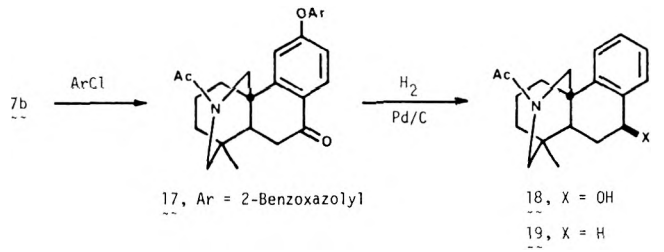
Reaction of enediones **6a–c** with pyridine hydrobromide perbromide[3] is significantly different from that of their 13-alkyl analogues. The latter substances are converted to 7-keto-12-phenols **7** (R^4 = alkyl) in high yield,[1a,3,4] the only complication arising from competitive 6α-bromination in the dehydroabietic acid series.[1a] Under comparable conditions ketophenol **7a** is produced in substantially lower yield from **6a,** and it is accompanied by a considerable amount of bromoenedione **9a** (IR and ^{1}H NMR identification) and a small amount of the corresponding 13-bromophenol **10a.** The bromoenedione becomes the major product and the amount of bromophenol is minimized when pyridine hydrobromide perbromide is added slowly, rather than rapidly, to **6a.** However, the bromoenedione is converted to ketophenol **7a** by collidine, so this two-step process represents a technique for aromatization of 13-unsubstituted enediones which is nearly as efficient (80% from **6a**) as is use of the brominating agent alone with the 13-alkyl compounds.[13]

These results are consistent with a course of events such as that shown in Scheme II for reaction of an enedione like **6** (R^4 = H or alkyl) with pyridine hydrobromide perbromide.[3,14] An alkyl group at C-13 blocks further enolization in the C-7–C-8–C-14–C-13–C-12 system of an initial 13-bromoenedione like **13,** and 1,4-dehydrohalogenation (or its equivalent) to ketophenol **7** (R^4 = H) is normally the favored process.[1a,3] However, in the absence of that alkyl group reenolization can compete with dehydrohalogenation, and an enol like **16**[14] can either ketonize (**9**) or brominate (**15** or an 8,13 dibromo isomer), with the latter event leading to bromophenol **10.**

Scheme II



Ketophenols **7b** and **7c** bear an obvious structural relationship to many diterpenoid alkaloids of the aconite–garrya family. Although it is not our plan to use these particular compounds as intermediates for elaboration of such structures, experimental relation of them to the natural products is desirable in order to confirm the structures of the ketophenols. For this purpose the phenolic and ketonic oxygens of the *N*-acetyl derivative **7b** were removed by the sequence **7b** → **17** → **19**.[1a] The reactions were conducted without ex-



tensive purification of intermediates or optimization of conditions, and are undoubtedly capable of improvement should that be desirable for other purposes. Nonetheless, the IR spectrum of amide **19** from this degradation is identical with that of an authentic sample.[15] This substantiates the structures which have been assigned to our compounds, particularly the trans A/B ring fusion in **2b** and **2c** and all of their progeny.[6] In addition, Tahara and Hirao have reported conversion of their enantiomer of **19** to intermediates which, in racemic form, have been transformed to (±)-atisine, (±)-veatchine, and (±)-garryine,[16] so this work also constitutes another total synthesis of these diterpenoid alkaloids, albeit only in the strictly formal sense.

Experimental Section

General procedures and techniques were the same as described earlier.[3] Unless otherwise specified, HCl, NaOH, KOH, NH_4OH, and $NaHCO_3$ solutions were aqueous and HOAc was glacial. Brine refers to saturated aqueous NaCl. General procedures for isolation of reaction products are abbreviated as follows: (A) the specified organic solution was washed with the indicated sequence of aqueous solutions followed by water or brine and dried ($MgSO_4$ or Na_2SO_4), and solvent was removed either in vacuo or by evaporation on the steam bath in a stream of dry N_2; (B) the indicated aqueous mixture was thoroughly extracted with the specified organic solvent followed by the steps in procedure A; (C) the reaction mixture was added to water or brine followed sequentially by the steps in procedures B and A. When no temperature is specified, operations were conducted at room temperature, ca. 23 °C. Mass spectral data is expressed in the form: *m/e* (percent base peak intensity). ^1H NMR spectra are reported for $CDCl_3$ solutions and IR spectra for $CHCl_3$ solutions unless otherwise indicated. Melting points (open capillary tubes) are corrected for stem exposure.

4β-Carbethoxy-10-cyano-8-hydroxymethylene-4α-methyl-5α-decal-7-one (3a). A solution of 500 mg (1.90 mmol) of **2a**, mp 68–75 °C,[6] in 30 mL of dry *t*-BuOH containing KO-*t*-Bu from prior dissolution of 500 mg (12.8 mg-atoms) of K was stirred for 15 min at 45 °C (N_2 atmosphere), treated dropwise during 30 min with 3 mL (37 mmol) of HCO_2Et in 15 mL of *t*-BuOH,[4] stirred at 45–50 °C for 9 h, treated with 1 mL of HCO_2Et, stirred at 50 °C for 5 h, and acidified to pH 6 with HOAc. The mixture was poured into brine and extracted with Et_2O and $CHCl_3$, which was extracted with 1% NaOH. Rapid acidification with 4 N HCl and isolation B ($CHCl_3$; 5% $NaHCO_3$ wash) afforded 455 mg (82%) of crude **3a** as tan crystals which recrystallized from hexane as colorless needles: mp 91–92 °C; UV max (95% EtOH) 270 nm (ε 9000); IR 2225, 1718, 1645, 1585 cm^{-1}; ^1H NMR τ 1.42 (s, 1 H), 5.80 (q, *J* = 7 Hz, 2 H), 8.70 (t, *J* = 7 Hz, 3 H), 8.75 (s, 3 H); mass spectrum 291 (42), 218)43), 217 (100), 190 (17), 148 (16), 41 (15).

Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.81. Found: C, 66.03; H, 7.21; N, 4.73.

4β,10-Acetyliminobismethyl-8-hydroxymethylene-4α-methyl-5α-decal-7-one (3b). Reaction of 800 mg (3.21 mmol) of once-distilled **2b**, bp 190–200 °C (0.25 mm),[6] with 2.2 mL of HCO_2Et and the KO-*t*-Bu from 800 mg (20.5 mg-atoms) of K in a total of 85 mL of *t*-BuOH was conducted as described for preparation of **3a**, but at ca. 23 °C throughout (HCO_2Et added in two portions: 1 mL in 10 mL of *t*-BuOH during 2 h, and after 6 h 1.2 mL in 10 mL of *t*-BuOH during 1 h). Isolation as described for **3a** afforded 795 mg (89%) of crude **3b** as a yellowish gum: UV max (95% EtOH) 281 (ε 7100); (base) 313 nm (ε 14 000); IR 1620 cm^{-1} (broad); ^1H NMR τ 1.26 (s) and 1.34 (s) (total 1 H), 5.88 and 7.32 (AB, *J* = 14 Hz) and 5.97 and 7.32 (AB, *J* = 14 Hz) (total 2 H), ~6.75 (br s, 2 H), 7.92 (s) and 7.94 (s) (total 3 H), 9.12 (s) and 9.14 (s) (total 3 H).[17] On some occasions the crude **3b** crystallized (mp 80–89 °C), but a suitable recrystallization technique was not found, and because many analogous compounds decompose extensively during attempted chromatography, sublimation, or distillation, crude **3b** was used directly.

8-Hydroxymethylene-4β,10-methanesulfonyliminobismethyl-4α-methyl-5α-decal-7-one (3c). Reaction of 500 mg (1.75 mmol) of crude **2c**, mp 182–185 °C,[6] with 2.85 g (38.5 mmol) of HCO_2Et and the KO-*t*-Bu from 546 mg (14.0 mg-atoms) of K in a total of 75 mL of *t*-BuOH was conducted as described for the preparation of **3b**, except that 30 min was allowed prior to addition of HCO_2Et (which was all added during 1 h) and reaction was continued for 12 h after addition of HCO_2Et. Acidification with HOAc[4,18] was followed by isolation C ($CHCl_3$; 5% $NaHCO_3$ wash) to provide 524 mg (96%) of crude **3c** as a yellowish solid: mp 177–184 °C. Sublimation [150–156 °C (1.0–0.25 mm); extensive material loss from decomposition] afforded an analytical sample: mp 185–187 °C dec; UV max (95% EtOH) 276 (ε 7500); (base) 316 nm (ε 12 500); IR 1640, 1580, 1340, 1150 cm^{-1}; ^1H NMR τ 1.41 (s, 1 H), 6.63 and 7.22 (AB, *J* = 12 Hz, 2 H), 6.69 and 7.24 (AB, *J* = 12 Hz, 2 H), 7.29 (s, 3 H), 9.13 (s, 3 H); mass spectrum 313 (34), 234 (100), 206 (63), 107 (33), 91 (34), 79 (34), 44 (62), 42 (57), 41 (59).

Anal. Calcd for $C_{15}H_{23}NO_4S$: C, 57.51; H, 7.35; N, 4.47; S, 10.22. Found: C, 57.60; H, 7.44; N, 4.48; S, 10.09.

10-Cyano-4,4-dimethyl-8-hydroxymethylene-5α-decal-7-one (3d). Reaction of 500 mg (2.44 mmol) of **2d**, mp 59–62 °C,[5] with 720 mg (9.73 mmol) of HCO_2Et and 174 mg (7.25 mmol) of NaH (as 300 mg of a 58% dispersion in mineral oil) in 20 mL of PhH was conducted as described for the 4,4,10-trimethyl analogue[3] to afford 480 mg (84%) of **3d** as pale yellow prisms, mp 104–114 °C, sublimation of which [110 °C (1 mm)] provided pure **3d** as colorless prisms: mp 113–116 °C; UV max (95% EtOH) 307 (ε 12 000); (base) 309 nm (ε 18 300); IR 2230, 1650, 1587 cm^{-1}; ^1H NMR τ −4.28 (br s, 1 H), 1.41 (s, 1 H), 8.90 (s, 3 H), 9.05 (s, 3 H); mass spectrum 233 (66), 218 (17), 136 (100), 98 (36), 70 (23), 41 (26).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.99; H, 8.30; N, 6.20.

4α-Carbethoxy-10-cyano-8-hydroxymethylene-4β-methyl-5α-decal-7-one (3e). Reaction of 318 mg (1.21 mmol) of **2e**, mp 84–85.5 °C,[6] with 1.7 g (23 mmol) of HCO_2Et and the KO-*t*-Bu from 356 mg (9.13 mg-atoms) of K in a total of 40 mL of *t*-BuOH was conducted at ~23 °C for 23 h as described for the preparation of **3c** to produce 307 mg (87%) of **3e** as a yellowish oil which crystallized. Recrystallization from $CHCl_3$–hexanes and trituration with hexanes afforded pure **3e** as colorless needles: mp 121.5–122 °C; UV max (95% EtOH) 275 (ε 11 400); (base) 310 nm (ε 20 800); IR 2220, 1718, 1650, 1590 cm^{-1}; ^1H NMR τ 1.42 (s, 1 H), 5.86 (q, *J* = 7 Hz, 2 H), 8.58 (s, 3

H), 8.75 (t, J = 7 Hz, 3 H); mass spectrum 291 (88), 218 (100), 217 (77), 190 (21), 98 (32), 83 (36), 55 (32), 41 (75).

Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.77; H, 7.22; N, 4.92.

4β-Carbethoxy-10-cyano-8-formyl-4α-methyl-5α-Δ⁸-octal-7-one (4a). A solution of 860 mg (2.96 mmol) of crude **3a** and 6 drops of HOAc in 17 mL of dioxane was treated with 762 mg (3.36 mmol) of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), mp 214–215 °C, stirred until homogeneous (5 min; N_2 atmosphere), and evaporated to dryness at 2 mm and ~23 °C (10 min required).[4] A $CHCl_3$ suspension of the residue was filtered and subjected to isolation A (5% $NaHCO_3$ wash; $CHCl_3$ back-wash[19]) to yield 683 mg (80%) of crude **4a** as a brown oil which could not be purified by crystallization or distillation; spectra showed no significant absorption from contaminants (~5% or less): IR 2220, 1720, 1700, 1690, 1615 cm^{-1}; ^1H NMR τ −0.13 (s, 1 H), 2.78 (s, 1 H), 5.76 (q, J = 7 Hz, 2 H), 8.68 (t, J = 7 Hz, 3 H), 8.71 (s, 3 H).

4β,10-Acetyliminobismethyl-8-formyl-4α-methyl-5α-Δ⁸-octal-7-one (4b). Reaction of 470 mg (1.70 mmol) of crude **3b** with 405 mg (1.78 mmol) of DDQ and 4 drops of HOAc in 12 mL of dioxane was conducted as described for the preparation of **4a**[19] to produce 400 mg (86%) of crude **4b** as a yellowish semisolid which recrystallized from EtOAc–cyclohexane as colorless prisms: mp 125–131 °C; IR 1700, 1685, 1635, 1608 cm^{-1}; ^1H NMR τ −0.07 (s) and −0.06 (s) (total 1 H), 2.67 (s, 1 H), 7.88 (s, 3 H), 9.07 (s) and 9.10 (s) (total 3 H);[17] mass spectrum 275 (13), 190 (11), 148 (100), 43 (19). Further recrystallization afforded an analytical sample of mp 152–153 °C.

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69. Found: C, 69.37; H, 7.54.

8-Formyl-4β,10-methanesulfonyliminobismethyl-4α-methyl-5α-Δ⁸-octal-7-one (4c). A solution of 100 mg (0.319 mmol) of crude **3c**, mp 176–182 °C dec, and 2 drops of HOAc in 2 mL of dry PhH was mixed with a solution of 79.0 mg (0.348 mmol) of DDQ, mp 211–213 °C, in 8 mL of hot PhH and the orange solution was boiled under reflux for 17 h (N_2 atmosphere), concentrated to 2 mL in a N_2 stream, diluted to 10 mL with $CHCl_3$, refluxed for 5 min, and filtered. The collected $DDQH_2$ was washed by suspension for 10 min in 10 mL of refluxing $CHCl_3$ and filtration. Combined filtrates were processed by isolation A (5% $NaHCO_3$ wash; $CHCl_3$ back-wash[19]) to provide 88 mg (89%) of crude **4c** as a yellowish solid, mp 213–224 °C dec, which recrystallized from CH_2Cl_2–pentane as colorless prisms: mp 218–220 °C dec; UV max (95% EtOH) 225 (ϵ 5900); (base) 318 nm (ϵ 15 200); IR 1705, 1682, 1612, 1344, 1155 cm^{-1}; ^1H NMR τ −0.02 (s, 1 H), 2.76 (s, 1 H), 7.25 (s, 3 H), 9.08 (s, 3 H); mass spectrum 311 (18), 232 (44), 148 (29), 122 (37), 91 (45), 79 (29), 77 (40), 55 (28), 44 (92), 42 (100).

Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.86; H, 6.80; N, 4.50; S, 10.30. Found: C, 57.71; H, 6.65; N, 4.45; S, 10.08.

10-Cyano-4,4-dimethyl-8-formyl-5α-Δ⁸-octal-7-one (4d). Reaction of 500 mg (2.15 mmol) of **3d**, mp 102–111 °C, with 500 mg (2.20 mmol) of DDQ and 5 drops of HOAc in 5 mL of dioxane was conducted as described for the preparation of **4a**. The residue from the evaporation of dioxane was extracted five times with 6:1 Et_2O–$CHCl_3$, which was diluted with Et_2O and subjected to isolation A (brine and 5% $NaHCO_3$ wash) to afford 140 mg (28%) of **4d** as a yellow oil which appeared by ^1H NMR to be free of significant contamination: IR (CCl_4) 2216, 1700, 1690, 1610 cm^{-1}; ^1H NMR τ −0.11 (s, 1 H), 2.67 (s, 1 H), 8.84 (s, 3 H), 9.03 (s, 3 H). Attempted purification by crystallization or chromatography failed.

4α-Carbethoxy-10-cyano-8-formyl-4β-methyl-5α-Δ⁸-octal-7-one (4e). A stirred solution of 118 mg (0.405 mmol) of **3e**, mp 122.5–124 °C, and 0.1 mL of HOAc in 15 mL of dry dioxane was treated with 138 mg (0.608 mmol) of DDQ (N_2 atmosphere), heated under reflux for 5 h, diluted with $CHCl_3$, and evaporated to dryness in vacuo. A suspension of the residue in $CHCl_3$ was heated to boiling, filtered (hot $CHCl_3$ wash of residue), and processed by isolation A (1% $NaHCO_3$ wash; $CHCl_3$ back-wash) to provide 117 mg (100%) of a ca. 1:1 mixture (^1H NMR assay) of **3e** and **4e** as a pale yellow oil: ^1H NMR τ −0.08 (s, 1 H), 2.70 (s, 1 H), 5.85 (q, J = 7 Hz, 2 H), 8.52 (s, 3 H), 8.73 (t, J = 7 Hz, 3 H), plus resonances of **3e**. No successful method for purifying **4e** was found.

Ethyl 10-Cyano-7,12-dioxo-5α,8β,9β,17-norpodocarp-13-en-16-oate (6a). A mixture of 535 mg (3.39 mmol) of $CH_3COCH_2CO_2$-t-Bu, bp 95–100 °C (20–25 mm),[20] and 81 mg (3.4 mmol) of NaH (as 140 mg of a 58% dispersion in mineral oil) in 20 mL of dry PhH was stirred for 15 min (N_2 atmosphere), treated with 635 mg (2.20 mmol) of crude **4a** in 15 mL of PhH, stirred for 2 h, and acidified with HOAc (pH 6).[4] Isolation C ($CHCl_3$; 5% $NaHCO_3$ wash) left 920 mg of a mixture of **5a** (^1H NMR shows only one diastereomer[10]) and $CH_3COCH_2CO_2$-t-Bu as a tan oil (estimated ~75% **5a** by ^1H NMR): ^1H NMR τ 1.40 (s, 1 H), 5.82 (q, J = 7 Hz, 2 H), 7.77 (s, 3 H), 8.55 (s, 9 H), 8.62 (s, 3 H), 8.71 (t, J = 7 Hz, 3 H) plus resonances of CH_3CO-CH_2CO_2-t-Bu at τ 6.67 (s, 2 H), 7.77 (s, 3 H), 8.55 (s, 9 H). Purification was not attempted.

A solution of 920 mg of this crude **5a** and 100 mg of TsOH in 40 mL of HOAc was boiled under reflux for 2 h (N_2 atmosphere), 0.5 g of NaOAc was added, and most of the HOAc was removed in vacuo.[4] The residue was partitioned between $CHCl_3$ and water, which was subjected to isolation B ($CHCl_3$; 5% $NaHCO_3$ wash) to afford 520 mg (72% from **4a**) of crude **6a** as a brown semisolid, the spectra of which indicated only minimal contamination. Chromatography over Florisil (2 × 20 cm; Et_2O elution) provided 210 mg (29%) of **6a** as a colorless solid (mp 197–200 °C) which recrystallized from EtOAc as colorless needles: mp 200–202 °C; UV max (95% EtOH) 211 nm (ϵ 2100);[10] IR 2233, 1720, 1685 cm^{-1}; ^1H NMR τ 2.95 (d, J = 10 Hz, 1 H), 3.82 (dd, J = 6 and 10 Hz, 1 H), 5.79 (d, J = 7 Hz, 2 H), 6.07 (br t, J = ~6 Hz, 1 H), 8.68 (t, J = 7 Hz, 3 H), 8.77 (s, 3 H); mass spectrum 329 (37), 256 (27), 235 (97), 207 (33), 161 (75), 133 (100), 128 (52), 120 (53), 95 (50), 66 (36).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.19; H, 7.13; N, 4.39.

16,17-Acetylimino-5α,8β,9β-podocarp-13-ene-7,12-dione (6b). Reaction of 515 mg (1.87 mmol) of crude **4b** with the enolate from 450 mg (2.85 mmol) of $CH_3COCH_2CO_2$-t-Bu and 120 mg of a 58% NaH–mineral oil dispersion (2.90 mmol) in a total of 60 mL of PhH was conducted as described for the preparation of **5a**, affording 850 mg of a mixture of **5b** (^1H NMR shows two diastereomers, ca. 1:1 ratio[10,17]) and excess keto ester as a brown oil: ^1H NMR τ 1.58 (s) and 1.63 (s) (total 1 H), 7.78 (s, 3 H), 7.93 (s) and 7.97 (s) (total 3 H), 8.55 (s, 9 H), 9.12 (br s, 3 H) plus resonances of $CH_3COCH_2CO_2$-t-Bu.

Reaction of 850 mg of this crude **5b** with 120 mg of TsOH in 30 mL of HOAc for 2.5 h was conducted as described for the preparation of **6a** to afford 600 mg of brown gum, which was washed with hexane to leave 470 mg (80% from **4b**) of crude **6b** as a tan solid: mp 138–155 °C; IR 1715, 1680, 1630 cm^{-1}; ^1H NMR τ 3.05 (d, J = 10 Hz, 1 H), 3.87 (dd, J = 6 and 10 Hz, 1 H), 7.87 (s) and 7.92 (s) (total 3 H),[17] 8.74 (s, impurity), 9.12 (br s, 3 H).[17] Enedione **6b** decomposed during attempted chromatography or recrystallization, and thus was not purified further.

16,17-Methanesulfonylimino-5α,8β,9β-podocarp-13-ene-7,12-dione (6c). A mixture of 120 mg (5.00 mmol) of NaH (obtained by repeatedly washing a 58% NaH–mineral oil dispersion with hexanes) and 270 mg (1.71 mmol) of $CH_3COCH_2CO_2$-t-Bu in 9 mL of freshly distilled Me_2SO was stirred for 30 min, treated with 177 mg (0.569 mmol) of **4c**, mp 210–217 °C dec, stirred for 6 min (N_2 atmosphere), and acidified with HOAc.[10] Isolation C (CH_2Cl_2) left 235 mg (88%) of crude **5c** as a yellowish glass (^1H NMR shows predominantly or only one isomer[10,21]). Trituration with hexanes and washing with Et_2O afforded **5c** as a colorless amorphous powder: mp 173–176 °C dec; IR 1720, 1700, 1622, 1570, 1330, 1145 cm^{-1}; ^1H NMR τ −4.55 (br s, 1 H), 1.57 (s, 1 H), 6.25 (d, J = 5 Hz, 1 H), 6.58 (d, J = 12.5 Hz, 2 H), 6.73 (d, J = 5 Hz, 1 H), 7.26 (d, J = 12.5 Hz, 2 H), 7.29 (s, 3 H), 7.77 (s, 3 H), 8.61 (s, 9 H), 9.12 (s, 3 H).[21]

Anal. Calcd for $C_{23}H_{35}NO_7S$: C, 58.83; H, 7.51; N, 2.89; S, 6.83. Found: C, 58.91; H, 7.68; N, 3.08; S, 6.77.

Reaction of 125 mg (0.267 mmol) of crude **5c**, mp 160–169 °C dec, with 51 mg (0.29 mmol) of $TsOH·H_2O$ in 15 mL of HOAc for 0.75 h was conducted as described for the preparation of **6a** to provide 116 mg of crude **6c** as a tan oil. Trituration and repeated washing with Et_2O afforded 94 mg (100%) of yellowish solid mixture containing ~70% of **6c** and 30% of an unknown contaminant (^1H NMR assay): mp 150–159 °C; IR 1710, 1680, 1602, 1332, 1150 cm^{-1}; ^1H NMR τ 3.05 (d, J = 10 Hz, 1 H), 3.86 (dd, J = 6 and 10 Hz, 1 H), 7.17 (s, 3 H), 9.13 (s, 3 H), and resonance from the 30% contaminant at τ 2.65 (dd, J = 10 and 2 Hz, 1 H), 3.97 (dd, J = 10 and 2 Hz, 1 H), 7.25 (s, 3 H), 9.10 (s, 3 H).[22] Attempted purification by recrystallization, sublimation, or chromatography led to decomposition, so this material was aromatized directly.

9α-(1′-Carbo-*tert*-butoxy-2′-oxopropyl)-10-cyano-4,4-dimethyl-8-hydroxymethylene-5α-decal-7-one (5d). Reaction of the enolate from 115 mg (0.728 mmol) of $CH_3COCH_2CO_2$-t-Bu and 16 mg (0.67 mmol) of NaH (as a 58% dispersion from which mineral oil was not removed) in 8 mL of Me_2SO (15 min for enolate formation) with 120 mg (0.519 mmol) of crude **4d** was conducted as described for the preparation of **5c** to afford 160 mg (79%) of crude **5d**. Washing with pentane left **5d** as a yellow powder (^1H NMR shows only one diastereomer[10]): mp 130–140 °C; ^1H NMR τ −4.33 (br s, 1 H), 1.43 (s, 1 H), 6.22 (d, J = 4 Hz, 1 H), 6.55 (d, J = 4 Hz, 1 H), 7.82 (s, 3 H), 8.68 (s, 9 H), 8.90 (s, 3 H), 9.04 (s, 3 H); mass spectrum 389 (11), 333 (35), 306 (50), 290 (56), 272 (97), 232 (52), 136 (93), 57 (100), 55 (40),

43 (79), 41 (62).

Ethyl 10-Cyano-12-methoxy-7-oxo-5α,17-norpodocarpa-8,11,13-trien-16-oate (8a). A solution of 48 mg (0.15 mmol) of **6a**, mp 197–200 °C, in 5 mL of HOAc was treated dropwise during 2 h with 47 mg (0.15 mmol) of pyridine hydrobromide perbromide ($pyHBr_3$; mp 132–135 °C)[23] in 5 mL of HOAc (N_2 atmosphere) and stirred for 6 h. Isolation C ($CHCl_3$; 5% $NaHCO_3$ wash) left 50 mg of a yellowish gum which appeared to consist predominantly of **9a** (^1H NMR). This could be crystallized from EtOAc: IR 2230, 1718, 1692 cm^{-1}; ^1H NMR τ 2.53 (d, J = 6 Hz, 1 H), 5.75 (q, J = 7 Hz, 2 H), 8.67 (t, J = 7 Hz, 3 H), 8.74 (s, 3 H). Normally the crude product was dissolved in 5 mL of *sym*-collidine, heated at ~90 °C for 3 h (N_2 atmosphere),[24] and processed by isolation C ($CHCl_3$; 2 N HCl and $NaHCO_3$ wash) to provide 50 mg (105%) of crude **7a** as a colorless solid: mp 190–230 °C; IR (KBr) 3320 (br), 1710, 1650, 1570 cm^{-1}; ^1H NMR (Me_2CO-d_6) τ 2.05 (d, J = 8.5 Hz, 1 H), 2.88 (d, J = 2 Hz, 1 H), 3.03 (dd, J = 2 and 8.5 Hz, 1 H), 5.81 (q, J = 7 Hz, 2 H), 8.68 (s, 3 H), 8.71 (t, J = 7 Hz, 3 H). TLC and ^1H NMR indicated the presence of a contaminant believed to be **10a** [~20%; τ 1.78 (s, 1 H), 2.58 (s, 1 H), 8.74 (s, 3 H)] which was very difficult to remove by recrystallization, sublimation, or chromatography, so the phenol was etherified for final characterization. A mixture of 50 mg of crude **7a**, mp 190–220 °C, 0.125 mL of Me_2SO_4, 2 g of anhydrous K_2CO_3, and 10 mL of dry Me_2CO was stirred at reflux for 9 h (N_2 atmosphere) and filtered,[4] Me_2CO was distilled in vacuo, and the residue was dissolved in $CHCl_3$. Isolation A (NH_4OH wash) left 54 mg of crude **8a**, mp 187–193 °C, which was fractionally sublimed to afford 40 mg (80% based on **6a**) of pure **8a** as colorless prisms, mp 197–200 °C. The analytical sample was resublimed: mp 197–200 °C; UV max (95% EtOH) 270 nm (ε 10 000); IR (KBr) 2215, 1720, 1670, 1590 cm^{-1}; ^1H NMR τ ~1.93, 2.99, and 3.07 (ABC, $J_{13,14}$ = 8.5, $J_{11,13}$ = 2.5, $J_{11,14}$ = 0 Hz, 3 H), 5.78 (q, J = 7 Hz, 2 H), 6.13 (s, 3 H), 8.68 (t, J = 7 Hz, 3 H), 8.68 (s, 3 H).

Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.00. Found: C, 69.99; H, 6.86; N, 3.89.

16,17-Acetylimino-5α-podocarpa-8,11,13-triene (19). A solution of 470 mg (1.49 mmol) of crude **6b**, mp 138–155 °C, in 30 mL of HOAc was treated with 330 mg (1.08 mmol) of $pyHBr_3$, mp 132–135 °C, in one portion (rapid precipitate formation[25]) and stirred for 45 min (N_2 atmosphere).[3] Isolation C ($CHCl_3$; 5% $NaHCO_3$ wash) provided 500 mg of a multicomponent mixture (TLC), which was taken up in $CHCl_3$ and extracted with 2% NaOH[26] which was immediately acidified with 2 N HCl and processed by isolation B ($CHCl_3$; 5% $NaHCO_3$ wash) to afford 130 mg (38%) of crude **7b** as a brown solid. Recrystallization from Me_2CO–MeOH afforded **7b** contaminated with a second compound (TLC), presumably **10b**, as tan prisms: mp 210–214 °C; IR 1675, 1625, 1580 cm^{-1}; ^1H NMR (80 °C)[17] τ 2.07 (d, J = 8.5 Hz, 1 H), 2.83–3.28 (m, 2 H), 7.88 (s, 3 H), 9.07 (s, 3 H), plus 1.83 (s) and 2.69 (s) presumably from **10b**. Phenol **7b** was not easily separated from the contaminant by recrystallization, chromatography (Al_2O_3), or fractional sublimation, so this mixture was used directly.

A mixture of 77 mg (0.25 mmol) of the crystalline **7b**, mp 210–214 °C, 60 mg (0.39 mmol) of 2-chlorobenzoxazole, and 200 mg of anhydrous K_2CO_3 in 20 mL of dry Me_2CO was stirred and boiled under reflux for 24 h,[1a] taken to dryness in vacuo, and partitioned between $CHCl_3$ and water which was processed by isolation B ($CHCl_3$). The residual 110 mg of crude oily **17** was chromatographed over 6 g of Florisil (5 × 10 cm; hexane, hexane–PhH, PhH, PhH–Et_2O, Et_2O, $CHCl_3$, and $CHCl_3$–MeOH elution). Excess chlorobenzoxazole was eluted with 50:50 hexane–PhH, and the 98:2 $CHCl_3$–MeOH fraction afforded 60 mg (57%) of **17** as a colorless amorphous solid: IR 1670, 1625, 1560 cm^{-1}; ^1H NMR τ 1.80 (d, J = 8.5 Hz, 1 H), 2.17–2.83 (m, 6 H), 5.38 (d, J = 14 Hz) and 5.63 (d, J = 14 Hz) (total 1 H), 6.48 (d, J = 14 Hz) and 6.56 (d, J = 14 Hz) (total 1 H), 7.27 (d, J = 14 Hz, 2 H), 7.90 (s, 3 H), 9.05 (s, 3 H).

A solution of 60 mg (0.14 mmol) of the chromatographed **17** in 10 mL of 95% EtOH was hydrogenated at 1 atm over 30 mg of 30% Pd/C for 18 h.[1a] The residue after filtration of Pd/C and evaporation was taken up in Et_2O, which was processed by isolation A (5 N KOH wash) to leave 25 mg of an oil which appeared to contain a small amount of **18** (IR) in addition to **19**: IR 3420 (w, **18**?), 1720 (w), 1625 cm^{-1}; ^1H NMR (CCl_4; 60 °C[17]) τ 2.67–3.17 (m, 4 H), 8.02 (s, 3 H), 9.07 (s, 3 H). Chromatography over 0.5 g of neutral Al_2O_3 (activity I; PhH, PhH–Et_2O, Et_2O, Et_2O–EtOAc, EtOAc elution) afforded in the PhH–Et_2O fraction 7 mg (18%) of **19** as an oil which slowly crystallized: mp 95–108 °C; IR (CCl_4) 1635 cm^{-1}, identical from 4000 to 800 cm^{-1} with a spectrum of authentic **19** provided by Professor A. Tahara.[15]

16,17-Methanesulfonylimino-12-hydroxy-7-oxo-5α-podocarpa-8,11,13-triene (7c). A solution of 94 mg (0.27 mmol) of crude **6c**, mp 150–159 °C, and 85 mg (0.28 mmol) of $pyHBr_3$ in 7 mL of HOAc was stirred for 0.5 h (N_2 atmosphere)[3] and added to 100 mL of 2% NaOH which was basified to pH ~10 with solid NaOH, diluted with 100 mL of 2% NaOH, washed with $CHCl_3$, and acidified with concentrated HCl. Isolation B ($CHCl_3$) left 51 mg (54%) of crude **7c** as a colorless powder, mp 255–268 °C dec. This was washed with $CHCl_3$ and recrystallized from MeOH (dry ice–Me_2CO bath) to afford **7c** as a colorless amorphous solid: mp 269–271 °C dec; UV max (95% EtOH) 220 (ε 10 000), 277 (13 000); (base) 242 (ε 5600), 332 nm (23 600); IR (KBr) 3280, 1650, 1575, 1330, 1288, 1154 cm^{-1}; ^1H NMR (Me_2CO-d_6) τ 2.02 (s, 1 H), 2.12 (d, J = 8.5 Hz, 1 H), 2.97 (d, J = 2.5 Hz, 1 H), 3.18 (dd, J = 8.5 and 2.5 Hz, 1 H), 7.20 (s, 3 H), 9.04 (s, 3 H).

Anal. Calcd for $C_{18}H_{23}NO_4S$: C, 61.86; H, 6.65; N, 4.00; S, 9.17. Found: C, 61.75; H, 6.65; N, 4.02; S, 9.17.

Registry No.—**2a**, 16981-46-7; **2b**, 62461-28-3; **2c**, 62461-29-4; **2d**, 56666-22-9; **2e**, 16981-47-8; **3a**, 63784-50-9; **3b**, 63784-51-0; **3c**, 63784-52-1; **3d**, 63784-53-2; **3e**, 63784-54-3; **4a**, 63784-55-4; **4b**, 63784-56-5; **4c**, 63784-57-6; **4d**, 63784-58-7; **4e**, 63784-70-3; **5a**, 63784-59-8; **5b** isomer 1, 63784-60-1; **5b** isomer 2, 63814-61-9; **5c**, 63784-61-2; **5d**, 63784-62-3; **6a**, 62461-84-1; **6b**, 62461-85-2; **6c**, 62461-86-3; **7a**, 63784-63-4; **7b**, 63797-56-8; **7c**, 63784-64-5; **8a**, 63784-65-6; **9a**, 63784-66-7; **10a**, 63784-67-8; **10b**, 63784-68-9; **17**, 63784-69-0; **19**, 38750-33-3; $CH_3COCH_2CO_2$-*t*-Bu, 1694-31-1; 2-chlorobenzoxazole, 615-18-9.

References and Notes

(1) (a) Part 11: W. L. Meyer and C. W. Sigel, *J. Org. Chem.*, **42**, 2769 (1977). (b) Abstracted in part from Ph.D. Dissertations of C.W.S., R.J.H., T.E.G., and R.A.M. and the M.S. Thesis of P.G.S., Indiana University, 1967, and University of Arkansas, 1972, 1974, 1971, and 1968, respectively. (c) Supported in part by Research Grant AM-10123 from the National Institute of Arthritis and Metabolic Diseases and by the University of Arkansas Research Reserve Fund; the UV and mass spectrometers were obtained with partial support of National Science Foundation Grants GP-8286 and GP-6978, respectively. (d) National Institutes of Health Predoctoral Fellow; 1965–1967. (e) Eastman Kodak Research Fellow, 1969–1970. (f) National Science Foundation Trainee, 1969–1970 and 1971–1972; National Aeronautics and Space Administration Trainee, 1970–1971; Phillips Petroleum Company Fellow, 1972–1973.

(2) For convenience all bicyclic and tricyclic compounds in this paper will be numbered by the steroid—terpenoid convention as in **1**, with the gem-disubstituted ring of decalins being ring A. The configurational notations α and β denote a trans or cis relation to the C-10 angular group, respectively. All synthetic substances were prepared only in racemic form, although the prefix (±) is omitted and only one enantiomer is depicted.

(3) W. L. Meyer, G. B. Clemans, and R. A. Manning, *J. Org. Chem.*, **40**, 3686 (1975).

(4) W. L. Meyer, R. A. Manning, E. Schindler, R. S. Schroeder, and D. C. Shew, *J. Org. Chem.*, **41**, 1005 (1976).

(5) W. L. Meyer, R. W. Huffman, and P. G. Schroeder, *Tetrahedron*, **24**, 5959 (1968).

(6) W. L. Meyer, T. E. Goodwin, R. J. Hoff, and C. W. Sigel, *J. Org. Chem.*, **42**, 2761 (1977).

(7) S. K. Pradham and H. J. Ringold, *J. Org. Chem.*, **29**, 601 (1964); A. B. Turner and H. J. Ringold, *J. Chem. Soc. C*, 1720 (1967).

(8) Oxidation of **3c** in hot *t*-BuOH also proceeds well, but is hampered by competitive HOAc-catalyzed conversion of **3c** to its *tert*-butyl enol ether, cf. footnote 13 of ref 4.

(9) We do not believe that these reactivity differences are due to differences in purity of the DDQ which was used in various reactions (although that is certainly a variable which can also produce capricious results) or to differences in technique among experimentalists. Although no single individual in our laboratory has conducted all of the dehydrogenations discussed here, each of these reactions has been examined by one or more persons, each of whom has also reproduced one or more of the successful reported dehydrogenations[1a,3,4] using the same DDQ.

(10) W. L. Meyer, R. A. Manning, P. G. Schroeder, and D. C. Shew, *J. Org. Chem.*, **42**, 2754 (1977).

(11) Further reactions were not examined in the 4,4-dimethyl-10-cyano and 4α-carbethoxy-10-cyano series owing to the inaccessibility of **4d** and **4e** in adequate quantity or purity.

(12) Cf. footnote 12 of ref 9.

(13) Detailed optimization of aromatization conditions and a search for **9b** and **9c** in the hydroxide-insoluble fraction were not pursued with **6b** and **6c**, but all data which were obtained in those series are in accord with qualitative similarity between their reactivity and that of **6a**.

(14) Scheme II portrays reactions through enols **12** and **16** rather than **14** (R^4 = H or alkyl and R^4 = Br) only for brevity. The latter are reasonable alternatives, although molecular models suggest that the trans-syn tricyclic system is less strained with a double bond at 7,8 than it is at 8,14, cf. ref 10. Initial bromination at C-8 is not discussed because it should lead to **7** whether R^4 is alkyl or H.[3] Pathways involving Br_2 addition to double bonds of various enediones can also be envisioned, but seem less likely because compound **12** of ref 1a undergoes 6-bromination and not $\Delta^{8,14}$ bromine addition.

(15) A. Tahara, K. Hirao, and Y. Hamazuki, *Chem. Ind. (London)*, 850 (1965); A. Tahara and K. Hirao, *Tetrahedron Lett.*, 1453 (1966). We are grateful to Dr. Tahara for the IR spectrum of his enantiomer of **19**.

(16) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Am. Chem. Soc.*, **85**, 2342 (1963); W. Nagata, M. Narisada, T. Wakabayashi, and T. Sugasawa, *ibid.*, **86**, 929 (1964).
(17) ^{1}H NMR spectra of the *N*-acetyl derivatives in this series indicate that they exist as nearly 50:50 mixtures of two conformers about the N–CO bond, with interconversion being slow on the NMR time scale at ambient probe temperature, cf. ref 6.
(18) Acidification with HCl induces variable amounts of *tert*-butyl enol etherification, cf. ref 4.
(19) It is particularly important to carefully reextract the $NaHCO_3$ wash solution so as to avoid loss of the formyl enone into the aqueous phases.
(20) We thank the Eastman Chemical Co. for a generous sample of this substance.
(21) In some preparations additional resonance from CH_3CO (τ 7.91) and $(CH_3)_3C$ (τ 8.55) indicate the presence of up to ~20% of a second diastereomer.[10]
(22) The ^{1}H NMR properties of this by-product, insofar as they are discernable in the spectrum of the mixture, would be consistent with its formulation as a trans-anti-trans diastereomer of **6c**. In view of the fact that we have not encountered such a stereoisomer in any other analogous system, however, we hesitate to make such an assignment until the substance can be examined in pure form.
(23) L. F. Fieser, "Experiments in Organic Chemistry", 3rd ed, D. C. Heath, Boston, Mass., 1957, p 65.
(24) C. W. Shoppee, S. K. Roy, and B. S. Goodrich, *J. Chem. Soc.*, 1583 (1961).
(25) Precipitation at this point has not been observed in analogous reactions, and is probably due to salt formation at the amide function.
(26) Use of more concentrated alkali brings about partial hydrolysis of the amide.

Synthesis of 6*H*,12*H*-indazolo[2,1,*a*]-6,12-diiminoindazoles and 3-Imino-2-phenylindazolines from Azo Compounds and Isocyanides in the Presence of Octacarbonyldicobalt[1]

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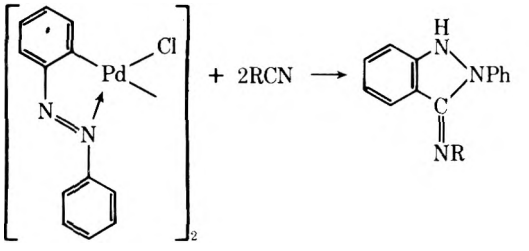
The reactions of azobenzenes and isocyanides in the presence of $Co_2(CO)_8$ gave 6*H*,12*H*-indazolo[2,1,*a*]-6,12-diiminoindazoles (**1**) and 3-imino-2-phenylindazolines (**2**). Orthometalation by a cobalt atom, which is considered as a first step in these reactions, occurs nucleophilically. The reaction mechanism is discussed.

Reactions of aromatic azo compounds with carbon monoxide are catalyzed by $Co_2(CO)_8$ to produce 3-oxo-2-phenylindazolines and 2,4-dioxo-1,2,3,4-tetrahydroquinazolines.[2] Similar reactions in the presence of $Ni(CO)_4$ give 6*H*,12*H*-indazolo[2,1,*a*]-6,12-dioxoindazoles.[3] We recently showed that reaction of cyclopalladation complexes of azobenzene with isocyanides gave 3-imino-2-phenylindazolines stoichiometrically (eq 1).[6] In attempts to examine the catalytic scope of

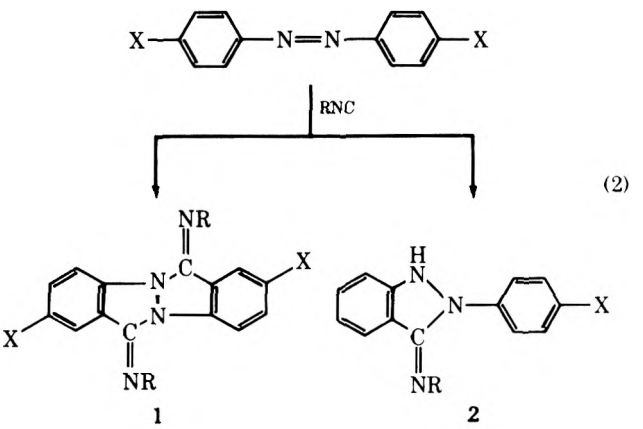


(1)

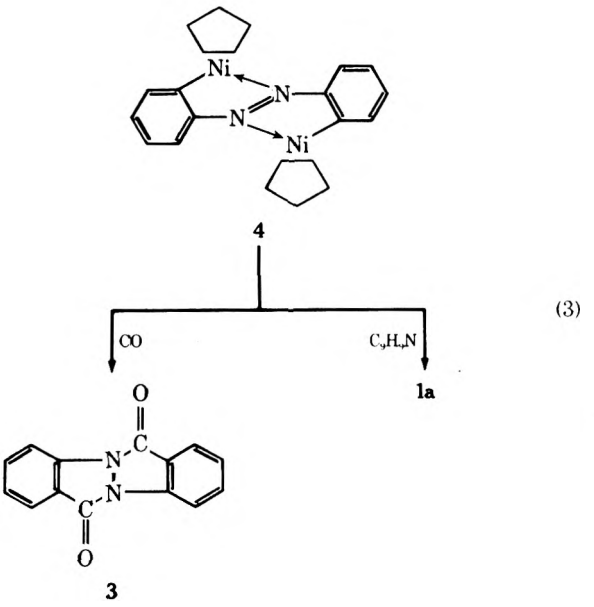
these reactions, the reactions of azobenzene derivatives with isocyanides were carried out in the presence of $Co_2(CO)_8$. We found that the aforementioned reactions produced 6*H*,12*H*-indazolo[2,1,*a*]-6,12-diiminoindazoles and 3-imino-2-phenylindazolines, depending on the substituent of RNC.

A mixture of azobenzene, 2,6-xylyl isocyanide, and $Co_2(CO)_8$ was heated in toluene at 120–125 °C. Chromatography of the mixture on alumina gave a yellow crystalline compound **1a** with the empirical formula $C_{30}H_{26}N_4$, M^+ 442 (442.54). The NMR spectrum showed one singlet due to the methyl groups at δ 2.16 ppm, suggesting a symmetrical molecular structure. The UV absorption pattern is similar to that of 6*H*,12*H*-indazolo[2,1,*a*]-6,12-dioxoindazole (**3**). The reaction of 2,6-xylyl isocyanide with a nickel azobenzene complex (**4**)[7] gave **1a** (eq 3).

A similar reaction with carbon monoxide produced **3** (eq 3). These results showed that **1a** is 6*H*,12*H*-indazolo[2,1,*a*]-6,12-[dixylyl]iminoindazole. Similar compounds were obtained when *p*-chloro- and *p*-methylazobenzene or 4-



(2)



(3)

Table I. Reactions of RNC with p-$XC_6H_4N{=}NC_6H_4X$-p[a]

R	Registry no.	X	Product	Registry no.	Product (mol) $Co_2(CO)_8$ (mol)
2,6-$(CH_3)_2C_6H_3$	2769-71-3	H	**1a**	63866-01-3	2.4
2,6-$(CH_3)_2$-4-BrC_6H_2	24139-49-9	H	**1b**	63866-00-2	2.9
2,6-$(CH_3)_2C_6H_3$		CH_3	**1c**	63865-99-6	3.9
2,6-$(CH_3)_2C_6H_3$		Cl	**1d**	63865-98-5	2.0
2-$(CH_3)C_6H_4$	10468-64-1	CH_3	**1e**	63866-08-0	0.6
2-$(CH_3)C_6H_4$		CH_3	**2e**	63866-10-4	1.5
$(CH_3)_3C$	7188-38-7	H	**2a**	62247-94-3	4.2
C_6H_{11}	931-53-3	H	**2b**	62247-95-4	3.1
Ph	931-54-4	H	**2c**	63866-09-1	3.5

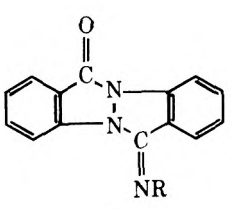
[a] Reaction temperature, 120–125 °C; time, 4 h; $Co_2(CO)_8$, ca. 0.20 g (0.58 mmol); azo compound, ca. 6.6 mmol; isocyanide, ca. 12 mmol.

bromo-2,6-dimethyphenyl isocyanide were used. However, the reactions of azobenzene with phenyl, *tert*-butyl or cyclohexyl isocyanide in the presence of $Co_2(CO)_8$ produced the corresponding 3-imino-2-phenylindazoline (**2**) without affording any compound of type **1** (eq 2). When *o*-tolyl isocyanide was used, the reaction gave a mixture of **1e** and **2e** in a 1:3 molar ratio. The results are summarized in Table I.

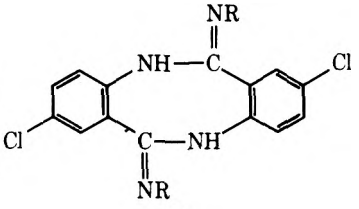
In an attempt to convert **2e** to **1e** the reaction of **2e** with *o*-tolyl isocyanide was carried out, but compound **2e** was recovered, suggesting that **2e** is not a precursor of **1e**.

Several attempts to examine the scope of catalysis with $Fe(CO)_5$, $Fe_2(CO)_9$, $Ni(CO)_4$, and $Mo(CO)_6$ led only to formation of metal isocyanide complexes such as $Fe(CO)_4(C_9H_9N)$, $Ni(C_9H_9N)_4$, and $Mo(CO)_4(C_9H_9N)_2$.

Treatment of **1a** with aqueous HCl in $CH_3OCH_2CH_2OH$ at reflux gave **5** and 2,6-xylylamine, but 6*H*,12*H*-indazolo[2,1,*a*]-6,12-dioxoindazole was not obtained. Similar treatment of **1d** on alcoholic KOH gave **6**.



5



6

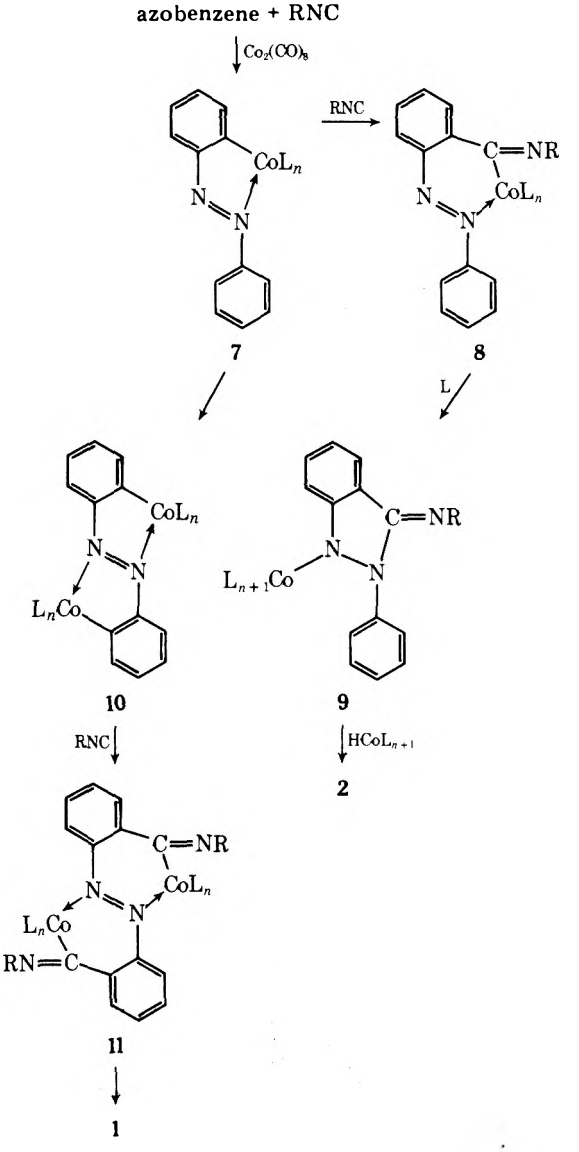
Compounds **1** and **2** are probably formed via initial orthometalation on the aromatic ring by a cobalt isocyanide complex[8] formed by the reaction of $Co_2(CO)_8$ with isocyanide, as well as the mechanism[9,10] proposed for the transition metal-catalyzed carbonylation of azobenzene, as shown in Scheme I.

An isocyanide insertion into **7**, forming **8**, and a rearrangement of a cobalt moiety to a nitrogen atom followed by cyclization of the azo function would give **9**. This species could be reduced with $HCoL_4$ to give **2**. The cobalt–isocyanide complex reformed in this reaction would again metalate the azobenzene and the catalytic cycle would be complete.

Before an isocyanide insertion into **7**, double metalation occurred to give a binuclear complex **10** in which both nitrogens are used for coordination to two metal atoms which bond to the two aromatic rings. The reaction would be completed by isocyanide insertion and cyclization of the azo function to produce **1**. A steric hindrance of bulky isocyanide would make the double metallation more favorable than an isocyanide insertion into a single metalated intermediate **7**.

Bruce and co-workers have shown that two different mechanisms (electrophilic and nucleophilic attack of metal on the aromatic ring) are operative in orthometalation of azobenzene derivatives based on a study of substituent effect.[11]

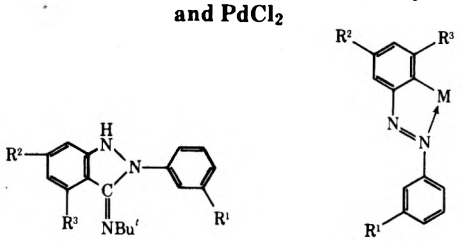
Scheme I. Formation of 3-Imino-2-phenylindazolines and 6*H*,12*H*-Indazolo[2,1,*a*]-6,12-[dixylyl]iminoindazolones



We have examined the reaction of *m*-fluoroazobenzene with *tert*-butyl isocyanide for the purpose of obtaining mechanistic information. Distribution of three isomers was determined by the proton NMR spectra. The results are summarized in Table II together with the results[11] of the metallation obtained by Bruce et al.

3-*tert*-Butylimino-2-phenyl-5-fluoroindazoline (**12c**) substituted at the ortho position to fluorine is ca. 70% of the resulting mixture. Although the process of an isocyanide in-

Table II. Isomers Formed in the Reactions of *m*-$FC_6H_4N{=}NC_6H_5$ with $Co_2(CO)_8Bu^tNC$, $CH_3Mn(CO)_5$, and $PdCl_2$



Compd[a]	*a*	*b*	*c*	Ref
12	30		70	This paper
13	20		80	11
14	80	20		11

[a] $R^1 = F, R^2 = R^3 = H$. [b] $R^2 = F, R^1 = R^2 = H$. [c] $R^3 = F, R^1 = R^2 = H$.

sertion into a cobalt-metal σ bond was included in addition to that of metalation in the reaction in question, this result appears to be consistent with nucleophilic attack of cobalt atom on a carbon atom greatly activated by the inductive effect of fluorine, compared with that of orthometalation of *m*-fluoroazobenzene by $CH_3Mn(CO)_5$ to give **13c** as the main product.

Experimental Section

General Considerations. All reactions were carried out under an atmosphere of nitrogen. Melting points were taken on a Laboratory Devices Mel-Temp apparatus and are uncorrected. The NMR spectra were recorded on JEOL C60HL and Varian HA-100B spectrometers, using tetramethylsilane as a reference. The mass spectra were measured on a Nippondenshi Type JPS-1S mass spectrometer with a direct-inlet system. The UV spectra were recorded on Cary 14 spectrometer. Dicobalt octacarbonyl was prepared from cobalt(II) acetate.[12] Various isocyanides[13] and di-*p*-methyl- and di-*p*-chloroazobenzene[14] were prepared by procedures described in the literature. *m*-Fluoroazobenzene was prepared from nitrosobenzene and *m*-fluoroaniline in acetic anhydride. The nickel[7] and π-cyclopentadienyl palladium[11] complexes of azobenzene were prepared by procedures described in the literature.

Preparation of 6*H*,12*H*-indazolo[2,1,*a*]-6,12-diiminoindazoles. A representative reaction is described in detail. A mixture of azobenzene (1.1 g, 6.5 mmol), 2,6-xylyl isocyanide (1.5 g, 1.15 mmol), and $Co_2(CO)_8$ (0.20 g, 0.58 mmol) in toluene (15 mL) was heated at 120–125 °C for 4 h. The mixture was chromatographed on alumina. Two bands (orange and yellow) were observed. Eluting with hexane gave unreacted azobenzene and isocyanide. Eluting with hexane–benzene (1:2) gave a yellow solution. The solvent was evaporated almost to dryness under reduced pressure, and crystallization of the residue from benzene–hexane gave 6*H*,12*H*-indazolo[2,1,*a*]-6,12-[di-2,6-xylyl]iminoindazole: mp 268 °C (0.61 g, 22%); NMR ($CDCl_3$) 2.16 (s, CH_3) 6.5–8.3 (c, aromatic protons); UV (in benzene) 406 (ϵ 2.16 × 10^4), 288 (ϵ 9.6 × 10^3), 279 (ϵ 9.0 × 10^3), 245 (ϵ 4.2 × 10^4), and 288 (ϵ 3.5 × 10^4) nm.

Anal. Calcd for $C_{30}H_{26}N_4$: C, 81.42; H, 5.92; N, 12.66. Found: C, 81.36; H, 5.94; N, 12.63.

Similar compounds were prepared according to procedures analogous to those described above. **1b**: mp 293–294 °C; NMR ($CDCl_3$) δ 2.16 (s, CH_3) and 6.6–8.4 (c, aromatic protons) ppm. Anal. Calcd for $C_{30}H_{24}N_4Br_2$: C, 60.02; H, 4.03; N, 9.33. Found: C, 60.21; H, 4.05; N, 9.38. **1c**: mp 274–275 °C; NMR ($CDCl_3$) δ 2.16 (s, 2 CH_3), 2.18 (s, 4 CH_3), and 6.2–8.1 (c, aromatic protons) ppm. Anal. Calcd for $C_{32}H_{30}N_4$: C, 81.67; H, 6.43; N, 11.91. Found: C, 81.67; H, 6.55; N, 11.74. **1d**: mp 253–255 °C; NMR ($CDCl_3$) δ 2.13 (s, CH_3) and 6.8–8.2 (*c*, aromatic protons) ppm. Anal. Calcd for $C_{30}H_{24}N_4Cl_2$: C, 70.45; H, 4.73; N, 10.95. Found: C, 70.43; H, 4.83; N, 10.99. **1e**: mp 269 °C; NMR ($CDCl_3$) δ 2.13 (s, 2 CH_3), 2.23 (s, 2 CH_3), and 6.4–8.2 (c, aromatic protons) ppm. Anal. Calcd for $C_{30}H_{26}N_4$: C, 81.42; H, 5.92; N, 12.66. Found: C, 81.00; H, 5.94; N, 12.70.

Preparation of 3-Imino-2-phenylindazolines. A representative reaction is described in detail. A mixture of azobenzene (1.1 g, 6.5 mmol), *tert*-butyl isocyanide (1.7 g, 2.0 mmol), and $Co_2(CO)_8$ (0.2 g, 0.58 mmol) in toluene (15 mL) was heated at 125 °C for 4 h. Chromatography of the mixture on alumina showed two bands. They were eluted with hexane–benzene (10:1) and benzene, giving orange and pale-yellow eluates, respectively. The product from the first eluate was unreacted azobenzene and *tert*-butyl isocyanide. The product from the second one was identified as *tert*-butylamino-2-phenylindazoline (**2a**), mp 83.5–84 °C (lit.[6] mp 84 °C), by the mixture melting point with and infrared spectrum of an authentic sample of *tert*-butylimino-2-phenylindazoline. Anal. Calcd for $C_{17}H_{19}N_3$: C, 76.95; H, 7.22; N, 15.84. Found: C, 76.89; H, 7.23; N, 15.93.

2b: mp 204–205 °C (lit.[6] mp 204–205 °C). Anal. Calcd for $C_{19}H_{21}N_3$: C, 78.31; H, 7.26: N, 14.42. Found: C, 78.49; H, 7.25; N, 14.55. **2c**: mp 135–135.5 °C. Anal. Calcd for $C_{19}H_{15}N_3$: C, 79.97; H, 5.30; N, 14.73. Found: C, 79.75; H, 5.44; N, 14.82. **2e**: mp 104–105 °C (lit.[6] mp 103–104 °C). Anal. Calcd for $C_{22}H_{21}N_3$: C, 80.70; H, 6.47; N, 12.84. Found: C, 80.56; H, 6.44; N, 12.81.

Reaction of a Binuclear Nickel–Azobenzene Complex 4 with 2,6-Xylyl Isocyanide. A mixture of **4** (0.6 g, 1.4 mmol) and 2,6-xylyl isocyanide (0.52 g, 4.0 mmol) in toluene (15 mL) was heated at 100 °C for 10 h. The mixture was chromatographed on alumina; two bands (yellow and blue) were observed. Each was eluted with benzene and benzene–CH_2Cl_2 (1:4). Eluting with benzene gave **1a** (0.18 g, 29%). The product from the second eluate was an unreacted nickel complex (ca. 0.1 g).

Reaction of 4 with Carbon Monoxide. A mixture of **4** (0.3 g, 0.7 mmol) and carbon monoxide (60 kg/cm²) in toluene (15 mL) in a 200-mL stainless steel autoclave was kept at 110 °C for 5 h. The mixture was chromatographed on alumina, using CH_2Cl_2 as an eluant. The yellow band was observed. Removal of the solvent gave crude **3** (0.11 g, 66.5%) as yellow crystals. Crystallization from CH_2Cl_2–hexane gave pure **3** (0.10 g), identified by an infrared spectrum of an authentic sample of 6*H*,12*H*-indazolo[2.1,*a*]-6,12-dioxoindazole.

The Reaction of Azobenzene with 2,6-Xylyl Isocyanide in the Presence of Metal Carbonyls. A mixture of azobenzene (0.9 g, 5.0 mmol), 2.6-xylyl isocyanide (1.3 g, 10 mmol), and $Ni(CO)_4$ (0.17 g, 1.0 mmol) in toluene was heated at 120 °C for 4 h. The mixture was chromatographed on alumina, using benzene as an eluant. Removal of the solvent and crystallization of the residue from benzene–hexane gave tetrakis(2,6-xylyl isocyanide)nickel (0.42 g, 72%) as yellow-orange crystals: mp 150–152 °C (dec); NMR (PhCl) δ 2.35 (s, CH_3) ppm. Anal. Calcd for $C_{36}H_{36}N_4Ni$: C, 74.11; H, 6.22; N, 9.60. Found: C, 73.99; H, 6.20; N, 9.81.

Similar reactions were carried out in the presence of $Fe(CO)_5$, $Fe_2(CO)_9$, and $Mo(CO)_6$. The reactions gave $Fe(CO)_4(C_9H_9N)$ and $Mo(CO)_4(C_9H_9N)_2$.

$Fe(CO)_4(C_9H_9N)$: yellow crystals, mp 78–80 °C (dec). The molecular weight by mass spectroscopy was 299 (calcd 299.07). Anal. Calcd for $C_{13}H_9NO_4Fe$: C, 52.21; H, 3.03; N, 4.68. Found: C, 51.97; H, 3.15; N, 4.64.

$Mo(CO)_4(C_9H_9N)_2$: yellow crystals, mp 148–151 °C (dec). The molecular weight by mass spectroscopy was 470 (calcd 470.34). Anal. Calcd for $C_{22}H_{18}N_2O_4Mo$: C, 56.18; H, 3.86; N, 5.96. Found: C, 58.22; H, 3.67; N, 6.00.

Reaction of a Mixture of 14a and 14b with *tert*-Butyl Isocyanide. A mixture of **14** (0.3 g) and *tert*-butyl isocyanide (1.2 mL) in THF (15 mL) was heated at 120 °C for 5 h. The mixture was chromatographed on alumina, using benzene as an eluant. Benzene was removed to dryness. The NMR spectrum of the residue showed the presence of two isomers, which were identified as **12a** and **12b** in a ca. 85:15 intensity ratio: NMR ($CDCl_3$) **12a** 1.03 (s, Bu^t) ppm and **12b** 1.48 (s, Bu^t) ppm.

Reaction of *m*-Fluoroazobenzene with *tert*-Butyl Isocyanide in the Presence of $Co_2(CO)_8$. A mixture of *m*-fluoroazobenzene (0.9 g, 5.2 mmol), *tert*-butyl isocyanide (0.83 g, 10 mmol), and $Co_2(CO)_8$ (0.2 g, 0.58 mmol) in toluene (15 mL) was heated at 125 °C for 4 h. The mixture was chromatographed on alumina. Benzene eluted a mixture of two isomers (0.57 g). The NMR spectrum showed two singlets at δ 1.03 and 0.97 ppm, consisting of a relative intensity of 69:31. The former signal was identified as **12a** and the latter as **12c**. The molecular weight of the mixture by mass spectroscopy was 283 (calcd 283.35).

Registry No.—**3**, 18428-89-2; **4**, 63866-71-7; **12a**, 63866-05-7; **12b**, 63866-03-5; **12c**, 63866-02-4; azobenzene, 103-33-3; $Co_2(CO)_8$, 10210-68-1; carbon monoxide, 630-08-0; $Ni(CO)_4$, 13463-39-3; tetrakis(2,6-xylyl isocyanide)nickel, 63866-70-6; $Fe(CO)_5$, 13463-40-6; $Fe_2(CO)_9$, 15321-51-4; $Mo(CO)_6$, 1393906-5; $Fe(CO)_4(C_9H_9N)$, 63866-73-9; $Mo(CO)_4(C_9H_9N)_2$, 63866-72-8; *m*-fluoroazobenzene,

331-19-1; *p*-chloroazobenzene, 1602-00-2; *p*-methylazobenzene, 501-60-0.

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Nucleophilic Substitution on Dialkoxy Disulfides. Reactions with Mercaptans or Amines

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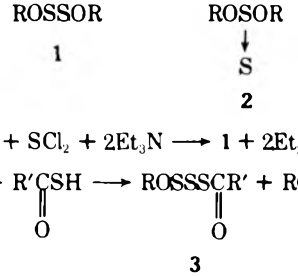
Dialkoxy disulfides (1) readily reacted with mercaptans or secondary amines to give alkoxyalkyl trisulfides (4) or alkoxyamino disulfides (5) with elimination of alcohol. These alkoxy sulfides (4 or 5) further reacted with mercaptans or secondary amines to give unsymmetrical dialkyl tetrasulfides (6), alkylamino trisulfides (7), and unsymmetrical diamino disulfide (8). However, reaction of 1 with *N,N*-dimethyl-*p*-phenylenediamine gave *p*-dimethylamino-*N*-thiosulfinylaniline (10). Reaction of 1 and benzylamine or furfurylamine afforded dibenzylideneamino tetrasulfide (11a) or difurfurylideneamino tetrasulfide (11b), whereas 1 and β-phenylethylamine or DL-α-phenylethylamine gave thioamides, PhC(=O)C(=S)NHR (13). Treatment of 1 with thiobenzamide afforded benzonitrile, sulfur, and alcohol.

Dialkoxy disulfides (1) were initially prepared by the reaction of sodium alcoholates with sulfur monochloride[1] with two structures, 1 and 2, proposed for the products. Raman spectra[2] and dipole-moment data[3] favored the structure 1, but 2 could not be rigorously excluded. In recent years, Thompson et al. reported an excellent method for the preparation of 1 by the reaction of alcohols and sulfur monochloride in the presence of triethylamine (eq 1) and proved that these compounds have the disulfide structure 1 by NMR and x-ray analysis.[4] Little attention has been paid to reactions of 1. Previous investigations were not extended beyond investigation of reactions with sodium alcoholate,[1c,5] alkyllithium,[4] and β-diketone.[4] It is seen that the products in these reactions are formed by attack of nucleophiles such as OR^-, R^-, $RCO\text{-}^-CHCOR$ on sulfur with cleavage of the sulfur–sulfur or sulfur–oxygen bond. Recently, we have also found that[6] equimolar thiocarboxylic acids readily displace an alcohol moiety and afford acylalkoxy trisulfides (3). We have now studied reactions of 1 with other nucleophiles.



$$2ROH + SCl_2 + 2Et_3N \longrightarrow 1 + 2Et_3NHCl \quad (1)$$

$$1 + R'\underset{\underset{O}{\|}}{C}SH \longrightarrow ROSSS\underset{\underset{O}{\|}}{C}R' + ROH \quad (2)$$

3

Results and Discussion

Dialkoxy disulfides (1) react readily with equimolar amounts of mercaptan in carbon tetrachloride. The alcohol is eliminated gradually, and monosubstituted products, alkoxyalkyl trisulfides (4), are obtained in 20–50% yields along with disubstituted products, symmetrical dialkyl tetrasulfides. Elimination of alcohol was confirmed by infrared spectra and gas chromatography. Results are shown in Table I. The IR spectra of 4 showed absorptions similar to those of 1 in –SO– (660–725 cm^1) and >CO– (880–1020 cm^{-1}) stretching bands (Table III, Supplementary Material). The NMR spectra of 4 showed simple absorptions in its protons of methylene adjacent to an oxygen atom, RCH_2O– (Table III, Supplementary Material), with no apparent magnetic nonequivalence.[7]

Secondary amines were less reactive than mercaptans and their reaction with 1 required refluxing in CCl_4 for 4–8 h. Alkoxyamino disulfides (5) (Scheme I) were obtained in 19–74%

Scheme I

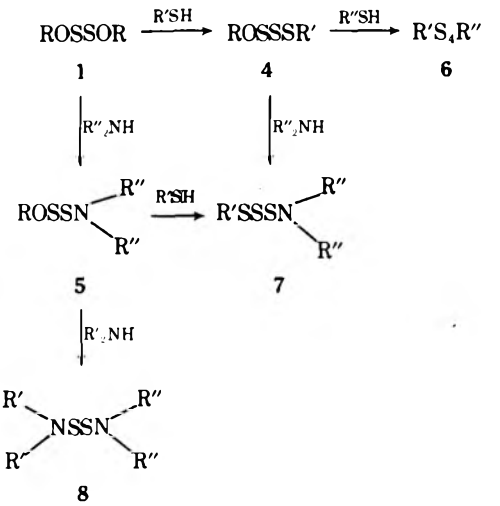


Table I. Monosubstituted Products of Dialkoxy Disulfides[a]

ROSSOR + XH → ROSSX + ROH

Compd	R	X	Bp, °C (mm)	Yield, %
4a	C_2H_5	C_2H_5S	72.5 (3.2)	45
4b	C_2H_5	n-C_3H_7S	66 (0.9)	43
4c	C_2H_5	i-C_3H_7S	72 (1.4)	50
4d	C_2H_5	t-C_4H_9S	53 (0.6)	40
4e	CH_3	t-C_4H_9S	51 (1.0)	22
5a	C_2H_5	$(C_2H_5)_2N$	58 (2.1)	74
5b	C_2H_5	$(CH_2)_5N$	85 (1.0)	41
5c	CH_3	$(C_2H_5)_2N$	63 (7)	54
5d	CH_3	$(CH_2)_4N$	53 (1.1)	19
5e	CH_3	$(i$-$C_3H_7)_2N$	53 (0.5)	22

[a] Satisfactory analytical data (±0.2% for C, H, S, and N) were reported for all compounds in the table.

yields as shown in Table I and Table III (Supplementary Material). The remaining alkoxy group in **4** and **5** could be further displaced with mercaptans or secondary amines to give unsymmetrical dialkyl tetrasulfides (**6**) and alkylamino trisulfides (**7**)[8] in good yields (Scheme I). These results are shown in Table II and Table IV (Supplementary Material). Unsymmetrical diamino disulfide (**8**) was obtained by the reaction of **5** with the other secondary amine, but the yield was lower than those of the other disubstituted products, **6** or **7**. Displacement of alkoxy groups as outlined in Scheme I by –SR or $-NR_2$ groups gives unsymmetrical polysulfides not readily prepared directly from sulfur halides.

Reactions of **1** with primary amines[9] gave a variety of products as follows. When *N*,*N*-dimethyl-*p*-phenylenediamine and equimolar amounts of diethoxy disulfide (**1a**) were refluxed in benzene, the color of the solution gradually turned to deep violet with elimination of ethanol. *p*-Dimethylamino-*N*-thiosulfinylaniline (**10**)[10] was obtained by column chromatography of the reaction mixture. Presumably **10** is generated by elimination of ethanol from the intermediate ethoxyamino disulfide (**9**) (eq 3 and 4).

$$p\text{-}Me_2NC_6H_4NH_2 + EtOSSOEt \xrightarrow{\mathbf{1a}} [p\text{-}Me_2NC_6H_4NHSSOEt] + EtOH \quad (3)$$

9

$$\mathbf{9} \longrightarrow p\text{-}Me_2NC_6H_4N{=}S{=}S + EtOH \quad (4)$$

10

Benzylamine and **1a** in benzene afforded dibenzylideneamino tetrasulfide (**11a**),[11] sulfur, and ethanol (eq 5). Considering the formation of **10** from **1a** and Me_2NPhNH_2, it seems reasonable to assume that this tetrasulfide (**11a**) would be formed also via the thiosulfinyl compound in the following way. Namely, benzylamine and **1a** initially afford the thiosulfinyl compound which isomerizes to benzylideneamino hydrogen disulfide (**12**) with proton transfer. Two molecules of **12** then attack **1a** to form the hexasulfide which decomposes to give **11a** with loss of sulfur (eq 6 and 7). According to this assumption, 2 mol of benzylamine should react with 3 mol of **1a**. This was indirectly supported by the fact that the yield of **11a** increased from 40 to 60% by varying the molar ratio of **1a** to benzylamine from 1 to 1.5. Similarly, furfurylamine reacted with **1a** to give difurfurylideneamino tetrasulfide (**11b**) (eq 8).

$$2PhCH_2NH_2 + 3EtOSSOEt \xrightarrow{\mathbf{1a}} PhC(H){=}NS_4N{=}C(H)Ph + 6EtOH + 2S \quad (5)$$

11a

Table II. Disubstituted Products of Dialkoxy Disulfides[a]

XSSOR + YH → XSSY + ROH (R = ethyl)

Compd	X	Y	Bp, °C (mm)	Yield, %
6a	C_2H_5S	n-C_3H_7S	79 (0.19)	60
6b	C_2H_5S	i-C_3H_7S	75 (0.07)	63
7a	C_2H_5S	$(C_2H_5)_2N$	72 (0.08)	60
7a	$(C_2H_5)_2N$	C_2H_5S		67
7b	i-C_3H_7S	$(C_2H_5)_2N$	80 (0.12)	73
7c	C_2H_5S	$(CH_2)_4N$	56 (0.23)	56
8a	$(C_2H_5)_2N$	$(CH_2)_4N$	86 (0.07)	37

[a] See footnote *a*, Table I.

$$PhCH_2NH_2 \xrightarrow[-2EtOH]{\mathbf{1a}} [PhCH_2N{=}S{=}S] \longrightarrow \left[\begin{matrix} PhC{=}NSSH \\ | \\ H \end{matrix}\right] \quad (6)$$

12

$$2\,[\mathbf{12}] + \mathbf{1a} \xrightarrow[-2EtOH]{} \left[\begin{matrix} PhC{=}NS_6N{=}CPh \\ | \qquad\qquad | \\ H \qquad\quad H \end{matrix}\right] \longrightarrow \mathbf{11a} + 2S \quad (7)$$

$$2\ \text{(furfurylamine)} + 3\,\mathbf{1a} \longrightarrow \text{(difurfurylideneamino tetrasulfide)} + 6EtOH + 2S \quad (8)$$

11b

The reaction of **1a** with β-phenylethylamine or DL-α-phenylethylamine differed from that observed with aniline or benzylamine. Although a thioamide (**13**) was separated by column chromatography on silica gel, the IR spectra of the crude products before being chromatographed showed no ν_{NH} or $\nu_{C=O}$ bands. This suggests that **13** is formed by the decomposition of unidentified intermediates during the chromatography. The exact mechanism of the reaction is still not elucidated. The structure of thioamides (**13**) was confirmed by NMR, IR, and mass spectra as described in the Experimental Section.

$$RNH_2 \xrightarrow[-EtOH,-S]{EtOSSOEt\ (\mathbf{1a})} \begin{matrix} PhC & -C & -NR \\ \| & \| & | \\ O & S & H \end{matrix} \quad (9)$$

13

(R = $PhCH_2CH_2$–, $PhCH(CH_3)$–)

13a **13b**

Diethoxy disulfide (**1a**) did not react with benzamide, but it did so with thiobenzamide to give benzonitrile, sulfur, and ethanol (eq 10). The reaction probably proceeded again via thiobenzoyl-*N*-thiosulfinylamine followed by elimination of sulfur (eq 11).

$$\begin{matrix} PhCNH_2 \\ \| \\ S \end{matrix} + EtOSSOEt \longrightarrow PhC{\equiv}N + 3S + 2EtOH \quad (10)$$

1a

$$\begin{matrix} PhCNH_2 \\ \| \\ S \end{matrix} \xrightarrow[-EtOH]{\mathbf{1a}} \left[\begin{matrix} PhC & -NSSOEt \\ \| & | \\ S & H \end{matrix}\right] \xrightarrow{-EtOH} \left[\begin{matrix} PhC & -N{=}S \\ \| & \| \\ S & S \end{matrix}\right]$$

$$\longrightarrow \left[\begin{matrix} Ph{-}C{=}N \\ S \quad S \\ \diagdown\ \diagup \\ S \end{matrix}\right] \xrightarrow{-S} PhC{\equiv}N \quad (11)$$

Experimental Section

IR spectra were measured with a Hitachi EPI-G2 spectrometer. NMR spectra were determined in CCl_4 or $CDCl_3$ solution with a Varian A-60 or JEOL JNM-PMX-60 (60 MHz) spectrometer. Mass spectra were obtained on Hitachi double-focusing mass spectrometer RMU-7M at 70 eV. Dialkoxy disulfides were prepared by the method of the literature.[4] All other reagents were obtained commercially.

Alkoxyalkyl Trisulfides (4). A solution of 4.34 g (0.07 mol) of ethyl mercaptan in 20 mL of CCl_4 was added to a stirred solution of 10.74 g (0.07 mol) of diethoxy disulfide (**1a**) in 30 mL of CCl_4 at room temperature, and then the temperature of the mixture was gradually raised to 50 °C and the stirring was continued for an additional 3 h. The reaction mixture was evaporated and EtOH was removed as its CCl_4 azeotrope. The residual liquid was distilled under reduced pressure to give 5.40 g of ethoxyethyl trisulfide (**4a**), bp 72.5 °C (3.2 mm). The other compounds (**4b–e**) were obtained in a similar way.

Alkoxyamino Disulfides (5). A solution of 9.42 g (0.06 mol) of **1a** and 4.38 g (0.06 mol) of diethylamine in 75 mL of CCl_4 was refluxed for 4 h. The solvent and EtOH were removed by evaporation, and the residue was distilled to give 8.04 g of ethoxydiethylamino disulfide (**5a**), bp 58 °C (2.1 mm). The other compounds (**5b–e**) were obtained in a similar way.

Unsymmetrical Dialkyl Tetrasulfides (6). A solution of 3.80 g (0.05 mol) of *n*-propylmercaptan in 20 mL of CCl_4 was added to a stirred solution of 8.50 g (0.05 mol) of **4a** in 30 mL of CCl_4 at room temperature, and the stirring was continued for an additional 1.5 h. Finally, the reaction mixture was refluxed for 2 h. Ethanol and CCl_4 were removed by evaporation and the residue was distilled to give 6.03 g of ethyl-*n*-propyl tetrasulfide (**6a**), bp 79 °C (0.19 mm). Ethylisopropyl tetrasulfide (**6b**) was obtained in a similar way.

Alkylamino Trisulfides (7). A solution of 6.80 g (0.04 mol) of **4a** and 2.92 g (0.04 mol) of diethylamine in 50 mL of CCl_4 was refluxed for 7 h. Ethanol and CCl_4 were removed, and the residue was distilled to give 4.73 g of ethyldiethylamino trisulfide (**7a**), bp 72 °C (0.08 mm). The other compounds, **7b** and **7c**, were obtained in a similar way. Ethyldiethylamino trisulfide (**7a**) was also obtained by refluxing **5a** and ethyl mercaptan in CCl_4 for 7 h.

Unsymmetrical Diamino Disulfide (8). A solution of 11.0 g (0.061 mol) of **5a** and 4.31 g (0.061 mol) of pyrrolidine in 60 mL of CCl_4 was refluxed for 5 h, CCl_4 and EtOH were removed, and the residue was distilled to give 4.64 g of diethylaminopyrrolidyl disulfide (**8a**), bp 86 °C (0.07 mm).

Reaction of 1a with *N,N*-Dimethyl-*p*-phenylenediamine. A solution of *N,N*-dimethyl-*p*-phenylenediamine (4.08 g, 0.03 mol) and **1a** (4.62 g, 0.03 mol) in 50 mL of benzene was refluxed for 6 h, the solvent was removed, and the residue was chromatographed on silica gel using dry benzene to give *p*-dimethylamino-*N*-thiosulfinylaniline (**10**). Recrystallization from *n*-hexane gave 0.2 g of deep violet needles, identified by melting point and IR spectra:[10] mp 112–113 °C dec (lit. 113–115 °C); IR (KBr) 1605, 1535, 1315, 1290, 1180, 830, and 680 cm^{-1}.

Reaction of 1a with Benzylamine or Furfurylamine. A solution of 4.62 g (0.03 mol) of **1a** and 2.14 g (0.02 mol) of benzylamine in 75 mL of benzene was refluxed for 16 h. Then EtOH was removed as its benzene azeotrope by evaporation. The residue was chromatographed on silica gel using *n*-hexane as eluent to give 0.81 g of sulfur and 2.01 g (60%) of dibenzylideneamino tetrasulfide (**11a**). Recrystallization from dry MeOH gave yellow needles, identified by elementary analysis, melting point, and spectral data in the literature:[11] mp 100–101 °C (lit. 100.5–102 °C); NMR (CCl_4) δ 7.88 (s, 2 H), 7.04–7.47 (phenyl, 10 H); IR (KBr) $\nu_{C=N}$ 1600 cm^{-1}. Anal. Calcd for $C_{14}H_{12}N_2S_4$: N, 8.32; S, 38.11. Found: N, 8.28; S, 37.98. Difurfurylideneamino tetrasulfide (**11b**) was obtained from **1a** and furfurylamine in a similar way, yield 55%, as yellow needles from a mixture of *n*-hexane and benzene (4:1): mp 95–95.5 °C; NMR ($CDCl_3$) δ 7.96 (s, 2 H), 7.44 (d, 2 H), 6.88 (d, 2 H), 6.40 (q, 2 H); IR (KBr) $\nu_{C=N}$ 1600 cm^{-1}. Anal. Calcd for $C_{10}H_8N_2O_2S_4$: C, 37.96; H, 2.55; N, 8.85; S, 40.53. Found: C, 37.87; H, 2.58; N, 8.68; S, 40.60.

Reaction of 1a with β-Phenylethylamine or DL-α-Phenylethylamine. A solution of 4.62 g (0.03 mol) of **1a** and 3.63 g (0.03 mol) of β-phenylethylamine in 75 mL of benzene was refluxed for 24 h, and the color of the solution turned to dark red. Benzene and EtOH were removed by evaporation, and the residue was chromatographed on silica gel. Sulfur (1.45 g) was first separated by elution with *n*-hexane. Further elution with benzene gave 1.23 g of benzoyl-*N*-(2-phenylethyl)thioformamide (**13a**), mp 86–90 °C, which was recrystallized from *n*-hexane to give light yellow needles, mp 91–92 °C; IR (KBr) $\nu_{C=O}$ 1675 cm^{-1}, ν_{NH} 3180 cm^{-1}; NMR ($CDCl_3$) δ 8.56–8.10 (br, 1 H), 8.04–7.24 (phenyl, 10 H), 4.08 (q, 2 H), 3.08 (t, 2 H). Anal. Calcd for $C_{16}H_{15}NOS$: C, 71.34; H, 5.61; N, 5.20; S, 11.90. Found: C, 71.35; H, 5.62; N, 5.19; S, 11.86. The mass spectrum exhibited peaks at *m/e* 269 (M^+), 178 ($M^+ - PhCH_2$), 169 ($M^+ - PhC_2H_4$), 149 ($M^+ - PhC_2H_4NH$), 120 ($M^+ - PhCOCS$), 105 ($PhCO^+$), 104, 103, 91. Similarly, DL-α-phenylethylamine (3.63 g) reacted with **1a** (4.62 g) to give sulfur (0.9 g) and benzoyl-*N*-(1-phenylethyl)thioformamide (**13b**) (1.62 g) as a reddish-orange liquid by chromatography using benzene–hexane (1:2) as eluent: IR of **13b** $\nu_{C=O}$ 1660 cm^{-1}, ν_{NH} 3250 cm^{-1}; NMR δ (CCl_4) 9.16 (br d, 1 H) 8.07–6.93 (phenyl, 10 H) 5.72 (m, 1 H) 1.57 (d, 3 H). Anal. Calcd for $C_{16}H_{15}NOS$: C, 71.34; H, 5.61; N, 5.20; S, 11.90. Found: C, 71.42; H, 5.68; N, 5.00; S, 11.83. Mass spectrum *m/e* 269 (M^+), 236, 164, 149, 120, 105, 104, 103.

Reaction of 1a with Thiobenzamide. Thiobenzamide (2.74 g, 0.02 mol) suspended in 30 mL of CCl_4 and **1a** (3.08 g, 0.02 mol) was refluxed for 2 h. Thiobenzamide gradually dissolved and sulfur began to precipitate. After the reaction was over, EtOH and CCl_4 were removed by evaporation, the sulfur was filtered, and the filtrate was distilled to give 1.6 g (78%) of benzonitrile, bp 90.5 °C (33 mm) [lit. 69 °C (10 mm)], which was identified by the IR spectrum.

Registry No.—**1a**, 28752-22-9; **1b**, 28752-21-8; **4a**, 63833-15-8; **4b**, 63833-16-9; **4c**, 63833-17-0; **4d**, 63833-18-1; **4e**, 63833-19-2; **5a**, 63833-20-5; **5b**, 63833-21-6; **5c**, 63833-22-7; **5d**, 63833-23-8; **5e**, 63833-24-9; **6a**, 63833-25-0; **6b**, 63833-26-1; **7a**, 63833-27-2; **7b**, 63833-28-3; **7c**, 63833-29-4; **8a**, 63833-30-7; **10**, 53692-08-3; **11a**, 25829-04-3; **11b**, 63833-31-8; **13a**, 63833-32-9; **13b**, 63833-33-0; C_3H_7SH, 107-03-9; *i*-C_3H_7SH, 75-33-2; *t*-C_4H_9SH, 75-66-1; $(CH_2)_5NH$, 110-89-4; $(CH_2)_4NH$, 123-75-1; $(i\text{-}C_3H_7)_2NH$, 108-18-9; ethyl mercaptan, 75-08-1; diethylamine, 109-89-7; *N,N*-dimethyl-*p*-phenylenediamine, 99-98-9; benzylamine, 100-46-9; furfurylamine, 617-89-0; β-phenylethylamine, 64-04-0; DL-α-phenylethylamine, 618-36-0.

Supplementary Material Available: Table III containing IR and NMR spectral data of **1, 4,** and **5** and Table IV containing NMR spectral data of **6, 7,** and **8** (2 pages). Ordering information is given on any current masthead page.

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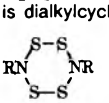

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Radical Nature of the [1,3]Sigmatropic Rearrangements of Electron-Rich Olefins[1]

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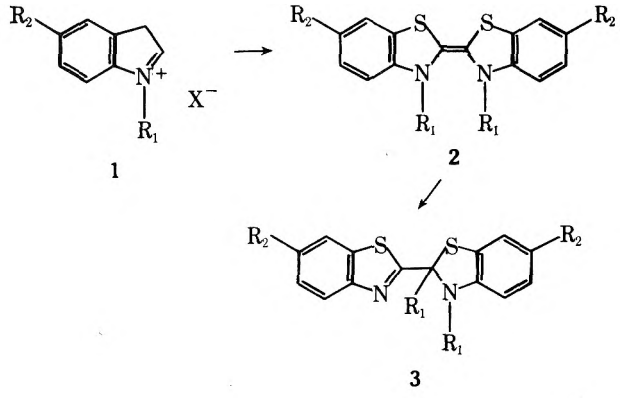
We have previously reported on the competing [1,3] and [3,3] rearrangements of the unstable dimer **2** formed by the action of triethylamine on appropriately substituted benzothiazolium salts **1**.[2] A significant rate enhancement in the rearrangement of the *p*-nitrobenzyl derivative **2a** relative to the benzyl derivative **2b** was cited as being consistent with a



Derivative	R_1	R_2	X (1 only)
a	$CH_2C_6H_4$ (*p*-NO_2)	H	Br
b i	$CH_2C_6H_5$	H	Br
b ii	$CH_2C_6H_5$	H	OTs
c	$CD_2C_6H_5$	H	OTs
d	$CH_2C_6H_5$	CH_3	Br

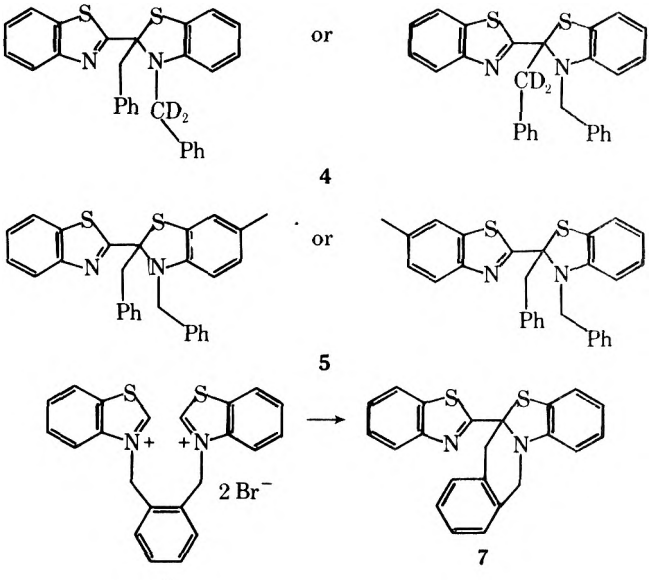
radical process. We now present evidence which demonstrates that a radical mechanism is responsible for the [1,3] rearrangement pathway.

If a concerted process were responsible for the [1,3] rearrangement,[3] then a mixture of **2b** and **2c** would rearrange to give only **3b** and **3c**, respectively. In fact, when this experiment was performed, a significant amount of the dideuterio stable dimer **4** was formed. The product ratios were determined by analysis of the molecular ions. The crossover product represented 28 ± 2% of the total. Although a statistically random intermolecular migration would provide for a 50% yield of dimer **4**, the lower yield is rationalized by a cage effect in a radical dissociation-recombination reaction. The observed product mixture is in accord with a dissociative mechanism having 57 ± 4% rearrangement within the cage.[4] A control experiment showed a mixture of **3b** and **3c** to be stable under the reaction conditions.

One possibility remained. The intermolecular crossover might be occurring prior to the [1,3]-benzyl shift; i.e., the formation of **2** might be reversible. Though there was much evidence against a dissociation to "nucleophilic carbenes",[6] the following experiment was devised to conclusively rule out this possibility. A mixture of **2b** and **2d**, allowed to rearrange under the standard conditions, gave a mixture of **3b** and **3d**. The monomethyl stable dimer **5** was undectable to the limits of the mass spectrometer.

The radical character of the [1,3]-benzyl shift was further confirmed by the gas chromatographic identification of bibenzyl in the crude product **3b**.

Knabe, Dyke, et al.[7] have studied a similar [1,3]-benzyl shift occurring when a 1-benzyl-1,2-dihydroisoquinoline is treated with aqueous acid. They have proposed a bimolecular double-exchange mechanism[8] to account for the intermolecular component which they too have found.[7c,10] The conversion of the bis(benzothiazolium salt) **6** to the stable dimer **7**, with no evidence for the formation of a tetramer, clearly rules out such a mechanism in the bibenzothiazoline series.



In conclusion, we have presented evidence that argues for a radical mechanism in this rearrangement. While it is somewhat unusual that a dissociative process should occur under such mild conditions, it is not without precedent. A number of [1,2] migrations are known to occur under mild conditions via a radical pathway.[11] Resonance stabilization of the bibenzothiazoline radical is surely responsible for the facility of this [1,3]-benzyl migration.

Experimental Section

General Procedures. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 700. Nuclear magnetic resonance spectra were recorded at either 60 MHz on a Varian Associates T-60 or at 90 MHz on a Perkin-Elmer R-22. Low-resolution mass spectra were determined at 70 eV on a Hitachi Perkin-Elmer RMU-6.

Analytical gas chromatography was performed on a Varian Aerograph Series 1200 with the appropriate column. Preparative TLC separations were carried out on Merck Silica Gel GF-254, No. 7730; column chromatography utilized Merck Silica Gel 60, No. 7734.

The microanalysis was performed by Midwest Microlab, Inc., Indianapolis, Indiana, and the high-resolution mass spectrum was obtained through the courtesy of Dr. Catherine E. Costello of this department.

3-Benzylbenzothiazolium Bromide [1b (i)]. Ten grams of benzothiazole (74.0 mmol) and 12.7 g of benzyl bromide (74.0 mmol) were heated in dry DMF (10 mL) for 6 h at 95 °C. On cooling, ether (150 mL) was added. The crude salt was collected by filtration and recrystallized from ethanol as pale-yellow needles, 14.7 g (65%): mp 184–186 °C (lit.[12] mp 184–186 °C); NMR (Me_2SO-d_6) δ 6.25 (s, 2 H), 7.3–8.0 (m, 7 H), 8.3–8.8 (m, 2 H), and 10.93 (s, 1 H).

Benzyl-α,α-d_2 Alcohol. A solution of 7.00 g of methyl benzoate

(51.4 mmol) in anhydrous ether (100 mL) was added dropwise (1.5 h) to a stirred suspension of 3.23 g of lithium aluminum deuteride (77.0 mmol) in anhydrous ether (200 mL). After stirring at reflux for 3 h, the reaction was carefully quenched with 5.60 mL of water (311 mmol). Filtration removed the solid residue which was washed with ether (four 50-ml portions). Removal of the solvent from the combined ether layers was followed by distillation. The isolated yield was 4.15 g (73%): bp 82–83 °C (3.2 mm) [lit.[13] 86–86.5 °C (9 mm)]; NMR ($CDCl_3$) δ 1.77 (s, 1 H) and 7.33 (s, 5 H); IR (film) 3350 cm^{-1} (br).

Benzyl Tosylate. Prepared by the method of Kochi and Hammond[14] from the sodium alkoxide and tosyl chloride. Recrystallization from hexane gave white needles, but yields were low due to a variable amount of decomposition which occurred during heating. The crude white product, isolable in nearly quantitative yield by removal of ether from the final solution at 0 °C, was sufficiently pure for further reaction: NMR ($CDCl_3$) δ 2.43 (s, 3 H), 5.03 (s, 2 H), 7.27 (s, 5 H), and 7.52 [(AB q)$_2$, J_{AB} = 8 Hz, $\Delta\nu_{AB}$ = 0.482 ppm, 4 H].

Benzyl-α,α-d_3 Tosylate.[15] Prepared as above from the sodium salt of benzyl-α,α-d_2 alcohol and tosyl chloride.

3-Benzylbenzothiazolium Tosylate [1b (ii)]. Benzothiazole (4.67 g, 34.5 mmol) and freshly prepared benzyl tosylate (8.67 g, 34.5 mmol) were heated in dry DMF (10 mL) for 2 h at 55 °C. On cooling, acetone (75 mL) was added. The white powdery precipitate was collected by filtration and washed with acetone (50 mL). The crude product was sufficiently pure for further use, although recrystallyzation from chloroform was possible: mp (crude) 134.5–135.5 °C; NMR ($CDCl_3$) δ 2.28 (s, 3 H), 6.20 (s, 2 H), 6.9–8.3 (m, 13 H), and 11.58 (s, 1 H).

3-Benzyl-α,α-d_2-benzothiazolium Tosylate (1c). Prepared as above from benzothiazole and benzyl-α,α-d_2 tosylate.

2-Mercapto-6-methylbenzothiazole. Prepared by the method of Sebrell and Boord[16] from *p*-toluidine, carbon disulfide, and sulfur. Recrystallized from benzene: mp 177–180 °C (lit.[16] 181 °C, lit.[17] 175.5–178.5 °C]; NMR ($CDCl_3$) δ 2.42 (s, 3 H) and 7.1–7.3 (m, 3 H).

6-Methylbenzothiazole. Prepared by the method of Blomquist and Diuguid[17] by reduction of 2-mercapto-6-methylbenzothiazole. Purification was accomplished by preparative TLC on silica gel with benzene/ether (1:1) as eluent: NMR ($CDCl_3$) δ 2.53 (s, 3 H), 7.27 (d of d, J_{AB} = 2 Hz, J_{BC} = 8 Hz, 1 H), 7.70 (d, J_{AB} = 2 Hz, 1 H), 8.05 (d, J_{BC} = 8 Hz, 1 H), and 8.92 (s, 1 H).

3-Benzyl-6-methylbenzothiazolium Bromide (1d). Prepared from 6-methylbenzothiazole and benzyl bromide by the procedure used for **1b**(i). The light pink crude product was recrystallized from ethanol as colorless prisms (48%): mp 210–214 °C; NMR (Me_2SO-d_6) δ 6.23 (s, 2 H), 7.2–8.5 (m, 8 H), and 10.88 (s, 1 H).

3,3′-(α,α'-o-Xylyl)bis(benzothiazolium bromide) (6). Five grams of benzothiazole (37.0 mmol) and 4.88 g of α,α'-dibromo-o-xylene (18.5 mmol) were heated in dry DMF (5 mL) for 2 h at 75 °C. The precipitate which formed was collected by filtration, washed with ether, and then dried in vacuo to give 6.94 g (70%). Recrystallization from ethanol gave a slightly yellow powder: charred ~180–200 °C, mp 216–219 °C; NMR (Me_2SO-d_6) δ 6.53 (s, 4 H), 7.0–8.8 (m, 12 H), and 10.63 (s, 2 H).

3,3′-Dibenzyl-$\Delta^{2,2'}$-bibenzothiazoline (2b). To 1.00 g of **1b**(i) (3.28 mmol) in DMF (15 mL) was added at 0 °C under nitrogen 2.00 mL of triethylamine (14.3 mmol). After 30 min of stirring, the mixture was poured into ice–water (100 mL) and quickly extracted with ether (four 50-mL portions). The combined extracts were washed with cold water (three 50-mL portions), dried ($MgSO_4$), and concentrated in vacuo to give 0.66 g (90%) of a light-yellow solid: NMR ($CDCl_3$) δ 4.68 (s, 4 H), 6.4–7.2 (m, 8 H), and 7.23 (s, 10 H).

This procedure for the preparation of **2b** could also be carried out starting instead with **1b**(ii).

3,3′-Di(benzyl-α,α-d_2)-$\Delta^{2,2'}$-bibenzothiazoline (2c). Prepared from **1c** as described above.

3,3′-Dibenzyl-$\Delta^{2,2'}$-bi(6-methylbenzothiazoline) (2d). Prepared from **1d** as described above.

2-(2-Benzothiazolyl)-2,3-dibenzylbenzothiazoline (3b). To 10.0 g of **1b**(i) (32.8 mmol) in DMF (150 mL) was added with stirring under nitrogen 20.0 mL of triethylamine (143 mmol). The mixture was heated to 90 °C for 2 h, cooled to ambient temperature, and poured into water (800 mL). Extraction with ether (four 400-mL portions) followed by washing the combined extracts with water (four 400-mL portions) gave, after drying ($MgSO_4$), and removal of the solvent in vacuo, 7.0–7.1 g of crude product. Recrystallization from ethanol–ethyl acetate gave 6.15 g (84%) of colorless prisms: mp 144–147 °C; NMR ($CDCl_3$) δ 4.05 (AB q, J_{AB} = 13 Hz, $\Delta\nu_{AB}$ = 0.595 ppm, 2 H), 4.70 (AB q, J_{AB} = 17 Hz, $\Delta\nu_{AB}$ = 0.548 ppm, 2 H), and 5.9–8.2 (m, 18 H); MS (70 eV) *m/e* 450 (M^+).

This procedure for the preparation of **3b** could also be carried out starting instead with **1b**(ii).

Anal. Calcd for $C_{28}H_{22}N_2S_2$: C, 74.63; H, 4.92. Found: C, 74.63; H, 5.06.

2-(2-Benzothiazolyl)-2,3-di(benzyl-α,α-d_2)benzothiazoline (3c). Prepared from **1c** as described above: mp 144.5–146.0 °C; MS (70 EV) *m/e* 454 (M^+).

2-[2-(6-Methylbenzothiazolyl)]-2,3-dibenzyl-6-methylbenzothiazoline (3d). Prepared from **1d** as described above. Recrystallized from ethanol–ethyl acetate as light-yellow prisms (78%): mp 151–152.5 °C; NMR ($CDCl_3$) δ 2.18 (s, 3 H), 2.45 (s, 3 H), 4.04 (AB q, J_{AB} = 13 Hz, $\Delta\nu_{AB}$ = 0.630 ppm, 2 H), 4.65 (AB q, J_{AB} = 17 Hz, $\Delta\nu_{AB}$ = 0.548 ppm, 2 H), and 5.8–8.1 (m, 16 H); MS (70 eV) *m/e* 478 (M^+).

10a-(2-Benzothiazolyl)-10,10a-dihydro-5*H*-11-thia-4b-azabenzo[*b*]fluorene (7). Prepared from **6** described above. The product was isolated in 16% yield by column chromatography on silica gel with hexane–benzene gradient elution and then recrystallized from ethanol–chloroform as white needles (12%): mp 171–174 °C; NMR ($CDCl_3$) δ 4.08 (AB q, J_{AB} = 14.5 Hz, $\Delta\nu_{AB}$ = 0.279 ppm, 2 H), 4.61 (AB q, J_{AB} = 16 Hz, $\Delta\nu_{AB}$ = 0.112 ppm, 2 H) and 6.6–8.0 (m, 12 H); MS (70 eV) *m/e* 372 (M^+).

Anal. Calcd for $C_{22}H_{16}N_2S_2$: mol wt, 372.07550. Found: mol wt 372.07902. There was no peak at *m/e* 744, indicating the absence of any tetramer.

Gas Chromatographic Identification of Bibenzyl as a Byproduct in the Formation of Stable Dimer 3b. The crude dimer, prepared as described above, was dried and then triturated with pentane. The pentane-soluble fraction contained bibenzyl. Its identity was established by coinjection with an authentic sample on two different columns (5% SE-30 on Chrom G and 5% Carbowax 20M on Chrom G). An upper limit of 0.1% can be placed on the yield of bibenzyl.[18]

Crossover Experiment Demonstrating Intermolecularity in the [1,3]-Benzyl Shift. Twenty-eight milligrams of each of freshly prepared **2b** (d_0) and **2c** (d_4), the unstable dimers, was dissolved in dry DMF (2.5 mL) under nitrogen and heated for 2 h at 90 °C. Workup was as usual. After eliminating the contribution of P + 2 and P − 2 ions, the mass spectrum showed approximately 28% formation of **4** (either of two d_2 isomers) with *m/e* 452 (M^+). This corresponds to 57 ± 4% rearrangement within a radical cage (and 43 ± 4% intermolecular rearrangement by escape from the radical cage).

Control Experiment Demonstrating the Stability of Dimers 3 under the Reaction Conditions. A mixture of 20 mg each of **3b** and **3c**, the stable dimers, was dissolved in DMF and subjected to the standard reaction conditions necessary to effect rearrangement. No dideuterio dimer **4** was detectable by mass spectral analysis (upper limit = 5%).

Control Experiment Demonstrating Irreversible Formation of Unstable Dimers. Forty-nine milligrams of **2b** (0.109 mmol) and 52 mg of **2d** (0.109 mmol) were allowed to rearrange under the standard conditions. Workup as usual.[19] The crossover product **5** (either of two monomethyl isomers) was undetectable by mass spectral analysis (upper limit = 3%).

Registry No.—**1b**(i), 4614-22-6; **1b**(ii), 63703-01-5; **1c**, 63703-11-7; **1d**, 63703-02-6; **2b**, 37128-00-0; **2c**, 63703-03-7; **3b**, 51479-81-3; **3c**, 63703-04-8; **3d**, 63703-05-9; **4** isomer 1, 63703-06-0; **4** isomer 2, 63703-07-1; **6**, 63703-08-2; **7**, 63703-09-3; benzothiazole, 95-16-9; benzyl bromide, 100-39-0; benzyl-α,α-d_2 alcohol, 21175-64-4; methyl benzoate, 93-58-3; benzyl tosylate, 1024-41-5; 2-mercapto-6-methylbenzothiazole, 2268-79-3; 6-methylbenzothiazole, 2942-15-6; α,α'-dibromo-o-xylene, 91-13-4.

References and Notes

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(3) Two possible thermally allowed pathways exist for the *N*-benzyl rearrangement: (1) antarafacial with retention of configuration at the migrating benzylic center, and (2) suprafacial with inversion of configuration at the migrating benzylic center. The former possibility seemed remote based on geometrical considerations, but the latter remained.

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Fluorene Derivatives: Friedel–Crafts Reaction of 2-Fluorenyl Basic Ethers

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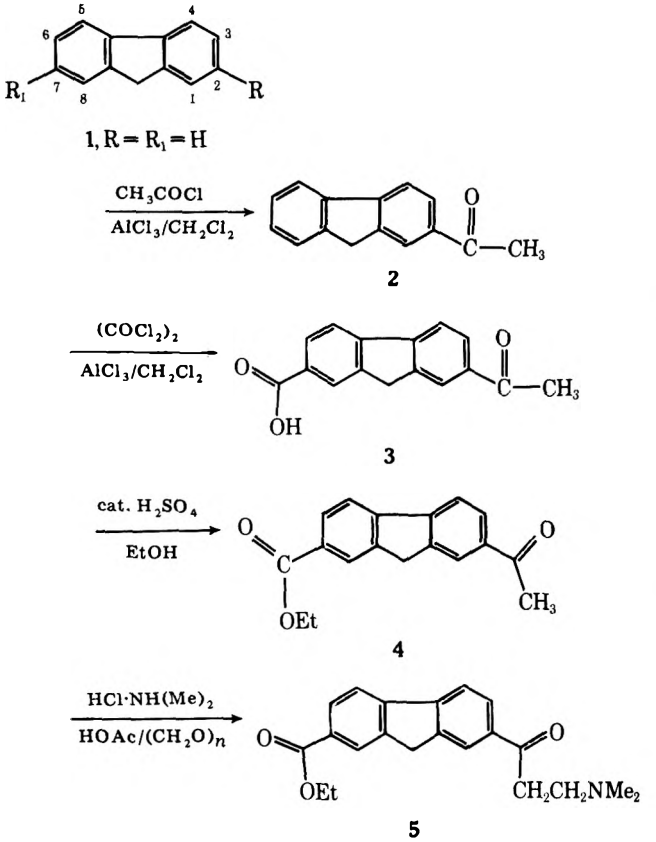
Fluorene **1** (R = R′ = H) has been reported to undergo bis-electrophilic substitution in the 2 and 7 positions.[1,2] While a great deal of synthetic effort has been concentrated on the preparation of symmetrically 2,7-disubstituted compounds, very little work has been done on derivatives of **1** in which R and R′ comprise different functional types.[3,4]

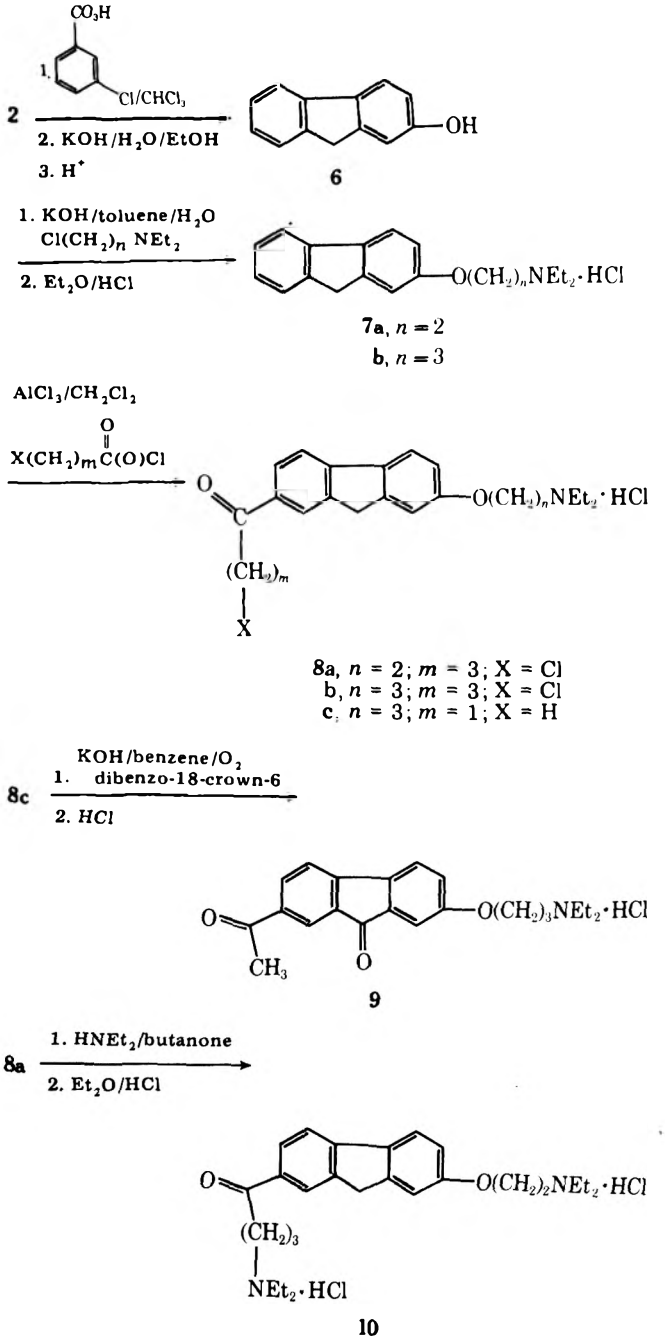
In connection with the synthesis of certain bis-basic derivatives of fluorene having antiviral activity, we were interested in devising synthetic routes to such disymmetric fluorenes. In particular we were interested in synthetic methods to compounds such as **4**, **8**, and **9**. These compounds would be valuable intermediates since simple chemical manipulations could lead to bis-basic fluorene and fluorenone derivatives having dissimilar substituents, e.g., **10**. The preparation and characterization of 2,7 disubstituted **1** compounds in which R and R′ comprise different functional types are described in this paper.

Treatment of 2-acetylfluorene (**2**) with oxalyl chloride led to the corresponding acid derivative **3**. Compound **3** was esterified to ester **4** and then converted to the base **5** (Scheme I). The ether analogues were prepared as shown in Scheme II. Baeyer-Villiger oxidation of **2** followed by hydrolysis of the intermediate acetate afforded **6**. Alkylation of **6** with the appropriate ω-halodialkylamine gave **7a** and **7b**. Although initial attempts to prepare compounds **8a–c** with BF_3-Et_2O used as the catalyst were unsuccessful, they were successfully prepared in good yield by acylation of **7** in methylene chloride with aluminum chloride used as the catalyst. Compounds of formula **8** were isolated as their hydrochloride salts by treatment of the reaction mixture with an aqueous hydrochloric

Scheme I



Scheme II



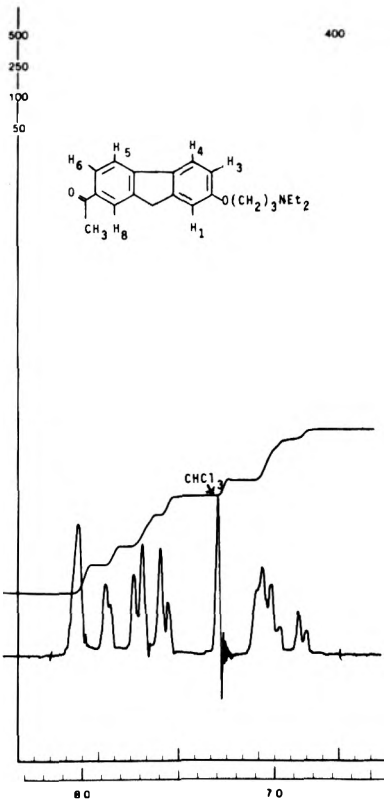


Figure 1. ^{1}H NMR spectrum (60 MHz) of 8c in $CDCl_3$.

acid–sodium chloride solution. This procedure was convenient since it eliminated possible isolation problems resulting from intractable Lewis acid complexes and probable side reactions of **8a** or **8b** arising from treatment with strong base.[5,6] A survey of the literature revealed very few reports of Friedel–Crafts acylations of basic substrates.[7] None of these authors isolated the products directly as the hydrochloride salts. This reaction and the accompanying workup should be general for aromatic nuclei, the solubility characteristics for which allow them to be salted out of water.

The 2,7 substitution patterns of **8a, 8b,** and **8c** were determined by ^{1}H NMR. These compounds all exhibited a complex signal (2 H) at δ 7.1 to 7.0 and the A portion of an ABC multiplet (1 H) at δ 8.1 to 8.0. For example, in the ^{1}H NMR spectrum of **8c** (Figure 1) the signals due to aromatic protons showed a broad singlet (1 H) with fine structure at δ 8.1 and absorption for the A portion of an ABC multiplet (1 H) at δ 7.1 superimposed on a doublet of doublets (1 H) centered at δ 7.0 (J_{AB} = 9.0 Hz, J_{AC} = 2.0 Hz). The absorptions at δ 7.0 and 7.1 were assigned to H_3 and H_1, respectively. The complex absorptions between δ 7.5 and 7.9 (3 H) along with the deshielded peak at δ 8.1 were tentatively assigned to H_4, H_5, H_6, and H_8. This ^{1}H NMR pattern along with the well-documented regioselectivity exhibited by the Baeyer–Villiger oxidation[8-10] definitively established that the basic ether was located in the 2 position of the fluorene nucleus. Moreover, the two proton signals at δ 7.0 and 7.1 and their splitting patterns required that the acetyl group be situated on a different aromatic ring than the basic ether. The ^{1}H NMR of **8c** did not establish the position of the acetyl group since the spectrum in Figure 1 was consistent with either a 2,7- or a 2,6-disubstitution pattern. The signal at δ 8.1 was inconsistent with an acetyl function at either H_5 or H_8 since the exhibited J values were incorrect for these substitutions (see Experimental Section). The problem of the position of the acetyl group was resolved by oxidation of **8c** to the fluorenone **9**. This oxidation was carried out in 41% yield with a modification of

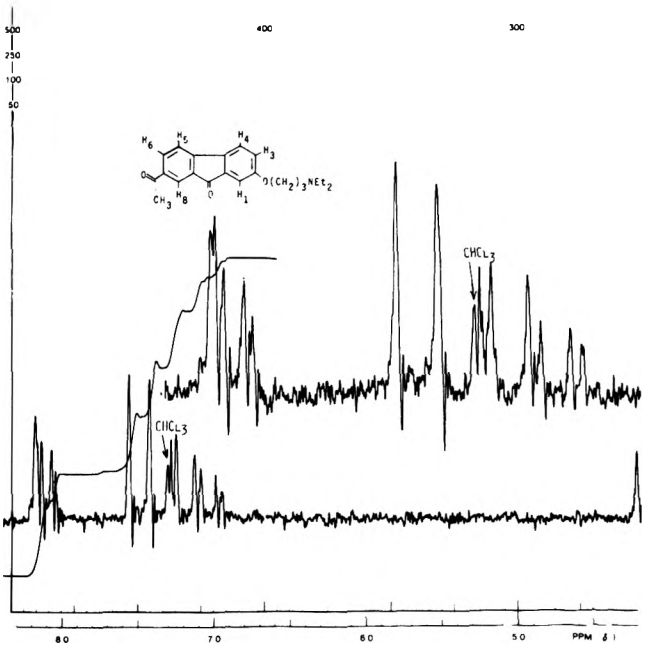


Figure 2. ^{1}H NMR spectrum (60 MHz) of **9** in $CDCl_3$.

the procedure of Gokel and Durst.[11] Fortuitously, a consideration of all of the signals due to the aromatic hydrogens of **9** permitted a structural assignment to be made (Figure 2). The doublet centered at δ 7.5 (J = 9.0 Hz, 2 H) was assigned to H_4 and H_5. Careful consideration of the theoretical pattern of 2,6 disubstitution vs. 2,7 disubstitution showed that only the latter was consistent with the observed doublet. In the 2,6-disubstituted fluorenone H_4 and H_8 would be expected to be part of ABC systems; however, one would not expect the chemical shifts of H_4 and H_8 to be equivalent with no further splitting. Additional support for 2,7 disubstitution was the expected downfield shift in the ABC multiplets that appeared at δ 8.1 (H_8) and 7.1 (H_1) in **8c** (Figure 1) to δ 8.2 and 7.3, respectively, in **9** (Figure 2). The doublet of doublets centered at δ 7.0 (J = 9.0, 2.0 Hz) was assigned to H_3 while the doublet of doublets superimposed on H_3 and centered at δ 8.1 (J = 9.0, 2.0 Hz) was assigned to H_6 (Figure 2). The two doublet of doublets added further support for the structural assignment since $J_{H_3H_4} = J_{H_5H_6}$ = 9.0 Hz. The assignment of the 2,7-disubstitution pattern to **8c** also necessitated the assignment of this pattern to all of the compounds of formula **8**.

Compounds **8a** and **8b** were especially valuable intermediates since they could be readily aminated to yield the desired bis-basic fluorene derivatives. For example, amination of **8a** with diethylamine in refluxing butanone gave **10**.

Experimental Section

Melting points were determined in open capillaries with a Thomas-Hoover apparatus and are uncorrected. The infrared and ultraviolet spectra were obtained on Perkin-Elmer 521 and Perkin-Elmer 350 recording spectrometers, respectively. Nuclear magnetic resonance spectra were obtained on a Varian A 60A spectrometer. Where analyses are indicated by symbols of the elements, results were within ±0.4% of the theoretical value.

7-Acetylfluorene-2-carboxylic Acid (3). To a stirred mixture of **2** (50.0 g, 0.24 mol) and $AlCl_3$ (101.0 g, 0.75 mol) in CH_2Cl_2 (1500 mL) chilled in a dry ice–acetone bath was added oxalyl chloride (64.0 g, 0.50 mol) dropwise over 45 min. The mixture was allowed to warm to room temperature, stirred for 3 days, and then heated at reflux for 5 h. The reaction mixture was hydrolyzed with cold aqueous HCl and the resulting emulsion was concentrated to remove CH_2Cl_2. Chilling and filtration gave a tan solid, 31.0 g (51%), mp 290–295 °C. Recrystallization of a small quantity of the acid from EtOH gave the analytical sample of **3**, mp 291–294 °C. Anal. C, H.

7-Acetylfluorene-2-carboxylic Acid Ethyl Ester (4). Com-

pound **3** was stirred and heated with absolute EtOH (400 mL) and H_2SO_4 (14.0 mL) for 2 days. After filtration of the hot dark-brown solution, the ester began to crystallize immediately and gave 25.6 g (78%) of a tan solid. Recrystallization (EtOH) gave tan needles of **4**: mp 141–143 °C; IR (KBr) 1695 (ester C=O), 1665 (unsaturated C=O), and 1600 cm^{-1} (aromatic CH); NMR ($CDCl_3$) δ 8.2–7.7 (m, 6 H), 4.4 (q, 2 H, J = 7.0 Hz), 3.8 (s, 2 H), 2.6 (s, 3 H), 1.4 (t, 3H, J = 7.0 Hz); UV_{max} 322 nm (ϵ 37 200). Anal. C, H.

7-[(3-Dimethylamino)propionyl)]7-fluorene-2-carboxylic Acid Ethyl Ester (5). Acetic acid (50 mL) was added to a mixture of **4** (11.3 g, 0.04 mol), paraformaldehyde (1.20 g, 0.04 mol), and dimethylamine hydrochloride (3.30 g, 0.04 mol). The mixture was stirred and heated on the steam bath for 3 h. Concentration in vacuo gave a solid that when recrystallized (CH_2Cl_2–EtOAc) gave 9.95 g (66%), mp 195–207 °C. A second recrystallization (CH_2Cl_2–butanone) gave the analytical sample of **5**: mp 206–207 °C; NMR ($CDCl_3$/TFA) δ 8.2–7.8 (m, 6 H), 4.5 (q, 2 H, J = 7.0 Hz), 3.9 (m, 2 H), 3.7 (m, 4 H), 3.1 (s, 3 H), 3.0 (s, 3 H), 1.4 (t, 3 H, J = 7.0 Hz); IR (KBr), 1712 (ester C=O) and 1670 cm^{-1} (broad unsaturated C=O). Anal. C, H, N.

2-Hydroxyfluorene (6). To a stirred solution of **2** (50.0 g, 0.24 mol) in hydrocarbon stabilized $CHCl_3$ (1 L) in a blackened flask (2 L)[14] was added *m*-chloroperbenzoic acid (30.3 g (82%), 0.24 mol) at 5 °C in divided portions. The reaction mixture was allowed to warm to room temperature and was then stirred at ambient temperature for 3 days. The resulting brown solution was extracted with saturated $NaHCO_3$, H_2O, and brine and then dried ($MgSO_4$), filtered, and concentrated to give a tan solid. The solid was hydrolyzed with a KOH (100.0 g), H_2O (2 L), EtOH (300 mL) mixture. Filtration and acidification (pH 2) gave 23.8 g (64%) of **6**, mp 169–170 °C (lit.[12] mp 171 °C).

3-(2-Fluorenyloxy)-*N,N*-diethylpropylamine Hydrochloride (7b). To a stirred solution of **6** (23.8 g, 0.13 mol) dissolved in 17% NaOH (300 ml) was added 3-diethylaminopropyl chloride (20.0 g, 0.13 mol) and toluene (300 mL). The two-phase reaction mixture was stirred and heated under reflux for 24 h. The organic layer was separated, washed with H_2O, and dried ($MgSO_4$). Filtration followed by acidification with gaseous HCl gave a tan precipitate. Recrystallization (MeOH–EtOAc) gave: 33.1 g (79%); mp 170–172 °C; IR (KBr) 2940, 2650, 2490, 1610, 1590, and 1450 cm^{-1}; NMR ($CDCl_3$) δ 7.7–7.1 (m, 5 H), 7.10 (m, 1 H), 6.8 (dd, 1 H, J = 8.0 Hz), 4.15 (t, 2 H, J = 7.0 Hz), 3.85 (s, 2 H), 3.4–2.9 (m, 6 H), 2.6–2.0 (m, 2 H), 1.4 (t, 6 H, J = 7.0 Hz); UV_{max} (EtOH) 272 nm (ϵ 20 700). Anal. C, H, N.

2-(2-Fluorenyloxy)-*N,N*-diethylaminoethane Hydrochloride (7a). This compound was prepared from **6** and β-diethylaminoethyl chloride in the same way as **7b**. The product was used in the next reaction without purification.

3-Chloropropyl-7-[2-(diethylamino)ethoxy]fluoren-2-yl Ketone Hydrochloride (8a). To a stirred solution of **7a** (50.0 g, 0.16 mol) and 4-chlorobutyryl chloride (45.6 g, 0.32 mol) in CH_2Cl_2 (2 L) cooled in a dry ice–acetone bath was added $AlCl_3$ (47.0 g, 0.35 mol) in divided portions over 20 min. The solution was allowed to slowly warm to room temperature and stirred for 3 days. The reaction mixture was poured onto cracked ice (1 L) and concentrated HCl (200 mL). The two-phase mixture was then stirred for 45 min. The CH_2Cl_2 layer was separated and washed with brine (2 L). The aqueous layer was extracted with CH_2Cl_2 (2 L) and the organic layers were combined and dried ($MgSO_4$). The resulting dark-brown solution was filtered and concentrated in vacuo to a dark oil. Crystallization of the oil gave 44.0 g (63%) of a solid mp 149–151 °C. Recrystallization (3.1 g charcoal MeOH–EtOAc) gave 19.7 g of **8a**, mp 168.5–170.5 °C. Anal. C, H, N.

3-Chloropropyl 7-[3-(Diethylamino)propoxy]fluoren-2-yl) Ketone Hydrochloride (8b). To a stirred solution of **7b** (18.9 g, 0.057 mol) and 4-chlorobutyryl chloride (16.0 g, 0.1 mol) in CH_2Cl_2 (1500 mL) chilled in a dry ice–acetone bath was added $AlCl_3$ (13.3 g, 0.1 mol). The reaction was then treated as above to give after recrystallization (MeOH–EtOAc): 15.8 g (63%) of **8b**; mp 175–177 °C; NMR ($CDCl_3$) δ 8.2 (m, 1 H), 7.9–7.7 (m, 3 H), 7.1 (m, 1 H), 7.0 (1 H, J = 9.0, 2.0 Hz), 4.7–4.5 (m, 2 H), 3.9–3.1 (m, 12 H), 2.3–2.1 (m, 2 H), 1.5 (t, 6 H, J = 7.0 Hz); IR (KBr) 2910, 2900, 2450, 1660, 1612, and 1550 cm^{-1}; UV_{max} (EtOH) 324 nm (ϵ 30 200). Anal. C, H, N.

Methyl 7-[3-(Diethylamino)propoxy]fluoren-2-yl Ketone Hydrochloride (8c). To a stirred solution of **7b** (7.07 g, 0.21 mol) and acetyl chloride (23.2 g, 0.30 mol) in CH_2Cl_2 2 L) chilled in a dry ice–acetone bath was added $AlCl_3$ (46.7 g, 0.35 mol) in divided portions over 30 min. The suspension was treated as in **8a**.[13] Recrystallization (MeOH–EtOAc) gave 52.0 g (65%) of **8c**; mp 173–175 °C; IR (KBr) 1670 cm^{-1} (unsaturated CO): UV_{max} (EtOH) 326 nm (ϵ 31 100); NMR ($CDCl_3$, free base) δ 8.1 (m, 1 H), 7.9–7.6 (m, 3 H), 7.1 (m, 1 H), 7.0 (m, 1 H), 4.1 (t, 2 H, J = 6.0 Hz), 3.9 (s, 2 H), 2.8–2.4 (m, 9 H), 2.1–1.8 (m, 2 H), 1.0 (t, 6 H, J = 7.0 Hz). Anal. C, H, N.

2-Acetyl-7-[3-(diethylamino)propoxy]-9*H*-fluoren-9-one (9). To a stirred mixture of **8c** free base (8.10 g, 0.024 mol) and dibenzo-18-crown-6 (420 mg, 0.0012 mol) in benzene (30.0 ml) was added KOH pellets (2.0 g, 0.036 mol) and the stirring rate was increased to the most rapid rate consistent with the solution remaining in the flask (125-mL Erlenmeyer). The suspension became dark red and then turned brown within 15 min. It was stirred open to the atmosphere for an additional 30 min and then poured into H_2O (200 mL)–CH_2Cl_2 (100 mL). The two-phase suspension was filtered and an orange solid was collected. The solid was acidified with dilute HCl and the resulting suspension was filtered. Recrystallization of the precipitate (MeOH–EtOAc) gave 3.8 g (41%) of **9** as an orange powder: mp 248–249 °C; IR (KBr) 2600, 2400 (amine hydrochloride), 1710 (9 carbonyl), 1655 cm^{-1} (acetyl carbonyl); NMR ($CDCl_3$ free base) δ 8.2 (m, 1 H, $J_{(m)}$ = 2.0 Hz, $J_{(p)}$ < 1.0 Hz), 8.1 (dd, 1 H, $J_{(o)}$ = 9.0 Hz, $J_{(m)}$ = 2.0 Hz), 7.5 (d, 2 H, $J_{(o)}$ = 9.0 Hz), 7.3 (m, 1 H, $J_{(m)}$ = 2.0 Hz, $J_{(p)}$ < 1.0 Hz), 7.0 (dd, 1 H, $J_{(o)}$ = 9.0 Hz, $J_{(m)}$ = 2.0 Hz), 4.1 (t, 2 H, J = 6.0 Hz), 2.7–2.3 (m, 9 H), 2.1–1.8 (m, 2 H), 1.1 (t, 6 H, J = 7.0 Hz). Anal. C, H, N.

3-Diethylaminopropyl 7-[2-(Diethylamino)ethoxy]fluoren-2-yl) Ketone Hydrochloride (10). To a stirred mixture of **8a** (21.2 g, 0.05 mol), KI (8.3 g, 0.05 mol), and K_2CO_3 (6.0 g, 0.043 mol) in butanone (300 mL) was added diethylamine (50.0 mL). The mixture was then heated and stirred at reflux for 24 h. An additional 50 mL of diethylamine was added and the burgundy colored solution was heated for an additional 4 h. The solution was allowed to cool, then filtered and concentrated in vacuo to a purple semisolid residue which was dissolved in dilute HCl, filtered, and made basic with NaOH in a two-phase Et_2O–H_2O mixture. The Et_2O layer was separated, washed with brine, separated, dried ($MgSO_4$), and filtered. Partial concentration of the filtrate gave a small amount of a yellow solid, which was filtered. The filtrate was further concentrated to a purple oil. The purple oil was dissolved in benzene (500 mL) and then concentrated in vacuo and the residue was dissolved in anhydrous Et_2O, which was then acidified with ethereal HCl. The resulting precipitate was washed with fresh Et_2O and then recrystallized (MeOH–butanone–charcoal) to give 9.0 g (36%) of **10** as a tan solid, mp 260–262 °C. Anal. Calcd for $C_{27}H_{38}N_2O_2 \cdot 2HCl \cdot 3H_2O$: C, 64.66; H, 8.17; N, 5.59; Cl, 14.14. Found: C, 64.91, H, 7.97; N, 5.24; Cl, 13.76; NE = 253.8.

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Registry No.—**2**, 781-73-7; **3**, 63715-82-2; **4**, 63715-83-3; **5**, 63715-84-4; **6**, 2443-58-5; **7a**, 63715-90-2; **7b**, 63715-85-5; **8a**, 63715-86-6; **8b**, 63715-87-7; **8c**, 63715-88-8; **8c** free base, 63715-92-4; **9**, 63715-89-9; **10**, 63715-91-3; dimethylamine HCl, 506-59-2; 3-diethylaminopropyl chloride, 104-77-8; β-diethylaminoethyl chloride, 100-35-6; 4-chlorobutyryl chloride, 4635-59-0; acetyl chloride, 75-36-5.

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(13) In later runs it was found that the 72 h stirring period could be eliminated without any loss in yield; however, it was necessary to heat for 30 min at reflux for the reaction to proceed.
(14) The blackened flask was prepared by covering a 2-L round-bottom flask with black epoxy paint.

Alkylations of Alkynols with Organoaluminum Reagents Promoted by Bis(η^5-cyclopentadienyl)titanium Dichloride

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We have been interested in adapting the chemistry of titanium–aluminum based Ziegler–Natta catalyzed olefin polymerization to effect the alkylation of isolated unsaturated carbon–carbon bonds in a manner useful for ordinary (i.e., nonmacromolecular) organic synthesis.[1,2] Ziegler–Natta catalyst systems are potent alkylating agents toward olefinic and acetylenic linkages as evidenced from their widespread use in synthesizing linear stereospecific polyhydrocarbons.[3] However, single nonrepetitive alkylations of isolated carbon–carbon multiple bonds useful for extending the carbon framework in organic systems are not common. The paucity of research reported in this area is somewhat surprising if one accepts the idea that organic synthesis can be divided into the broad areas of (1) formation of carbon skeletons and (2) introduction, modification, and/or removal of functionality[4] and that within these areas the first is generally the more difficult.[5] Recently, we have had some success in utilizing organoaluminum–titanium systems capable of polymerizing ethylene to alkylate alkynols to give olefinic alcohols.[1,2] Specifically, an alkynol such as 3-butyn-1-ol was incorporated into the complex (3-butyn-1-oxy)chlorobis(2,4-pentanedionato)titanium(IV), $[Ti(OR)Cl(acac)_2]$, and allowed to react with diethylaluminum chloride at −78 °C. After hydrolysis a ~50% yield of the terminally alkylated cis-addition product *trans*-3-hexen-1-ol was obtained. Several additional alkynols were alkylated, and in all cases the alkyl group added to the carbon furthest from the hydroxyl functionality and gave the cis-addition product.

In this paper we wish to report a new alkylation system which gives significant improvements in yields and synthetic convenience and also demonstrates the potential for control of regiospecificity through variation of ligand environments. In previous work it was necessary to first synthesize and isolate a titanium–alkynoxy complex, $[Ti(OR)Cl(acac)_2]$, by the reaction of $[TiCl_2(acac)_2]$, alkynol, and pyridine. The pyridinium chloride was filtered from the reaction mixture, and the complex was then isolated from the filtrate. A much simpler procedure would be the addition of an alkynol to a solution of the organoaluminum reagent liberating an alkane and generating an $[Al_2(OR)R_xCl_{5-x}]$ species which subsequently could be added to a solution of $[TiCl_2(acac)_2]$. Through ligand exchange this system might become equivalent to the initial one and thus eliminate the inconvenience of preparing the titanium–alkynoxy complexes. Attempts to effect alkylation by this latter route were unsuccessful. However, upon replacing $[TiCl_2(acac)_2]$ with titanocene dichloride, Cp_2TiCl_2, in the 3-butyn-1-ol-diethylaluminum chloride system a 55% yield of the ethylated products *trans*-3-hexen-1-ol (I) and 3-ethyl-3-buten-1-ol (II) (ca. 50:50) was obtained as represented in reactions 1 and 2. On lowering the quantity of Cp_2TiCl_2 relative to 3-butyn-1-ol yields improved significantly (see Table I). Using 10 mol % of Cp_2TiCl_2, 80–90% yields of ethylated products were obtained with the ratio of terminal to internal addition products varying from ca. 50:50 to 60:40, respectively. Thus the titanium species in the cyclopentadienyl system functions catalytically with an average turnover number of 8–9. Cp_2TiCl_2 at 5 and 1 mol % gave decreasing yields again. Hydrolysis with D_2O gave greater than 95% deuterium incorporation at the olefinic carbon atoms. Additional alkylation data are presented in Table I.

$$2.5Al(C_2H_5)_2Cl + HC{\equiv}CCH_2CH_2OH \xrightarrow[CH_2Cl_2]{0\ ^\circ C} \underset{(III)}{Al_{2.5}(OCH_2CH_2C{\equiv}CH)(C_2H_5)_4Cl_{2.5}]} + C_2H_6 \quad (1)$$

$$Cp_2TiCl_2 + III \xrightarrow[(2)\ H_2O]{(1)\ CH_2Cl_2,\ 0\ ^\circ C,\ 6\ h} I + II \quad (2)$$

Reference to Table I shows that methyl-group substitution at the hydroxy end (4-pentyn-2-ol) and at the acetylenic position (3-pentyn-1-ol) reduces the yield of alkylated products somewhat. With 3-pentyn-1-ol addition was observed only at the 4-carbon whereas 4-pentyn-2-ol gave a mixture of terminally and internally ethylated products similar to 3-butyn-1-ol. 4-Pentyn-1-ol also gave a mixture of two products. In all alkylation reactions a significant portion of Cp_2TiCl_2 is recovered in the workup procedure.

In summary, the mild conditions, the catalytic possibilities

Table I. Alkynol Alkylations[a]

Alkynol	Registry no.	Temp, °C	Mol % Cp_2TiCl_2[b]	Products	Registry no.	Total % yield of Products	Reaction time, h
3-Butyn-1-ol	927-74-2	0	50	*trans*-3-Hexen-1-ol (I) and 3-ethyl-3-buten-1-ol (II)	928-97-2 1170-98 1	85[c]	6
		−22	50	I and II		80	6
		−78	50	None			6
	d	0	100	I and II		55	6
		0	25	I and II		78	6
		0	10	I and II		88	6
		0	10	I and II		80	6
3-Pentyn-1-ol	10229-10-4	0	50	4-Methyl-3-hexen-1-ol	63714-11-4	46[e]	4
4-Pentyn-2-ol	2117-11-5	0	50	4-Ethyl-4-penten-2-ol and *trans*-4-hepten-2-ol	63714-12-5 58927-81-4	66[f]	4
4-Pentyn-1-ol	5390-04-5	0	50	*trans*-4-Hepten-1-ol and 4-ethyl-4-penten-1-ol	24469-79-2 59518-08-0	72[g]	4

[a] All reactions are of the type $x Cp_2TiCl_2 + [Al_{2.5}(OR)(C_2H_5)_4Cl_{2.5}]$, OR = alkynoxy. Solvent is methylene chloride. [b] Relative to OR in $[Al_{2.5}(OR)(C_2H_5)_4Cl_{2.5}]$. [c] For all 3-butyn-1-ol ethylations the ratio of I to II ranged between 50:50 and 60:40, respectively, with no systematic variation apparent. [d] Solvent is benzene. [e] The *E* configuration is suggested by the absence of observable methyl group splitting by the proton attached to the double bond. This configuration, which arises from cis addition of a metal–alkyl group, is also consistent with the fact that terminal ethylation of the terminal alkynols reported herein gives products arising from cis addition. [f] Product ratio ca. 55:45 internal to terminal addition. [g] Product ratio ca. 50:50.

with titanium, the availability of organoaluminum reagents, and the possible control of regioselectivity through a variety of available titanium compounds indicate that titanium–organoaluminum systems offer synthetic promise for the alkylation of γ and δ alkynols. Furthermore, the deuterium incorporation mentioned indicates the possibility of additional functional conversions of the reaction intermediates.

Experimental Section

Materials. All alkynols were purchased from Farchan Division, Story Chemical Corp., and were dried over 3-A Molecular Sieves. Methylene chloride was distilled from P_2O_5 under nitrogen. Liquid materials were transferred under N_2 or argon using syringe techniques. Cp_2TiCl_2 was purchased from Strem Chemicals, Inc., and used without further purification.

Alkylation Procedure. Reactions were carried out in glassware which had been dried at 110 °C, assembled while hot, and flushed with argon while cooling. In a typical reaction 50 mmol of 2 M $Al(C_2H_5)_2Cl$ solution in methylene chloride was transferred to a 250-mL three-necked round-bottom flask equipped with a gas inlet, magnetic stirrer, and 50-mL dropping funnel. Additional solvent was added to dilute the organoaluminum reagent to 0.75 M. The alkynol (20 mmol) was added to the dropping funnel with a syringe (weighed before and after) along with 25 mL of methylene chloride. The $Al(C_2H_5)_2Cl$ solution was cooled to 0 °C, and the alkynol was added dropwise to form the mixed ethylchloroalkynoxyaluminum system (solution I).

A second 250-mL flask equipped as described above was charged with the appropriate amount of Cp_2TiCl_2 followed by 50 mL of methylene chloride and cooled to the desired temperature. Solution I was transferred to the dropping funnel with a syringe and added dropwise. The reactions were terminated by addition of 8 mL of methanol followed by 50 mL of a 5% H_2SO_4 solution saturated with sodium chloride. The resulting mixture was stirred over an oxygen atmosphere for 1 h, filtered, and then extracted with 5 50-mL portions of diethyl ether. The ether extract was dried over $MgSO_4$ and filtered. The product solutions were then reduced in volume, filtered, and analyzed by GLC.

Gas Chromatographic Analyses. All yields were determined by GLC (Hewlett-Packard 5750) using an 8 ft × ⅛ in. XE-60 column and are corrected for response factors. Samples were isolated for spectral investigations by preparative GLC using 0.25 in. Carbowax 20M and SE-30 columns.

Spectra. NMR spectra were run on a Perkin-Elmer R-20 B spectrometer. IR spectra were taken with a Perkin-Elmer 457 spectrophotometer.

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Registry No.—Cp_2TiCl_2, 1271-19-8; $Al(C_2H_5)_2Cl$, 96-10-6.

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Selective Reduction of Some *N*-Formyl Dipeptide Esters with Borane–Tetrahydrofuran

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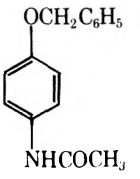
In recent years there have been reported a number of examples of selective reduction of carbonyl groups in polyfunctional molecules by borane–tetrahydrofuran (BH_3·THF).[1-4] We describe here some results that we obtained while investigating the reduction products of peptide derivatives as compounds of possible biological interest.

The *N*-formyl dipeptide esters **3a–c**, prepared by the EEDQ coupling method,[5] were reduced for 1.5 h at reflux temperature in tetrahydrofuran with limited amounts of borane. To avoid the drastic workup conditions (refluxing methanolic HCl) recommended by Kornet et al.[1] for borane reductions of acylamino esters, we tried HBr in acetic acid for this purpose. When reduction of the amide **1** was followed by addition of HBr–HOAc to the reaction mixture, a 90% yield of analytically pure *N*-ethyl-4-benzyloxyaniline (**2**·HBr) was



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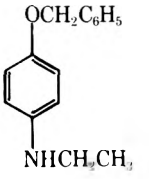

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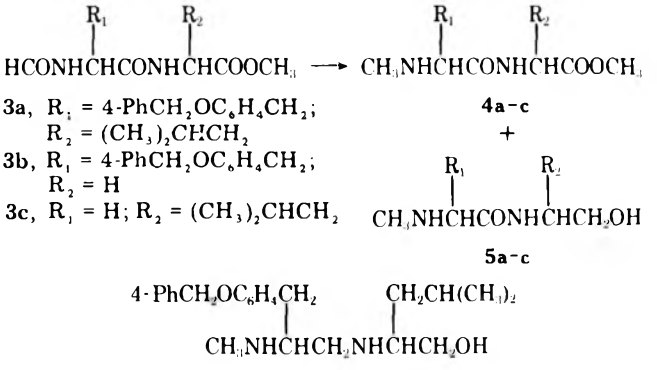
obtained directly. We therefore adopted this procedure for all of our reductions and have found it useful whenever a mild or nonaqueous workup is desirable.[6]

Reduction of *N*-formyl-*O*-benzyl-L-tyrosyl-L-leucine methyl ester (**3a**) with different amounts of BH_3·THF gave as principal isolated products (by crystallization) the *N*-methyl dipeptide ester **4a** and the (*N*-methylaminoacyl)amino alcohol **5a**; these and subsequent *N*-methylated products were easily recognized by the NMR singlet at δ 2.5–3.1. The results (Table I) show that the *N*-formyl group in **3a** is reduced more easily than the peptide or ester functions (runs 1 and 2). An increase in the hydride ion–substrate ratio leads to larger amounts of direduction product **5a** at the expense of mono-



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reduction product **4a** (run 3); however, with further increases in hydride, separation of products by crystallization becomes more difficult, and interpretation of the results is correspondingly less certain. Possibly under these conditions some

Table I. BH_3 Reduction of Formyl Dipeptide Ester 3a

Run	Mequiv of hydride ion mmol of substrate	Products,[a] % yield 4a·HBr[b]	5a·HBr[c,d]	6·2HBr[e]
1	4	40	6	
2	5	53	9	
3	6	20	27	
4	7	1	15	9
5	11			34

[a] Satisfactory analytical data (±0.3% for C, H, N, Br) were reported for all new compounds listed in the table. [b] Mp 166–176 °C (MeOH–Et_2O); $[\alpha]^{26}_D$ −30° (*c* 1, DMF). [c] Mp 218–222 °C (MeOH–Et_2O); $[\alpha]^{26}_D$ −27° (*c* 1, DMF). [d] Microanalysis obtained on free base: mp 128–129 °C (EtOAc); $[\alpha]^{23}_D$ −60° (*c* 0.8, $CHCl_3$). [e] Mp 166–170 °C (MeOH–Et_2O); $[\alpha]_D$ +29° (*c* 0.5, $CHCl_3$).

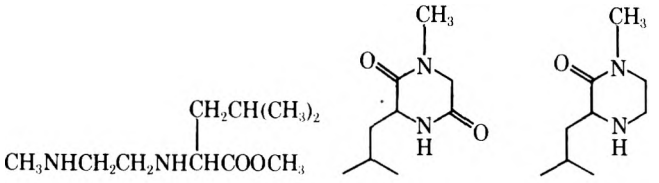
Table II. BH_3 Reduction[a] of Formyl Dipeptide Esters 3a–c

Run	Substrate[b]	Products[b] (% yield)
1[c]	**3a**[d]	**4a**·HBr (53), **5a**·HBr (9)
2	**3b**[e]	**4b**·HBr[f] (52), **5b**·HBr[g] (1)
3	**3c**[h]	**4c**[i] (28, 38),[j] **5c**[k] (28, 40),[j] **7**·2HBr[l] (19, 16)[j,m]

[a] 5 mequiv of hydride per mmol of dipeptide. [b] Satisfactory analytical data (±0.2% for C, H, N, Br) were reported for all new compounds listed in the table except as noted. [c] Data from Table I, run 2. [d] Mp 110–112 °C (C_6H_6–Et_2O); $[\alpha]^{26}_D$ +13° (*c* 1, C_6H_6). [e] Mp 120–120.5 °C (EtOAc); $[\alpha]^{26}_D$ +11° (c 1, $CHCl_3$). [f] See Experimental Section. [g] Mp 152–157 °C ($CHCl_3$–Et_2O); $[\alpha]^{23}_D$ −3° (c 0.5, DMF). [h] Mp 78.5–80.5 °C (EtOAc); $[\alpha]^{23}_D$ +8° (c 1, $CHCl_3$). [i] Estimated and microanalyzed as neutralization product **8**; see text and Experimental Section. [j] Second figure estimated from NMR spectrum of crude neutralization product (see Experimental Section). [k] Microanalysis on bis(*p*-bromophenyl carbamate). [l] Mp 148–153 °C (MeOH–Et_2O); $[\alpha]^{23}_D$ +16° (c 0.6, MeOH). [m] Includes product isolated as **7**·2HBr and that estimated as **9** (see text and Experimental Section).

racemization occurred, complicating the isolation of products. At the highest hydride–substrate ratios, fully reduced diamino alcohol **6** could be isolated (runs 4 and 5).

Since the use of 5 mequiv of hydride per mol of peptide gave the highest yield of monoreduction product **4a**, the same ratio was used to reduce peptide esters **3b** and **3c** (Table II). As only a small amount of a single crystalline product (identified as diamino ester **7**·2HBr) was obtained on reduction and workup of **3c**, the products and yields were determined indirectly. Neutralization of the noncrystalline portion of the reaction product from run 3 gave *N*-sarcosylleucinol (**5c**), diketopiperazine **8**, and ketopiperazine **9**. That **8** and **9** arose by cyclization of reduction products **4c** and **7**, respectively, was indicated by disappearance of the strong methyl ester IR (1740 cm^{-1}) and NMR (δ 3.77) peaks upon neutralization. Moreover, the roughly 2:3 ratio of ester to *N*-methyl peaks in the NMR spectrum before neutralization accounted for all of the reduction product subsequently estimated as **8** and **9**; thus **9** probably was not formed by reduction of **8**. Yields for run 3 (Table II) were also estimated from the NMR spectrum of the crude neutralization product and showed the same trend as the isolated yields.



7 **8** **9**

When *N*-methyl dipeptide ester **4a** was subjected to the standard reduction conditions and workup, 69% of unchanged starting material was recovered as well as about 1% of **5a**. Chromatography of the mother liquor gave, in addition to small amounts of unidentified materials, a substance whose IR spectrum showed only ester carbonyl absorption and which was probably *N*-(2-methylamino-3-(4-benzyloxyphenyl)-propyl)leucine methyl ester dihydrobromide (8%). As in the previous examples, the amount of material unaccounted for does not permit conclusions on the extent of racemization. However, exposure of **4a** to BH_3·THF at room temperature for 1.5 h followed by HBr–HOAc workup gave a 95% recovery of crystalline **4a** of unchanged optical rotation; thus little if any racemization is due to the workup procedure.

Discussion

Tyrosylglycine derivative **3b** (run 2, Table II) showed the same preference for reduction at the formyl group as did the tyrosylleucine derivative **3a**. However, reduction of the glycylleucine derivative **3c** was much less selective; substantial reduction of ester and peptide carbonyl groups occurred. A similar loss of selectivity was noted by Roeske et al. in a report[4] that appeared during the preparation of this manuscript. These workers found that reduction of Boc-Gly-Leu-OMe and Cbz-Gly-Leu-OMe with BH_3·THF at −20 °C gave 26–30% of the peptide bond reduction products and 40–42% recovered starting materials, while reduction of Cbz-Leu-Leu-OMe gave 7% of the peptide bond reduction product and 79% recovered starting material. Although no comment was made on the difference in reducibility a strong steric influence is consistent with our results and with those of Brown and Heim.[7]

We conclude that BH_3·THF reduction of formamide groups in structures containing both ester and secondary amide functions can be selective and preparatively useful. However, with peptide substrates, racemization may be extensive enough to preclude the use of this reaction to modify the structures of larger peptides and proteins.[8–10]

Experimental Section

Borane in tetrahydrofuran (1 M) was obtained from Ventron Corp. Melting points (Kofler hot stage) are uncorrected. Satisfactory IR and NMR spectra were obtained for all compounds. Microanalyses were performed by Galbraith Laboratories. Optical rotations were determined on a Perkin-Elmer Model 141 polarimeter.

Borane Reductions. General Procedure. The procedure for reduction of *N*-formyl-*O*-benzyl-L-tyrosylglycine methyl ester (**3b**) is typical. To 10.0 mL (30 mequiv) of 1 M BH_3·THF, stirred magnetically at 0 °C under N_2, was added over 5–10 min a solution–suspension of 22.2 g (6.00 mmol) of **3b** in 20 mL of dry THF. The clear solution was then heated at reflux for 1.5 h and allowed to cool. Saturated HBr in HOAc (6 mL, 30 mequiv) was added, dropwise at first (H_2!), and stirring was continued for about 1.5 h. The resulting solution was partially concentrated in vacuo and reconcentrated with toluene to remove some of the acetic acid. The colorless residue was treated with THF–$CHCl_3$ to provide a crystalline white solid (1.66 g); an additional 0.15 g was obtained on evaporation of the mother liquor and treatment with $CHCl_3$–Et_2O. Total crude **4b**·HBr: 1.83 g (70%); $[\alpha]^{28}_D$ +4° (*c* 1, DMF). Recrystallization of **4b**·HBr from MeOH–Et_2O gave three crops totaling 1.36 g (52%); all three crops had identical spectra and optical rotations: $[\alpha]^{27}_D$ +46° (c 1, MeOH); mp 195–198 °C.

In the case of **3a** and **3c**, the residue from concentration of the reaction mixture was diluted with a large volume of ether and the resulting semisolid was triturated with several portions of ether before attempting recrystallization from MeOH–Et_2O.

Reduction of 4-Benzyloxyacetanilide (1). A 2.41-g sample (10.0 mmol) of **1** was reduced as above using 30 mequiv of BH_3. After addition of HBr–HOAc (7 mL) and stirring for 30 min, addition of seed crystals (obtained by diluting a drop of the reaction mixture with ether) induced crystallization. The slurry was stirred for 1 h, then filtered quickly and washed immediately with THF and with ether to give 2.12 g of **2**·HBr (69%): mp 142–144 °C with resolidification; remelts 160–162 °C.

Anal. Calcd for $C_{15}H_{17}NO$·HBr: C, 58.45; H, 5.88; Br, 25.92; N, 4.54. Found: C, 58.31; H, 5.83; Br, 25.94; N, 4.49.

A second crop, 0.45 g (15%), obtained by dilution of the filtrate with ether, had mp 142–144 °C and remelts 159–161 °C.

Anal. Found: C, 58.28; H, 5.92; Br, 26.08; N, 4.46.

A third crop (0.18g, 6%) had mp 142–144 °C and remelts 161.5–162.5 °C. Total yield, 2.75 g (90%).

Estimation of Products from Reduction of 3c. The ether-triturated product from reduction of 6.00 mmol of **3c** failed to crystallize from MeOH–Et_2O. Crystallization from $CHCl_3$–Et_2O gave white crystals of **7**·2HBr; physical data appear in footnotes to Table II.

The filtrate of **7**·2HBr failed to yield other crystalline products. After evaporation the residue in 3 mL of MeOH was treated with 11 mmol of 85% aqueous hydrazine for 23 h at 40 °C. Evaporation and treatment with 2-PrOH gave a crystalline precipitate of hydrazine hydrobromide. Filtration, evaporation of the filtrate, and extraction of the residue with $CHCl_3$ left a small additional amount of the salt.

The IR spectrum of the $CHCl_3$-soluble fraction showed complete absence of ester carbonyl.

Evaporation of the $CHCl_3$ solution and repeated treatment with Et_2O gave a soluble fraction which on reduction in volume and standing at room temperature gave colorless prisms of diketopiperazine 8; this plus additional material from the mother liquor and from later fractions (see below) amounted to 0.31 g (28% from **3c**). An analytical sample recrystallized from benzene had mp 139.5–141 °C (sublimes about 130 °C) and $[\alpha]^{23}_D$ −10° (*c* 0.5, $CHCl_3$).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.79; H, 8.68; N, 15.22.

The ether-insoluble material was further fractionated by extraction with cyclohexane and with water (from $CHCl_3$ solution). The cyclohexane fractions contained slightly impure compound **9** as an oil, characterized by IR and NMR spectra and by conversion to a *p*-bromophenyl carbamate, the latter being purified by preparative-layer chromatography on SiO_2 (EtOAc, two passes) for analysis (glass).

Anal. Calcd for $C_{16}H_{22}BrN_3O_2$: C, 52.18; H, 6.02; Br, 21.70; N, 11.41. Found: C, 52.27; H, 6.11; Br, 21.58; N, 11.30.

A sample of 7·2HBr on neutralization with aqueous hydrazine cyclized to an oil that was spectrally (IR, NMR) identical with **9** obtained in the solvent fractionation.

The water-soluble fraction contained **5c** plus a small amount of 8 (by NMR); integration of the NMR spectrum gave the yield of **5c**. The bis(*p*-bromophenyl carbamate) of **5c** had: mp 122 °C, 136–152 °C (dimorphic) (EtOAc); $[\alpha]^{24}_D$ −14° (*c* 1, MeOH).

Anal. Calcd for $C_{23}H_{28}Br_2N_4O_4$: C, 47.27; H, 4.83; Br, 27.35; N, 9.59. Found: C, 47.28; H, 4.88; Br, 27.29; N, 9.49.

A small additional amount of 8 was recovered from the insoluble material remaining from the cyclohexane and water extractions.

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Registry No.—**1**, 41927-14-4, 2·HBr, 63714-68-1; **3a**, 63714-61-4; **3b**, 63714-62-5; **3c**, 60457-02-5; **4a**·HBr, 63714-63-6; **4b**·HBr, 63714-64-7; **5a**, 63714-65-8; **5a**·HBr, 63714-69-2; **5b**·HBr, 63714-66-9; **5c**, 63714-70-5; **5c** bis(*p*-bromophenyl carbamate), 63714-73-8; **6**·2HBr, 63743-86-2; 7·2HBr, 63714-67-0; **8**, 60421-32-1; **9**, 63714-71-6; **9** *p*-bromophenyl carbamate, 63714-72-7; BH_3, 13283-31-3; THF, 109-99-9.

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Asymmetric Synthesis in Optically Active 2-Methyltetrahydrofuran

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Several examples have been reported for successful asymmetric syntheses effected through the use of chiral media.[1] In these cases, the enantiomeric enrichment ordinarily has not been large and this is particularly true for additions and reductions employing Grignard reagents (values range as high as 18% but are generally less than 5%). For these reactions, chiral dialkyl ethers and amines commonly have been used. It has been recognized that the asymmetric bias should increase the more intimate the involvement of the solvent in the reaction transition state. Thus, the omission of the use of chiral derivatives of tetrahydrofuran is notable in view of the known greater ability of Grignard reagents to associate more effectively with tetrahydrofuran than to noncyclic ethers.[2] We wish to report our examination of the use of optically active 2-methyltetrahydrofuran (2-MeTHF) as a chiral solvent for a number of reactions involving Grignard reagents.

Experimental Section

Analytical gas chromatography was obtained using an F and M Model 720 instrument with twin 5 ft columns (10% DEGS on Diatoport S). Preparative chromatography was performed on an Aerograph Autoprep Model 700 using a 20 ft × ⅜ in. column (20% DEGS on Chromosorb W). NMR spectra were recorded using a Varian Model A-60 spectrometer. Optical rotations were measured using a Rudolph Model 62 polarimeter with a sodium lamp source. Fractional distillation employed a 20 × 300 mm column having approximately 30 theoretical plates and packed with stainless steel Helipak.

Optically Active 2-Methyltetrahydrofuran (2-MeTHF). Following reported procedures, optically active 2-MeTHF was prepared from racemic tetrahydrofurfuryl alcohol. The alcohol was resolved via the phthalate half-ester using brucine.[3] The recovered optically active alcohol was converted to the tosyl ester and reduced to 2-MeTHF with lithium aluminum hydride.[4] All conversions were 88–95% and the physical properties of the intermediates corresponded to literature values. The initially prepared 2-MeTHF, as well as that later recovered from reactions, was collected in an ethyl ether extract which was concentrated and fractionally distilled (bp 78–80 °C). The lower and and higher boiling fractions yielded additional product by preparative GC. Repeated isolation of the optically active solvent in this manner caused no racemization and routinely provided enantiomer samples for the several experiments having specific rotations of $[\alpha]_D^{20}$ +27.01° and $[\alpha]_D^{20}$ −27.47° (neat).[5]

All reactions described below were first run in racemic solvent to develop procedures before using the optically active solvent. Since the 2-MeTHF forms peroxides readily, it was always distilled from lithium aluminum hydride and in a nitrogen atmosphere immediately prior to use. A nitrogen atmosphere was employed in all reactions.

After a reaction was completed, in each case the product was hydrolyzed by the careful addition of 10 mL of 5% sulfuric acid solution. The organic layer was isolated and washed with 5% sodium bisulfite and 5% sodium bicarbonate solutions. After it was dried with anhydrous magnesium sulfate, it was distilled to recover the reaction solvent and then the product was isolated by either vacuum distillation or preparative gas chromatography. The aqueous layer and all subsequent aqueous washings were extracted continuously for 24 h with ethyl ether to recover additional solvent as described above.

Formation of (+)-1-Phenylethanol. Phenylmagnesium bromide was prepared from 0.610 g (0.0251 mol) of magnesium with 3.93 g (0.025 mol) of bromobenzene in 17.1 g (20 mL) of (+)2-MeTHF ($[\alpha]_D^{20}$ +27.01°). To this solution maintained at −10 °C there was added in 30 min 1.50 g (0.034 mol) of freshly distilled acetaldehyde dissolved in 10 mL of pentane. After hydrolysis a 49% yield (preparative GC) of 1-phenylethanol was obtained: $[\alpha]_D^{20}$ +0.93° (neat, 1-1); optical purity 2.15%. The retention time was identical with that for authentic 1-phenylethanol. Downer and Kenyon[6] report a specific rotation $[\alpha]_D^{17}$ −43.3 (neat) for the pure levo enantiomer. Also, this optically active alcohol was obtained from racemic 1-phenylethanol by resolution according to the method of Downer and Kenyon.[6] When this sample was subjected to the same preparative GC conditions, no loss in activity was noted. Repetition of this experiment without the use of pentane where pure acetaldehyde was added directly to the Grignard reagent during 30 min provided 1-phenylethanol having 1.6% optical purity.

Formation of (+)-*tert*-Butylphenylcarbinol. a. In 2-MeTHF. Phenylmagnesium bromide was prepared from 0.489 g (0.0201 mol) of magnesium and 3.14 g (0.02 mol) of bromobenzene in 8.55 g (10 mL) of (+)2-MeTHF. A solution containing 2.58 g (0.03 mol) of freshly distilled pivaldehyde in 10 mL of pentane was added with stirring in 90 min with the reaction temperature maintained at −10 °C. The reaction mixture was hydrolyzed at once and yielded (by distillation) 1.8 g (57%) of the carbinol: bp 68–75 °C (1 mm); mp 53–54 °C; $[\alpha]_D^{20}$

+2.82° (c 10.87, benzene), optical purity 11% (lit.[7] mp 54–54.5 °C, $[\alpha]_D^{22}$ +25.9° (c 2.24, benzene)). The carbinol was both recrystallized from ether–pentane and sublimed under reduced pressure, but neither process resulted in a product of higher rotation. The structure of the product was confirmed by NMR spectra (four singlet signals). This preparation of *tert*-butylphenylcarbinol was repeated with levo 2-MeTHF ([α] −22.40, optical purity 81.5%) and using the same amounts of reactants indicated above. In this case, pure pivaldehyde was added to refluxing (85 °C) Grignard reagent mixture. A 78% yield of levo product distilled at 70–72 °C (1.4 mm). The specific rotation was $[\alpha]_D^{20}$ −1.52° (c 25, benzene). This corresponds to an optical purity of 5.87% and stereoselectivity of 7.2%.

b. In Ethyl Ether–2-MeTHF (1:1). Phenylmagnesium bromide was prepared from 0.510 g (0.021 mol) of magnesium and 3.14 g (0.02 mol) of bromobenzene in 3.75 g (0.05 mol) of ethyl ether. After the reaction was complete, 4.31 g (0.05 mol) of (+)2-MeTHF was added and the mixture was stirred for 30 min to equilibrate the solvated 2-MeTHF. Pivaldehyde (2.15 g, 0.025 mol) was added as in part a. After hydrolysis and isolation as above, 1.9 g (58%) of *tert*-butylphenylcarbinol was obtained. This product was racemic and provided an NMR spectrum identical with that of the authentic carbinol.

c. In Ethyl Ether–2-MeTHF with Excess 2-MeTHF (Solvent Exchange). Phenylmagnesium bromide was prepared as in part b except using 7 g (0.1 mol) of ethyl ether. When the Grignard reagent formation was complete, the solvent was removed at reflux with a stream of dry nitrogen. Finally the reagent was pumped at 1 mm to leave a viscous residue. After 7.0 g of 2-MeTHF was added, the mixture was stirred 30 min to attain solvent equilibration. Pivaldehyde (2.15 g, 0.025 mol) was added and the reaction and product isolation were completed as above. The *tert*-butylphenylcarbinol (2.1 g, 64%) was optically active: $[\alpha]_D^{19}$ +0.15°, optical purity 0.6%.

Asymmetric Reduction of Isobutyrophenone. Isobutylmagnesium chloride was prepared by the reaction of magnesium (0.0563 g, 0.024 mol) with isobutyl chloride (1.85 g, 0.02 mol) in 8.55 g (10 mL) of (+)2-MeTHF at reflux. The reaction was difficult to start and was assisted by the addition of a trace of bromobenzene. The isobutylmagnesium chloride solution was cooled to 20 °C and a solution of 2.52 g (0.017 mol) of isobutyrophenone in 10 mL of pentane was added during 2 h. The reaction mixture was hydrolyzed immediately and after the usual workup 2.20 g (86%) of 2-methyl-1-phenylpropanol was isolated by distillation: bp 57–62 °C (0.5 mm); $[\alpha]_D^{22}$ +1.59° (c 10.09, ether); optical purity 3.3%. Levene and Mikeska[8] report $[\alpha]_D^{20}$ +47.7° (c 6.997, ether) for a pure enantiomer. The reaction mixture was shown by GC to contain no unreacted ketone and the NMR spectra of the product was consistent with the indicated structure. The reaction was repeated with the temperature maintained at −10 °C during the addition of the isobutyrophenone. In this case the optical purity of the product was 2.1%.

Kinetic Resolution of 2-Bromo-1-phenylpropane. Magnesium (0.365 g, 0.015 mol) and 2-bromo-1-phenylpropane (5.97 g, 0.03 mol) were reacted in 5.4 g of (+)2-MeTHF and 5 mL of pentane. After the reaction started the reaction flask was cooled in an ice–water bath. During 2 h most of the magnesium dissolved. The reaction mixture was hydrolyzed and the unreacted 2-bromo-1-phenylpropane was isolated and purified by preparative GC and finally vacuum distilled: bp 47–50 °C (0.3 mm); $[\alpha]_D^{20}$ −0.5 °C (c 8.01, ethanol), optical purity 2.1% (lit.[9] $[\alpha]_D^{20}$ −22.96° (c 4.964, ethanol)).

Discussion and Results

Each type of reaction examined produced optically active products when active 2-MeTHF was used as solvent (2.1 to 11% optical purity). Each example was chosen so that steric factors would be as significant as possible in the developing diasteromeric reaction transition states leading to chiral products. Nevertheless, the extent of enantiomeric enrichment was not superior to that reported earlier with Grignard reagents in chiral ethers. For example, the reaction of phenylmagnesium bromide with pivaldehyde in (+)2-MeTHF provided *tert*-butylphenylcarbinol in 11% optical purity. For a comparison, the reaction of the same Grignard with 2-butanone (which has a carbonyl group with less difference in steric requirement for it's attached groups than that in pivaldehyde) in (+)-2,3-dimethoxybutane gave methylethylphenylcarbinol in about 18% optical purity.[10]

Optically active *tert*-butylphenylcarbinol was prepared by addition of pivaldehyde to phenylmagnesium bromide at −10 and 85 °C with the greater stereoselectivity at the lower temperature. At the concentration used with this Grignard reagent a viscous unstirrable mixture developed at −30 °C and precluded lower temperature experiments.

The attempts to achieve asymmetric synthesis from the Grignard reagent first prepared in ethyl ether and followed by an equal molar amount of (+)-2-methyltetrahydrofuran added before reaction with pivaldehyde or solvent exchange with (+)2-MeTHF effected before reaction with the aldehyde, resulted in lower enantiomeric enrichment in the carbinol product. This suggests that the 2-methyltetrahydrofuran may be less competitive in solvating the Grignard reagent than expected. A thermodynamic measure of the basicity of 2-methyltetrahydrofuran compared to tetrahydrofuran relative to an acid having steric requirements comparable to the magnesium atom site in the Grignard reagent would be desirable.

Other reactions in 2-MeTHF including Grignard reduction and kinetic resolution also gave products having observable but low enantiomeric enrichment.

Registry No.—(+)2-MeTHF, 63798-12-9; (−)2-MeTHF, 63798-13-0; acetaldehyde, 75-07-0; (+)-1-phenylethanol, 15157-69-7; phenyl bromide, 108-86-1; (+)-*tert*-butylphenylcarbinol, 23439-91-0; pivaldehyde, 630-19-3; (−)-*tert*-butylphenylcarbinol, 24867-90-1; (±)-*tert*-butylphenylcarbinol, 57377-60-3; isobutyl chloride, 513-36-0; isobutyophenone, 611-70-1; (+)-2-methyl-1-phenylpropanol, 14898-86-3; (±)-2-bromo-1-phenylpropane, 14367-52-3; (−)-2-bromo-1-phenylpropane, 63798-14-1.

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Cycloadditions of 2,5-Dimethyl-3,4-diphenylcyclopentadienone to Cyclooctene, Cyclooctadienes, and the 76 °C Melting Dimer of Cyclooctatetraene

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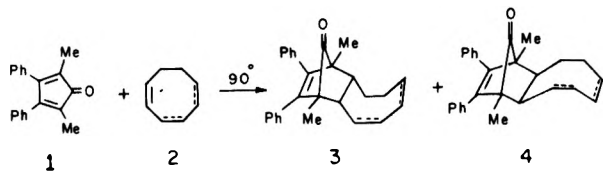
The cycloaddition reactions of the potent electron-deficient diene, 2,5-dimethyl-3,4-diphenycyclopentadienone (**1**) to a remarkable variety of alkenes have been reported. These adducts have been used in the synthesis of novel substances,[2] and the structures of the Diels–Alder adducts have given some insight into the origins of cycloaddition stereoselectivity.[3,4] We wish to report facile and remarkably stereoselective cycloadditions of **1** to cyclooctenes and cyclooctadienes and to show that attempted cycloadditions to cyclooctatetraene give mainly cycloadducts of **1** to a cyclooctatetraene dimer.

Heating the dimer of **1** with cyclooctene at 90 °C for 1 day gave a product which appeared, by NMR, to be a 96:4 mixture of 1:1 adducts. The bridged carbonyl at 5.69 μm established the Diels–Alder nature of the adduct. Recrystallization from methanol gave a pure adduct **3a**, mp 171–172 °C, which had a methyl singlet at 1.25 ppm in the NMR spectrum ($CDCl_3$).



a: cyclooctene
b: 1,5-cyclooctadiene
c: 1,3-cyclooctadiene

The crude product mixture displayed, in addition to the intense methyl resonance due to **3a**, a small singlet at 1.14 ppm whose area was about 4% that of the 1.25-ppm resonance. The endo stereochemistry, **3a**, is tentatively assigned to the major adduct on the basis of the similarity of the chemical shift of the methyl resonances in **3a** (1.25 ppm) to those of the endo adducts of cyclohexene and **1** (1.25 ppm),[4c] or of cyclopentene and **1** (1.32 ppm).[4b] The minor adduct from cyclooctene has a methyl resonance (1.14 ppm), similar in location to those in the exo adducts of cyclohexene and **1** (1.10 ppm)[4c] or of cyclopentene and **1** (1.15 ppm).[4b] The minor adduct is, therefore, assigned the exo structure, **4a**.

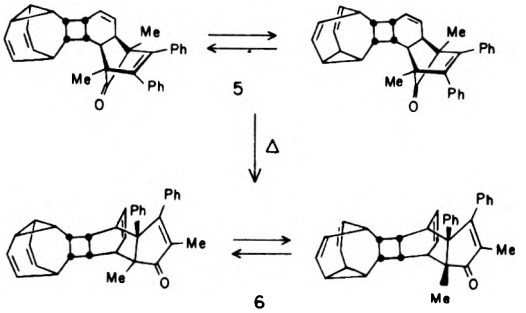
A solution of **1** in 1,5-cyclooctadiene was heated at 97 °C for 1 day. After evaporation of excess 1,5-cyclooctadiene, the NMR spectrum of the crude product had an intense singlet at 1.24 ppm and a singlet at 1.10 ppm whose area was less than 5% of the 1.24-ppm singlet. Recrystallization gave the major adduct, mp 124–126 °C, **3b**, with a bridged carbonyl at 5.69 μm in the IR. The chemical shifts of the methyl resonances indicate that the major adduct is the endo adduct. Catalytic hydrogenation of **3b** (5% Pd/C, EtOAc) resulted in the uptake of 1 mol of hydrogen to give a product identical in all respects to **3a**.

The reaction of **1** with 1,3-cyclooctadiene gave a single adduct, **3c**, mp 144 °C, in 84% yield, with methyl resonances at 1.08 and 1.27 ppm. Catalytic hydrogenation again resulted in the formation of a dihydro adduct identical to **3a**. A rigorous proof of the endo *nature* of adducts **3a**, **3b**, and **3c** could not be accomplished, since **3c** did not undergo photochemical cyclization (decarbonylation is observed), and no Cope rearrangement occurs upon heating. The endo adducts of **1** with cyclopentadiene and with 1,3-cyclohexadiene undergo Cope rearrangements at 90 °C with half-lives of 30 min and 159 h, respectively.[4b,c] Thus, the failure of **3c** to undergo Cope rearrangement after heating at 120–125 °C for 5 days is not unlikely even if the adduct has the endo structure.

The difficulty of the Cope rearrangement in the eight-membered adduct is undoubtedly the result of the difficulty with which the requisite boat-like transition state can be attained. The similarity (but not identity) of a secondary orbital interaction-stabilized transition state for the Diels–Alder reaction leading to **3c** and the hypothetical Cope rearrangement transition state of **3c** indicates that secondary orbital interactions cannot be of much importance in the transition state leading to **3c**. The similar adduct mixtures from **2a,b,c**, only the last of which can have attractive secondary orbital interactions in the endo transition state, also suggests that the origin of the endo preference in the reactions of cyclooctene, 1,5-cyclooctadiene, and 1,3-cyclooctadiene with **1** probably arises from minimization of steric effects in the endo transition states.[4]

Whereas we found that **1** gives approximately equal amounts of endo and exo adducts with cyclopentadiene,[4b] and a 2:1 mixture of endo and exo adducts with 1,3-cyclohexadiene,[4c] Jones found that the analogous cyclopentadienone having a phenanthrene moiety in the place of the stilbene unit in **1** gives mainly the endo adduct with cyclopentene.[4d] This was attributed to the absence of repulsion between the out-of-plane phenyls in **1** and the cyclopentene hydrogens. Why then do the cyclooctenes appear to give mainly the endo adducts with **1**? We speculate that this could well be due to the preferred tub conformations of cyclooctenes, which may place most of the bulk of the cyclooctane rings away from the out-of-plane phenyl hydrogens. We are then left with the difficulty of explaining predominant endo addition. Perhaps Furukawa et al.'s attractive interactions between saturated and unsaturated centers,[5] a hypothesis we have heretofore argued against,[1a] must be invoked.

Cyclooctatetraene dimerizes more rapidly than it undergoes cycloaddition to **1**. Thus, heating **1** in freshly distilled cyclooctatetraene at 40 °C for 2 weeks gave a 2:1 adduct, **5**, mp 168–169 °C, of cyclooctatetraene and **1**.[6] The 2:1 nature was shown by mass spectrometry and elemental analysis, while the bridged carbonyl at 5.70 μm ($CHCl_3$) in the IR indicated that a Diels–Alder adduct had been formed. Confirmation of the adduct structure was achieved by independent reaction of the cyclooctatetraene 76 °C melting dimer,[7] with **1**. Reaction of equimolar amounts of the 76 °C dimer of COT and **1** at 60 °C in acetone for 12 h gave a 79% yield of **5**. Both **5** and **6** (see below) show temperature-dependent NMR spectra



similar to the 76 °C dimer and to other adducts of the dimer retaining the dihydrobullvalene moiety.[8–10] Thus, at −80 °C coalescence occurred in the spectra of both **5** and **6**, while sharpening of the resonances occurred at −100 °C.

When the reaction of **1** and cyclooctatetraene was carried out at higher temperatures, or upon heating of **5** at 120 °C for 2 h, a rearranged 2:1 adduct, **6**, mp 233–234 °C, IR 5.99 μm (C=O, $CHCl_3$), was formed. The relatively rapid Cope rearrangement is most likely due to the increased rigidity of the cyclohexene ring compared to that in the 1,3-cyclohexadiene adduct.[4c] This rigidity facilitates achievement of the Cope rearrangement transition state.

The reaction of the 1,3-cyclohexadiene moiety of the 76 °C dimer of cyclooctatetraene with the dienophile, vinylene carbonate, has been reported earlier.[9] Cyclopentadiene was believed to add the 76 °C dimer, in the same fashion,[10] but Fray and co-workers recently showed that the adduct actually has a structure analogous to the Cope rearrangement product **6**.[11] The 76 °C dimer itself dimerizes to a tetramer, in which the 1,3-cyclohexadiene moiety of dimer acts as both diene and dienophile.[12] By contrast to our results with **1**, 1,3-dipoles add readily to monomeric cyclooctatetraene.[13]

Cyclooctenes react faster than cyclopentenes, which, in turn, react faster than cyclohexenes with cyclopentadienones. Thus, the times and temperatures required for complete conversion to adducts using alkenes as solvents are 3 days at 115 °C, 1 day at 90 °C, and 8 days at 90 °C for cyclopentene,[4b] cyclooctene, and cyclohexene,[4c] respectively. This relatively high reactivity of the eight-membered ring has also been noted in hexachlorocyclopentadiene cycloadditions and diethylaluminum additions to cycloalkenes.[14] The sterically unencumbered nature of the cyclooctene double bond in additions seems to be verifed by these results.

Experimental Section

Preparation of 3a. A solution of 1.30 g (2.5 mmol) of the dimer of **1** in 10 mL of cyclooctene was heated under nitrogen at 90 °C for 17

h. Excess cyclooctene was removed in vacuo and the solid residue was recrystallized from methanol to give colorless **3a:** mp 171–172 °C; 1.70 g (92%); IR 5.69 μm ($CHCl_3$); NMR ($CDCl_3$) δ 1.24 (6 H), 1.2–2.2 (14 H), 6.9–7.3 (10 H). Anal. Calcd for $C_{27}H_{30}O$: C, 87.52; H, 8.16, O, 4.32. Found: C, 87.27; H, 8.24.

Preparation of 3b. A solution of 0.26 g (0.5 mmol) of the dimer of 1 in 10 mL of 1,5-cyclooctadiene containing 50 mg of hydroquinone was heated under nitrogen at 97 °C for 23 h. Excess diene was removed in vacuo and the residue was purified by TLC (silica gel, 5% ethyl acetate–petroleum ether), followed by three recrystallizations from methanol, to give colorless prisms, **3b:** mp 124–126 °C; 0.35 g (94%); IR 5.69 μm ($CHCl_3$); NMR ($CDCl_3$) δ 1.24 (6 H), 1.5–2.6 (10 H), 5.7–6.0 (2 H), 6.9–7.3 (10 H). Anal. Calcd for $C_{27}H_{28}O$: C, 88.00; H, 7.66; O, 4.34. Found: C, 88.20; H, 7.68.

Preparation of 3c. A solution of 0.26 g (0.5 mmol) of the dimer of 1 in 8 mL of 1,3-cyclooctadiene containing 50 mg of hydroquinone was heated under nitrogen at 100 °C for 72 h. Column chromatography (silica gel, benzene) and recrystallization from methanol gave colorless plates, **5:** mp 144 °C; 0.31 g (84%); IR 5.69 μm ($CHCl_3$); NMR ($CDCl_3$) δ 1.08 (3 H), 1.27 (3 H), 1.3–2.4 (9 H), 3.2 (br d, 1 H), 5.3 (dd, 1 H), 5.4–4.9 (1 H), 6.8–7.2 (10 H). Anal. Calcd for $C_{27}H_{28}O$: C, 88.00; H, 7.66; O, 4.34. Found: C, 87.71, H, 7.81.

Hydrogenation of 3b and 3c. Hydrogenations were carried out in ethyl acetate using 5% Pd/C as a catalyst. Quantitative yields of **3a** were obtained in both cases.

Preparation of 5. A solution of 0.26 g (0.5 mmol) of the dimer of 1 in 9 mL of cyclooctatetraene containing 50 mg of hydroquinone was heated under nitrogen at 40 °C for 2 weeks (similar results were obtained by heating at 65 °C for 3 days). Evaporation of excess tetraene in vacuo followed by preparative TLC (2% ethyl acetate–petroleum ether, three elution) and recrystallization from acetone–methanol gave **5:** mp 168–169 °C; 210 mg (45%); IR 5.69 μm ($CHCl_3$). The mass spectrum of **5** had intense peaks at 468 (parent), 338, and 260 (**1**) in the high-mass region. Anal. Calcd for $C_{35}H_{32}O$: C, 89.70; H, 6.88; O, 3.41. Found: C, 89.69; H, 7.10.

The same adduct was made from the 76 °C dimer[6] of cyclooctatetraene by heating 2.5-mmol amounts of **1** (as the dimer) and the 76 °C dimer in 10 mL of acetone under nitrogen at 61 °C for 18 h. Evaporation of solvent and recrystallization from acetone–methanol gave **5:** mp 168–169 °C; 0.92 g (79%).

Cope Rearrangement of 5. A solution of 100 mg of **5** was heated in acetone under nitrogen for 2 h at 120 °C. Evaporation of solvent and recrystallization from acetone–methanol gave **6:** mp 233–234 °C; 85 mg (85%); IR 5.99 μm ($CHCl_3$). The mass spectrum had intense peaks at *m/e* 468 (parent), 338, and 260 (**1**), in the high-mass region. Anal. Calcd for $C_{35}H_{32}O$: C, 89.70; H, 6.88; O, 3.41. Found: C, 89.70; H, 7.01.

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Registry No.—**1**, 26307-17-5; **1** dimer, 38883-84-0; **2a**, 931-88-4; **2b**, 111-78-4; **2c**, 1700-10-3; **3a**, 63904-18-7; **3b**, 63904-19-8; **3c**, 63904-20-1; **5** isomer I, 63866-53-5; **5** isomer II, 63866-54-6; **6** isomer I, 63866-55-7; **6** isomer II, 63866-56-8; cyclooctatetraene, 629-20-9; cyclooctatetraene dimer, 14375-95-2.

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An Alternate Synthesis of 5,6-Dihydroxy-2,3-dihydroindole-2-carboxylates (Cyclodopa)

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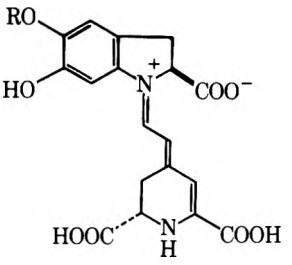
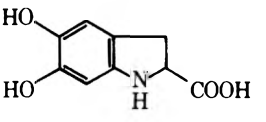
For the total synthesis of betanin (**1**),[1] the red-violet pigment of the beet (*Beta vulgaris*), and the corresponding aglycone betanidin (**2**)[1,2] an efficient synthesis of cyclodopa (**3**) (5,6-dihydroxy-2,3-dihydroindole-2-carboxylic acid) was required. The methyl ester of this acid was prepared previously by oxidation of dopa methyl ester (**7**) with potassium ferricyanide followed by reduction of the intermediate methyl 6-hydroxy-5-oxo-2,3-dihydroindole-2-carboxylate (dopachrome methyl ester) (**4**) with sodium dithionite.[3] This method serves poorly on a preparative scale because acceptable yields of product are obtained only when the oxidations are performed in less than 0.05 M solutions. The irreversible isomerization of dopachrome methyl ester (**4**) to methyl 5,6-dihydroxyindole-2-carboxylate in the basic oxidation medium creates further problems. In later work that led to a preparatively useful cyclodopa synthesis, the isomerization of dopachrome ester was avoided by performing the oxidation on dopa (**6**) itself rather than its esters.[4] A further improvement resulted when it was noticed that solutions of cyclodopa (**3**) could be stabilized by complexation with borate.[4]



1, R = glucose
2, R = H



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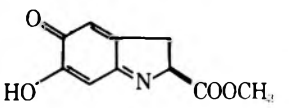

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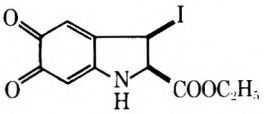

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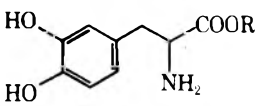
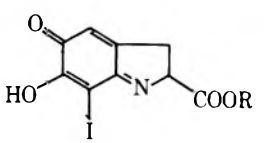


6, R = H
7, R = CH_3
8, R = C_2H_5

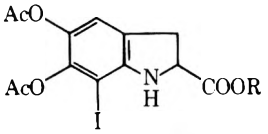


9, R = CH_3
10, R = C_2H_5

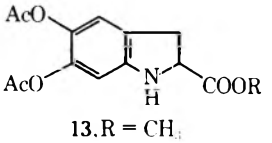
While the latter study was in progress we reinvestigated some older work of Bu'Lock and Harley-Mason.[5] They found that oxidation of dopa ethyl ester hydrochloride (**8**) with po-

tassium iodate in aqueous 1-butanol yielded a red, crystalline iodoquinone which was formulated as **5**.

In this laboratory their procedure gave approximately 25% of this iodoquinone, but superior yields were obtained by performing the oxidation in a two-phase system employing chloroform as the organic phase. The infrared spectrum in Nujol of the iodoquinone exhibited bands at 3100, 1740, 1673, and 1625 cm^{-1} in general agreement with structure **5**, but the NMR spectrum of the compound measured immediately after dissolution in DMSO-d_6 indicated the presence of at least three species and within 2 h anything resembling an iodoquinone had vanished. To avoid manipulation of this sensitive compound the crude iodoquinone was immediately reduced with sodium dithionite and the reduction product was stabilized further by acetylation. If the previously postulated structure **5** of the iodoquinone were correct, an *O,O,N*-triacetate should have resulted. In contradiction to this proposal, a mass spectrum of the product showed it to be a diacetate. Furthermore, the spectrum lacked both M − 1 and M − HI peaks, in better agreement with the presence of an aromatic rather than a benzylic iodide. Indeed, an NMR spectrum of this iodide exhibited a triplet (J = 1 Hz) caused by a single aromatic proton. The magnitude of the coupling constant suggests *o*- rather than *m*-benzylic coupling,[6] and the iodoquinones **9** and **10** and their reduction products **11** and **12** thus all are 7-iodo derivatives. Catalytic reduction of the iodides **11** and **12** over a palladium catalyst in ethanol containing



11, R = CH_3
12, R = C_2H_5



13, R = CH_3
14, R = C_2H_5

triethylamine afforded the racemic *O,O*-diacetylcyclodopa esters **13** and **14** in 40% overall yield based on dopa methyl ester, characterized further by crystalline hydrochlorides. Their NMR spectra show singlets and triplets (J = 1 Hz) corresponding to one aromatic proton each. The newly formed protons show no long-range coupling, while the second signals again display *o*-benzylic coupling, thus providing confirmation for the location of the iodine atom in the iodinated intermediates. The ability of potassium iodate to cause iodinations was recognized earlier[5] but whether iodination in the present case occurs before or after formation of the dihydroindole remains unknown. Treatment of cyclodopa methyl ester with potassium iodate followed by reduction with dithionite and acetylation gave iodide **11**, identical with that prepared from dopa methyl ester (**7**) using the same sequence of reactions. Earlier investigators have developed efficient methods for the hydrolysis of cyclodopa esters to cyclodopa.[3,4]

Experimental Section

Methyl 5,6-Diacetoxy-7-iodo-2,3-dihydroindole-2-carboxylate (11). To a stirred mixture of 2.5 g of racemic 3,4-dihydroxyphenylalanine (dopa) methyl ester hydrochloride (**7**), 40 mL of water, and 400 mL of chloroform was added a solution of 8.56 g of potassium iodate in 100 mL of water. After stirring for 12 min, the aqueous phase was separated and extracted twice with chloroform. The combined extracts were washed with brine and evaporated to dryness under reduced pressure at 50 °C. The residue was dissolved in 200 mL of 40% aqueous ethanol and sodium dithionite ($Na_2S_2O_4$) was added until the red color disappeared. The mixture was filtered and the filtrate was extracted three times with ether. The ether extract was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Treatment of the residue with 50 mL of acetic anhydride and 10 mL of pyridine for 4 h at room temperature, followed by the standard workup afforded a crude acetate (2.06 g) which was purified by chromatography over 60 g of silicic acid. Elution with CH_2Cl_2–acetone (97:3) gave the crystalline iodoacetate **11** (2.03 g). Recrystallization from methanol gave prisms: mp 126–127 °C; positive Beilstein test; UV_{max} (C_2H_5OH) 218 (ϵ 31 400), 245 (shoulder, ϵ 7710), and 307 nm (ϵ 4690); IR (Nujol) 3350, 3250, 1760, 1730, 1690, 1215, 935, and 883 cm^{-1}; NMR ($CDCl_3$) δ 2.17 (s, 3), 2.27 (s, 3), 3.42 (d of d, 2, J = 1, 8 Hz), 3.69 (s, 3), 4.44 (t, 1, J = 8 Hz), 4.70 (d, 1, exchangeable with D_2O), and 6.82 ppm (t, 1, J = 1 Hz). Anal. Calcd for $C_{14}H_{14}O_6NI$: C, 40.11; H, 3.37; N, 3.34; I, 30.28. Found: C, 40.22; H, 3.43; N, 3.39; I, 30.09.

Methyl 5,6-Diacetoxy-2,3-dihydroindole-2-carboxylate (13). The iodo acetate **11** (1.827 g), 360 mg of 10% palladium-on-carbon, and 0.73 mL of triethylamine in 110 mL of ethanol were stirred under hydrogen (1 atm). After reduction was complete (hydrogen uptake, 118 mL; calcd, 102 mL), the catalyst was filtered and washed with ethanol, and the filtrate was evaporated under reduced pressure. The residue was dissolved in dichloromethane, washed with aqueous sodium thiosulfate and brine, and dried (Na_2SO_4). Removal of solvent gave 1.2 g of a gum which was chromatographed on 36 g of silicic acid. Elution with CH_2Cl_2–acetone (95:5) gave pure (±)-di-*O*-acetylcyclodopa methyl ester as a gum (1.165 g, 40% from dopa methyl ester hydrochloride): NMR ($CDCl_3$) δ 2.25 (s, 6), 3.31 (d, 2, J = 8 Hz), 3.76 (s, 3), 4.43 (t, 1, J = 8 Hz), 4.36 (broad s, 1, exchangeable with D_2O), 6.55 (s, 1), and 6.95 (t, 1, J = 1 Hz).

Methyl 5,6-Diacetoxy-2,3-dihydroindole-2-carboxylate Hydrochloride. Di-*O*-acetylcyclodopa methyl ester, **13** (100 mg), was dissolved in absolute ether and the solution was saturated with dry hydrogen chloride under ice cooling to give a white precipitate. Filtration and recrystallization from methanol–ether afforded colorless prisms (81 mg): mp 117–121 °C; UV_{max} (C_2H_5OH) 244 (ϵ 6840) and 304 nm (ϵ 3810); IR (Nujol) 3060, 3040, 2500–2400, 1758, 1770, 1753, 910, 883, and 860 cm^{-1}; NMR (DMSO-d_6) δ 2.22 (s, 6), 3.27 (AB part of ABX, 2), 3.70 (s, 3), 4.66 (X part of ABX, 1), 6.69 (s, 1), and 7.03 (broad s, 1). Anal. Calcd for $C_{14}H_{16}ClNO_6$: C, 50.99; H, 4.89; Cl, 10.76; N, 4.25. Found: C, 51.05; H, 4.96; Cl, 10.65; N, 4.18.

(±)-Ethyl 5,6-Diacetoxy-2,3-dihydroindole-2-carboxylate. Di-*O*-acetylcyclodopa ethyl ester was prepared using the same method described for the methyl ester.

7-Iodo-5,6-di-*O*-acetylcyclodopa ethyl ester (**12**): mp 141–142 °C (from CH_3OH); IR (Nujol) 3380, 1770, 1745, 1730, 1600, 1580, 938, 900, and 875 cm^{-1}; NMR ($CDCl_3$) δ 1.28, (t, 3), 2.22 (s, 3), 2.30 (s, 3), 3.44 (d of d, 2, J = 1, 8 Hz), 4.17 (q, 2), 4.39 (t, 1, J = 8 Hz), 6.75 (t, 1, J = 1 Hz); mass spectrum *m/e* (rel intensity) 433 (27.7), 391 (42.6), 349 (100), 276 (66.8), and 149 (40.0). Anal. Calcd for $C_{15}H_{16}INO_6$: C, 41.60; H, 3.72; I, 29.30; N, 3.27. Found: C, 41.67; H, 3.74; I, 29.37; N, 3.23.

Di-*O*-acetylcyclodopa ethyl ester (**14**): IR ($CHCl_3$) 3360, 1760, 1730, 1668, 1620, 910, and 895 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (t, 3), 2.20 (s, 6), 3.26 (d, 2, J = 8 Hz), 4.13 (q, 2), 4.32 (t, 1), 6.35 (s, 1), and 6.75 (t, 1, J = 1 Hz).

Di-*O*-acetylcyclodopa ethyl ester hydrochloride: mp 121–123 °C (from CH_3OH–ether): IR (Nujol) 3040, 2500–2300, 1775, 1740, 910, 880, and 855 cm^{-1}. Anal. Calcd for $C_{15}H_{18}ClNO_6$: C, 52.43; H, 5.28; Cl, 10.31; N, 4.08. Found: C, 52.64; H, 5.39; Cl, 10.19; N, 3.99.

Methyl 6-Hydroxy-5-oxo-2,3-dihydroindole-2-carboxylate (9). The crude *o*-quinone was dissolved in acetone, filtered, and concentrated without heating until crystals had separated. These were collected and washed with ether to afford red needles: mp 118–20 °C dec and remelt at 193–194 °C; IR (Nujol) 3100, 1740, 1673, 1625, 1567, and 885 cm^{-1}; NMR (DMSO-d_6) δ 3.44 (AB part of ABX), 3.77 (s), (3.87 (s), 4.82 (X part of ABX), 6.44 (t, J = 3 Hz), 7.03 (s), 7.20 (d), and 10.48 (broad s). After 2 h, the peaks at δ 3.44, 3.77, and 6.44 had disappeared and were replaced by a very broad peak centered at 6.27 ppm.

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Registry No.—**7**, 40611-00-5; **9**, 63797-93-3; **11**, 63797-94-4; **12**, 63797-95-5; **13**, 63864-75-5; **13**·HCl, 63864-76-6; **14**, 63797-96-6; **14**·HCl, 63797-97-7.

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Syntheses of α- and β-Sorigenin Methyl Ethers

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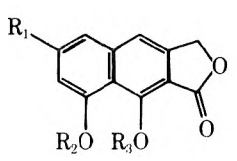
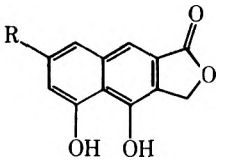
Received June 7, 1977

New, abbreviated syntheses of β- and α-sorigenin methyl ethers (**1a** and **1b**) have been accomplished using our recently reported synthetic strategy and reaction sequence for the regioselective construction of linear polynuclear aromatic systems.[1]

The first examples of natural products with a naphthalene nucleus, two primosides, α- and β-sorinin and their aglycones, β-sorigenin (**1c**) and α-sorigenin (**1d**), were isolated by Nikuni

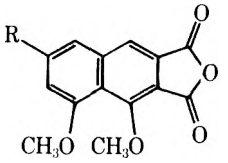


1a, $R_1 = H$; $R_2 = R_3 = CH_3$
b, $R_1 = OCH_3$; $R_2 = R_3 = CH_3$
c, $R_1 = R_2 = R_3 = H$
d, $R_1 = OCH_3$; $R_2 = R_3 = H$



2a, R = H
b, R = OCH_3

in 1938 from the bark of *Rhamus japonica*.[2,3] Initially, structures **2a** and **2b** were proposed for the sorigenins, but these were later revised to **1c** and **1d** by Haber, Nikuni, et al.[4] Lengthy syntheses of the sorigenin methyl ethers by Horii et al.[5,6] followed, but these preparations, performed through anhydrides **3a** and **3b**, failed to establish the disposition of the



3a, R = H
b, R = OCH_3

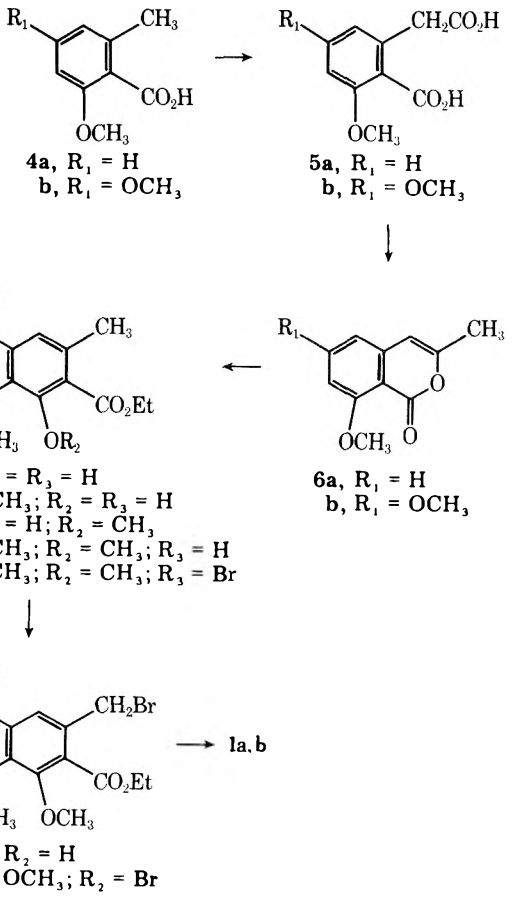
lactone moiety. Finally, Nikuni et al.[7] and Horii et al.[6] independently published unequivocal but protracted syntheses of the sorigenin methyl ethers.

Scheme I shows our parallel reaction sequences followed to transform 2-methoxy-6-methylbenzoic acid[9] (**4a**) and dimethylorsellinic acid[10] (**4b**) to β- and α-sorigenin methyl ethers (**1a** and **1b**), respectively. A high-yield, one-pot transformation of benzoic acid **4a** to homophthalic acid **5a** was described by us earlier.[11] Under identical conditions, dimethylorsellinic acid[10] (**4b**) was efficiently transformed to homophthalic acid **5b** in 76% yield.[12] Preparations of isocoumarins **6a**[18] and **6b**[13,16] from homophthalic acids **5a** and **5b** have been described. The best yields (65–70%) were obtained using the three-step sequence outlined by Wendler et al.[13]

Substantially improved yields over those reported for transformation of isocoumarins to ethyl 1-hydroxy-2-naphthoates by Reformatsky reaction were achieved by dropwise addition of the precursor ethyl bromoacetate rather than batch addition.[19] Employing the modified conditions, naphthoates **7a** and **7b** were obtained in 72 and 34% yield respectively from isocoumarins **6a** and **6b**.[20] Naphthoates **7a** and **7b** were converted in quantitative yield to their corresponding methyl ethers **7c** and **7d** employing potassium carbonate and dimethyl sulfate.

Final conversion of naphthalene **7c** to β-sorigenin methyl ether was accomplished by initial bromination of the 3-methyl group of **7c** with *N*-bromosuccinimide (NBS) to give bromomethyl compound **8a**. Treatment of **8a** with sodium hydroxide resulted in initial bromide displacement followed by anchimerically assisted hydrolysis of the ortho ester functionality furnishing β-sorigenin methyl ether in 85% yield.

Scheme I



4a, $R_1 = H$
b, $R_1 = OCH_3$

5a, $R_1 = H$
b, $R_1 = OCH_3$

6a, $R_1 = H$
b, $R_1 = OCH_3$

a, $R_1 = R_2 = R_3 = H$
b, $R_1 = OCH_3$; $R_2 = R_3 = H$
c, $R_1 = R_3 = H$; $R_2 = CH_3$
d, $R_1 = OCH_3$; $R_2 = CH_3$; $R_3 = H$
e, $R_1 = OCH_3$; $R_2 = CH_3$; $R_3 = Br$

8a, $R_1 = R_2 = H$
b, $R_1 = OCH_3$; $R_2 = Br$

→ 1a,b

A more circuitous route was necessary to convert naphthalene **7d** to α-sorigenin methyl ether (**1a**). Treatment of naphthalene **7d** with an equivalent of NBS resulted in nearly exclusive formation of ring-brominated product **7e**. Successful bromination of the 3-methyl group of **7e** to bromomethyl compound **8b** was accomplished with a second equivalent of NBS. Treatment of **8b** with sodium hydroxide followed by catalytic reduction with palladium on charcoal to cleave the arylbromine gave α-sorigenin methyl ether **1b**. The overall yield of **1b** from **7d** was 53% after purification.

These syntheses demonstrate that the synthetic strategy and reaction sequence described earlier by us[1] have general applicability and can be used to regiospecifically construct highly functionalized naphthalenes. Further studies on the preparation of more complex polynuclear aromatic systems are in progress.

Experimental Section

Melting points were taken on a Kofler hot-stage microscope and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 337 spectrophotometer. Ultraviolet spectra were run on a Perkin-Elmer 202 ultraviolet-visible spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Model HA-100, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in δ units. TLC analyses were performed on silica gel using 5% ethyl acetate–chloroform as the eluent.

2-Carboxy-3,5-dimethoxybenzeneacetic Acid (5b). Benzeneacetic acid **5b** was prepared in a manner analogous to that described for **5a**.[11] From orsellinic acid (**4b**) (10 g, 50 mmol), there was obtained, after recrystallization (acetone–hexane), 9.3 g (76%) of pure **5b** with mp 171–173 °C (lit.[13] mp 171–173 °C).

8-Methoxy-3-methyl-1*H*-2-benzopyran-1-one (6a) and 6,8-Dimethoxy-3-methyl-1*H*-2-benzopyran-1-one (6b). Pyridine (2.5 mL) was added to a magnetically stirred mixture of benzeneacetic acid

5a (5.0 g, 23.8 mmol) in acetic anhydride (13 mL) under nitrogen. The solids instantly dissolved to give a greenish orange solution and within 10 min crystals began to separate. Dry ether (75 mL) was added to facilitate stirring, which was continued overnight. The reaction was diluted with additional dry ether (100 mL) and filtered and the cake of acetylated chromandione was washed repeatedly with ether to remove traces of acetic anhydride and pyridine.

The dried cake was suspended in water (40 mL) and the solution was magnetically stirred and heated on the steam bath. A sodium hydroxide solution (10%) was added dropwise so that the carbon dioxide effervescence did not create excessive foaming. When the foaming ceased, additional sodium hydroxide solution was added to a final pH 9–10. Stirring and heating of the reaction was continued for another hour at which time the solution was acidified to pH 1 with hydrochloric acid. The reaction was extracted with ethyl acetate (2 × 100 mL). The organic extract was dried ($MgSO_4$) and filtered.

To the magnetically stirred ethyl acetate extract was added acetic anhydride (10 mL) and perchloric acid (3–5 drops); the solution darkened immediately on addition of the acid. The reaction was stirred for 1 to 2 h before a saturated bicarbonate solution (50 mL) was added. When the foaming ceased, the organic layer was separated, dried ($MgSO_4$), and evaporated at reduced pressure. Residual acetic anhydride was removed by taking the residue up in ethyl acetate (200 mL) and adding small portions of bicarbonate solution until no further carbon dioxide evolution was observed. The organic layer was again separated, dried, and evaporated to give a brown oil which slowly crystallized. Final purification was effected by chromatography (100 g, silica gel, 3% EtOAc–CH_2Cl_2) and gave 3.08 g (68%) of pure **6a** with mp 109 °C (lit. mp 109.5–110.5 °C).

Using the above procedure, benzeneacetic acid **5b** was converted to benzopyran **6b** in 70% yield, mp 151–152 °C (lit.[13] mp 151–152 °C).

Ethyl 1-Hydroxy-8-methoxy-3-methyl-2-naphthalenecarboxylate (7a) and Ethyl 6,8-Dimethoxy-1-hydroxy-3-methyl-2-naphthalenecarboxylate (7b). A solution of ethyl bromoacetate (14.8 g, 88.4 mmol) in benzene (225 mL) was added dropwise (drop/7–10 s) to a magnetically stirred refluxing mixture of dry, acid washed zinc (14.5 g, 221 mmol, 20 mesh) and benzopyran **6a** (4.2 g, 22.1 mmol) in benzene (20 mL). Approximately 30 min after the addition was started, yellow crystals began forming in the reaction. After the addition was completed, the solution was refluxed for 1 h, cooled, diluted with ethyl acetate (200 mL), and acidified with hydrochloric acid. The organic layer was separated and washed with water (2 × 100 mL), sodium bicarbonate solution (200 mL), water (100 mL), and brine (100 mL). The solution was dried ($MgSO_4$), filtered, and evaporated to give a brown oil which slowly crystallized.

Final purification was accomplished by chromatography (100 g, silica gel, benzene to 3% EtOAc–benzene) and gave 4.1 g (72%) of pure **7a** with mp 59 °C: NMR ($CDCl_3$) δ 1.40 (t, J = 6 Hz, 3, CH_2CH_3), 2.42 (s, 3, $ArCH_3$), 3.96 (s, 3, OCH_3), 4.4 (q, J = 6 Hz, 2, OCH_2CH_3), 6.68 (d, J = 4 Hz, 1, ArH), 6.72 (d, J = 4 Hz, 1, ArH), 7.05 (s, 1, ArH), 7.30 (t, J = 4 Hz, 1, ArH), 10.30 (s, 1, OH). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.17; H, 6.26.

An identical reaction performed on benzopyran **6b** gave a 34% yield of naphthoate **7b** with mp 68–70 °C: NMR (CCl_4) δ 1.40 (t, J = 6 Hz, 3, CH_2CH_3), 2.40 (s, 3, $ArCH_3$), 3.80 (s, 3, OCH_3), 3.90 (s, 3, OCH_3), 4.35 (q, J = 6 Hz, 2, OCH_2CH_3), 6.23 (d, J = 4 Hz, 1, ArH), 6.38 (d, J = 4 Hz, 1, ArH), 6.74 (s, 1, ArH). Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.26; H, 6.27.

Ethyl 1,8-Dimethoxy-3-methyl-2-naphthalenecarboxylate (7c) and Ethyl 3-Methyl-1,6,8-trimethoxy-2-naphthalenecarboxylate (7d). A magnetically stirred mixture of naphthoate **7a** (4.8 g, 18.5 mmol), dimethyl sulfate (3.50 g, 27.8 mmol), and anhydrous potassium carbonate (5.10 g, 37 mmol) in acetone (125 mL) was refluxed until TLC analysis indicated that the naphthoate was completely converted to methyl ether product **7c** (5–7 h). The solution was cooled, filtered, and evaporated to give an oil. Excess dimethyl sulfate was removed by dissolving the oil in ether (200 mL), adding triethylamine (5 mL), and allowing the turbid solution which formed to stand for 1 h. The ether solution was washed with water (2 × 50 mL), hydrochloric acid (50 mL), and brine (50 mL) and finally dried ($MgSO_4$). Evaporation of the solvent gave 5.04 g (100%) of pure **7c** as an oil: NMR (CCl_4) δ 1.36 (t, J = 7 Hz, 3, CH_2CH_3), 2.33 (s, 3, $ArCH_3$), 3.79 (s, 3, OCH_3), 3.84 (s, 3, OCH_3), 4.36 (q, J = 7 Hz, 2, OCH_3), 6.62 (d, J = 5 Hz, 1, ArH), 6.67 (d, J = 5 Hz, 1, ArH), 7.16 (s, 1, ArH), 7.0 (t, J = 5 Hz, ArH).

A similar preparation was performed on **7b** to give **7d** (100%): NMR (CCl_4) δ 1.34 (t, J = 7 Hz, 3, CH_2CH_3), 2.29 (s, 3, $ArCH_3$), 3.73 (s, 3, OCH_3), 3.75 (s, 3, OCH_3), 3.85 (s, 3, OCH_3), 4.33 (q, J = 7 Hz, 2, CH_2CH_3), 6.31 (d, J = 5 Hz, 1, ArH), 6.46 (d, J = 5 Hz, 1, ArH), 7.07 (s, 1, ArH).

8,9-Dimethoxynaphtho[2,3-*c*]furan-1(3*H*)-one (1a). Naphthoate **7c** (700 mg, 2.6 mmol), *N*-bromosuccinimide (480 mg, 2.6 mmol), and a catalytic amount (~5 mg) of benzoyl peroxide in carbon tetrachloride (50 mL) were refluxed while irradiating with a sunlamp until the *N*-bromosuccinimide had been consumed. The solution was cooled and then filtered to remove succinimide. An ^1H NMR spectrum of the crude product showed that approximately 87% reaction had occurred and that a new singlet at δ 4.56 ppm ($ArCH_2Br$) was present. Evaporation of the solvent gave 1.1 g of bromo product **8a** which was dissolved in dioxane (20 mL) without further purification. Sodium hydroxide (500 mg) in water (20 mL) was added and the solution was refluxed under nitrogen for 2 h; TLC analysis indicated that all of the bromo compound had reacted. The dioxane was removed at reduced pressure and the remaining aqueous solution was acidified with concentrated hydrochloric acid. The aqueous solution of hydroxy acid was then heated on the steam bath to effect lactonization. While hot, the aqueous layer was extracted with ethyl acetate (2 × 100 mL), which was then washed with water (50 mL) and brine and finally dried ($MgSO_4$). The semisolid which remained after evaporation of the ethyl acetate was further purified by thick-layer chromatography (silica gel; 5% EtOAc–CH_2Cl_2) to give 529 mg (85%) of pure **1a** as a powder. A sample recrystallized from acetone–hexane had: mp 174.5–176 °C (lit.[8] mp 176–177.5 °C); NMR (acetone-d_6) δ 4.01 (s, 3, OCH_3), 4.03 (s, 3, OCH_3), 5.37 (s, 2, $ArCH_2O$), 7.0 (d, J = 6 Hz, 1, ArH), 7.03 (d, J = 6 Hz, 1, ArH), 7.70 (s, 1, ArH), 7.53 (t, J = 3 Hz, 1 ArH).

6,8,9-Trimethoxynaphtho[2,3-*c*]furan-1(3*H*)-one (1b). Naphthoate **7b** (1.4 g, 4.6 mmol) was brominated with *N*-bromosuccinimide (910 mg, 5.1 mmol) and then isolated in the same manner that was described for naphthoate **8a**. The ^1H NMR spectrum of the product (**7e**) showed that exclusive nuclear bromination had occurred: NMR (CCl_4) δ 1.37 (t, J = 7 Hz, 3, CH_2CH_3), 2.39 (s, 3, $ArCH_3$), 3.70 (s, 3, OCH_3), 3.82 (s, 3, OCH_3), 3.84 (s, 3, OCH_3), 4.45 (q, J = 7 Hz, 2, OCH_2CH_3), 6.41 (s, 1, ArH), 7.71 (s, 1, ArH).

A second equivalent of *N*-bromosuccinimide (910 mg, 5.1 mmol) was added, and the bromination and workup were performed as previously described to give 3.8 g of crude dibromo product **8b**: NMR (CCl_4) δ 1.42 (t, J = 7 Hz, 3, CH_2CH_3), 3.71 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 3.84 (s, 3, OCH_3), 4.40 (q, J = 7 Hz, 2, OCH_2CH_3), 4.62 (s, 2, $ArCH_2Br$), 6.39 (s, 1, ArH), 7.86 (s, 1, ArH).

Dibromoproduct **8b** was hydrolyzed without purification according to the procedure described for the preparation of β-sorigenin methyl ether (**1a**). This gave 1.17 g (81%) of lactone as a fine powder. A sample recrystallized from ethanol had: mp 240–242 °C; NMR (acetone-d_6) δ 4.05 (s, 3, OCH_3), 4.10 (s, 6, OCH_3), 5.42 (s, 2, $ArCH_2O$), 7.02 (s, 1, ArH), 8.04 (s, 1, ArH).

The bromo lactone (0.72 g, 2.5 mmol) was suspended in warm ethyl acetate–ethanol (50 mL, 1:1) with triethylamine (2 mL) and palladium on charcoal (150 mg, 10%) and hydrogenated (30 psi) until reduction ceased. The catalyst was removed by filtration through a celite bed and the solvent was evaporated to give crude lactone **1b**. Final purification was effected by thick-layer chromatography (silica gel; 5% EtOAc–CH_2Cl_2) and gave 510 mg (73%) of pure **1b** as a powder. Recrystallization from acetone–hexane gave colorless needles: mp 184–186 °C (lit.[7,8] mp 185 °C); NMR (acetone-d_6) δ 3.92 (s, 3, OCH_3), 3.98 (s, 3, OCH_3), 4.00 (s, 3, OCH_3), 5.31 (s, 2, $ArCH_2O$), 6.60 (d, J = 3 Hz, 1, ArH), 6.92 (d, J = 3 Hz, 1, ArH), 7.55 (s, 1, ArH).

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Registry No.—**1a**, 63744-12-7; **1b**, 63744-13-8; **1b** bromo derivative, 63744-14-9; **4b**, 3686-57-5; **5a**, 1137-31-1; **5b**, 4778-99-8; **6a**, 830-54-6; **6b**, 18110-66-2; **7a**, 63520-14-9; **7b**, 63744-15-0; **7c**, 63744-16-1; **7d**, 63744-17-2; **7e**, 63744-18-3; **8a**, 63744-19-4; **8b**, 63744-20-7; ethyl bromoacetate, 105-36-2.

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Synthesis via Chloroketene Adducts. Synthesis of Demethylsesquicarene[1]

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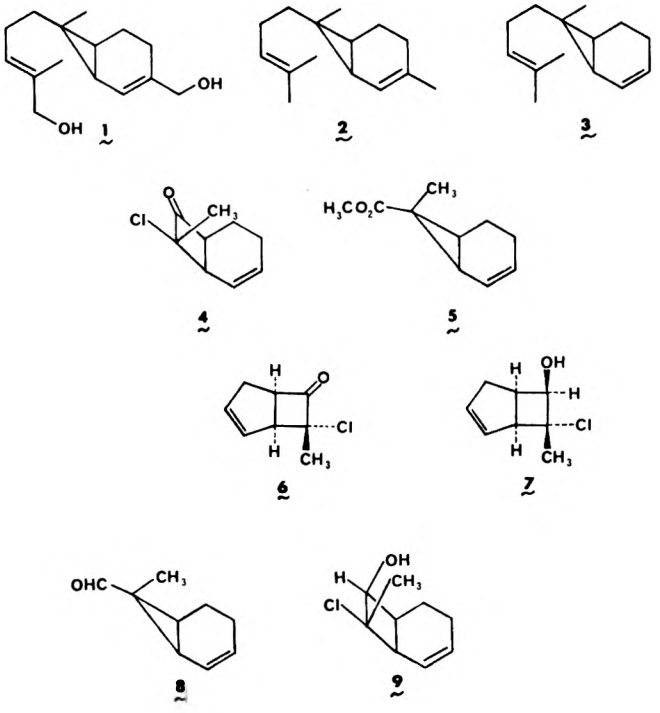
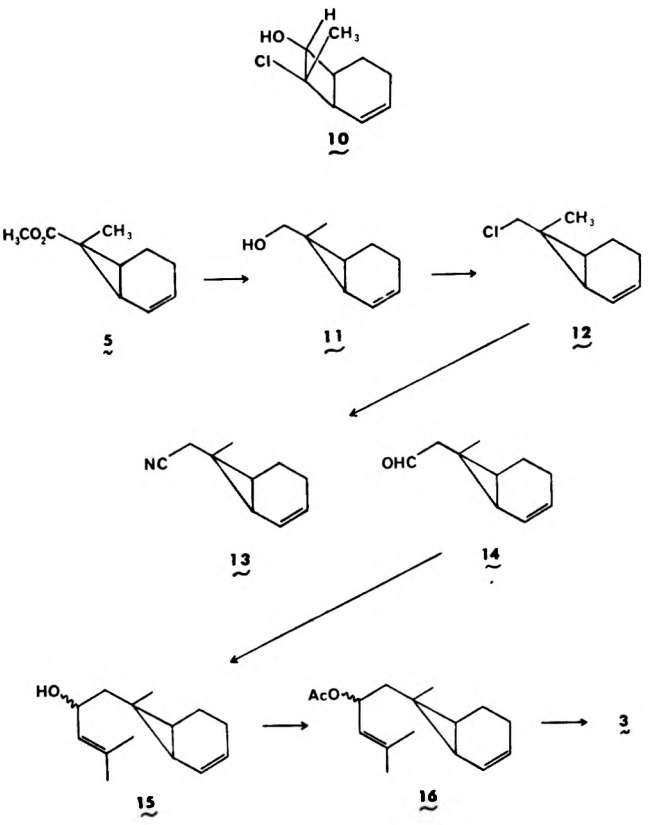
Sirenin (**1**) and sesquicarene (**2**) are novel sesquiterpenes with a carbon skeleton that can be considered an isoprenoid homologue of 2-carene. These compounds have been the object of numerous synthetic studies[2] since the initial reports of their isolation and structure.[3] The major consideration in devising a synthesis of sirenin (**1**) and sesquicarene (**2**) is the introduction of the proper stereochemistry at C-7 in the bicyclo[4.1.0]heptane skeleton. We have utilized the stereospecific ring contraction of chlorocyclobutanone **4** to ester **5** for the total synthesis of demethylsesquicarene (**3**), an analogue of the natural products.

Cyclobutanone ring contractions related to the conversion of **4** → **5** have been well documented.[4] However, at the time of our research, the only examples of this rearrangement with cyclobutanones fused to a six-membered ring had involved cine substitution prior to the ring contraction.[4c] Chlorocyclobutanone **4**[5] was obtained in 47% yield by cycloaddition of methylchloroketene to 1,3-cyclohexadiene followed by column chromatography to remove the *exo*-methyl isomer formed in 10% yield. Our initial attempts to ring contract cyclobutanone **4** following established procedures for ketone **6** were unsuccessful. The facile rearrangement of chloro alcohol **7**[4] led us to investigate this procedure for ring contraction. Reduction of chloro ketone **6** has been effected readily by a number of reducing agents.[4g,h] Chloro ketone **4** could not be reduced cleanly with lithium aluminum hydride, sodium borohydride, lithium tri-*tert*-butoxyaluminum hydride, or sodium diethylaluminum hydride. However, treatment of **4** with aluminum hydride or diisobutylaluminum hydride produced a single alcohol in modest yield (40–50%). Rearrangement of this alcohol using sodium hydroxide in aqueous methanol[4g,h] or sodium nitrate in ethanol[7] gave a cyclobutanone product rather than the desired aldehyde **8**. This result as well as spectral evidence suggests that reduction of ketone **4** gives the exo alcohol **10** rather than the endo alcohol **9** necessary for ring contraction.

The observation that reduction of ketone **4** with charged nucleophiles was unsuccessful but reduction could be effected with the Lewis acids, aluminum hydride, and diisobutyl aluminum hydride led to attempts to rearrange ketone **4** under nonbasic conditions. We found that chlorocyclobutanone **4** could be converted cleanly to ester **5** by refluxing in methanolic silver nitrate for 24 h.[6] There was no evidence that a second isomer was formed in the reaction. The use of the lanthanide shift reagent $Eu(fod)_3$[7] confirmed the exo nature of the carbomethoxy group. Creary has recently reported[8] that this ring contraction can be effected with lithium hydroxide to give the acid corresponding to **5**.

Ester **5** was reduced with lithium aluminum hydride to form alcohol **11** in 97% yield. Alcohol **11** appeared to be stable and could be stored under nitrogen at 0 °C for several weeks. Treatment with carbon tetrachloride and hexamethylphosphorus triamide in ether resulted in formation of chloride **12**.[9] This compound was quite unstable and underwent decomposition upon silica gel chromatography.[10] It generally was not purified but was used directly in the next reaction. Sodium





(or potassium) cyanide in dimethyl sulfoxide at room temperature converted **12** to nitrile **13** in a 30% yield. Although the yield in this step is only modest it did allow formation of a carbon–carbon bond at the C-8 carbon.

Attempts to react isobutenyllithium with nitrile **12** gave a complex mixture of products. Therefore, this nitrile was reduced with diisobutylaluminum hydride and hydrolyzed to give aldehyde **14** in 74% yield.[11] This aldehyde readily formed allylic alcohol **15** in 89% yield upon treatment with isobutenyllithium. Acetylation with acetic anhydride in pyridine formed acetate **16**. Then treatment of **16** with lithium in ethylamine formed demethylsesquicarene (**3**) in 97% yield.[12] It is interesting to note that the vinylcyclopropane portion of the molecule was unaffected by this reduction. The spectral properties of **3** were quite similar to those of sesquicarene. The synthesis of demethylsesquicarene confirms the validity of chloroketene adducts as synthetic intermediates for stereoselective synthesis of the basic sesquicarene skeleton although considerable modification of this scheme may be necessary for application to synthesis of the natural products.

Experimental Section

All compounds prepared in this section are racemic; the prefix *"dl"* is omitted. Infrared spectra were recorded on a Perkin-Elmer Model 237B or Beckmann Instruments Model IR8 spectrophotometer. High-resolution mass spectra were obtained on a CEC Model 21-110 spectrometer under the supervision of Dr. R. Grigsby.

The ^{1}H NMR spectra were obtained in CCl_4 solution on a Varian Associates T-60 spectrometer. The ^{13}C NMR spectra were obtained in $CDCl_3$ solution in the Fourier transform mode on a JEOL PFT-100 spectrometer system operating at 25.034 MHz (proton resonance frequency 99.539 MHz) and equipped with a Nicolet 1085 data system. All chemical shifts (^{1}H and ^{13}C) are reported on the δ scale as parts per million downfield from tetramethylsilane (TMS) as internal reference.

Evaporation distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. The temperatures cited for these distillations are the maximum temperature of the oven during the distillation. "Acid" refers to 10% hydrochloric acid. "Bicarbonate" refers to a saturated aqueous solution of sodium bicarbonate. "Brine" refers to a saturated aqueous solution of sodium chloride. "Concentration" of solvent refers to solvent removal by rotary evaporation at ca. 80 mm. Tetrahydrofuran was distilled from lithium aluminum hydride or the sodium–benzophenone dianion just before use. Anhydrous ether was stored over calcium hydride. Triethylamine was distilled from barium oxide before use. All reactions were performed under a nitrogen atmosphere.

8-*exo*-Chloro-8-*endo*-methyl-*cis*-bicyclo[4.2.0]oct-2-en-7-one (4). The procedure of Brady and Roe[5] was used. A solution of 25.4 g (0.2 mol) of 2-chloropropionyl chloride in 50 mL of pentane was added over a 30-min period to a magnetically stirred solution of 40.0 g (0.5 mol) of 1,3-cyclohexadiene, 20.0 g (0.2 mol) of triethylamine, and 250 mL of pentane. The mixture was stirred for an additional 3 h and then filtered to remove the triethylammonium chloride. After the pentane and remaining cyclohexadiene were removed by rotary evaporation, the cyclohexadiene could be recovered for re-use by fractional distillation. The crude product was chromatographed on 300 g of silica gel (2% ether in hexane). The desired *endo*-methyl isomer was eluted first. Evaporative distillation (100 °C (0.1 mm)) yielded 16.0 g (47%) of adduct **4**: IR (film) 1780 cm^{-1}; ^{1}H δ 1.5 (s, CH_3), 1.7–2.3 (m, 4 H), 3.2 (dd, C-1 methine), 4.2 (m, C-6 methine), and 6.0 (bs, olefinic protons); ^{13}C NMR δ 205.5 (C-7), 131.6 and 124.2 (C-2 and C-3), 77.1 (C-8), 54.6 (C-6), 40.3 (C-1), 21.3 (C-4 or C-5), 19.3 (C-9), and 18.7 (C-4 or C-5). The *exo*-methyl isomer was obtained in 10% yield (3.5 g) after evaporative distillation: IR (film) 1780 cm^{-1}; ^{1}H NMR δ 1.9 (s, CH_3), 1.7–2.3 (m, 4 H), 3.0 (dd, C-1 methine), 3.8 (m, C-6 methine), and 5.9 (bs, olefinic protons); ^{13}C NMR δ 206.2 (C-7), 130.0 and 124.7 (C-2 and C-3), 76.1 (C-8), 52.3 (C-6), 37.9 (C-1), 26.3 (C-9), and 21.0 and 19.0 (C-4 and C-5).

7-*endo*-Methyl-7-*exo*-carbomethoxybicyclo[4.1.0]hept-2-ene (5).[7] Silver nitrate (7.5 g, 44.1 mmol) was added to 6.0 g (35.2 mmol) of ketone **4** in 150 mL of methanol, and the solution was refluxed for 24 h. Brine was added, and the mixture was filtered to remove the silver chloride. The oily residue obtained after concentration was dissolved in ether and washed with bicarbonate and brine. The aqueous extracts were washed with ether (2×), and the combined ether solutions were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on 150 g of silica gel (2% ether in hexane) to give, after evaporative distillation (110 °C (0.2 mm)), 4.0 g (68%) of ester **5**: IR (film) 1710 cm^{-1}; ^{1}H NMR δ 1.1 (s, CH_3), 1.3–2.2 (m, 6 H), 3.6 (s, OCH_3), and 5.8 (bs, olefinic protons); ^{13}C NMR δ 175.6 (C-9), 128.9 (C-3), 122.7 (C-2), 51.8 (C-10), 30.8 (C-7), 23.9 and 23.4 (C-1 and C-6), 21.6 (C-4), 15.6 (C-5), and 9.1 (C-8); MS *m/e* (rel intensity) 166 (M^+, 60), 138 (20), 135 (25), 134 (37), 107 (60), 106 (60), 105 (84), 91 (100), 80 (21), 79 (90), 78 (29), 77 (52), 67 (20), 65 (25), 53 (29), 51 (29), 41 (36), 39 (53). Anal.[13] Calcd for $C_{10}H_{14}O_2$: 166.099370. Found: 166.100152 (MS); 4.7 ppm error.

7-Hydroxy-8-*exo*-chloro-8-*endo*-methyl-*cis*-bicyclo[4.2.0]-hept-2-ene (10). To 5 mL of a 25% solution (7.5 mmol) of diisobutylaluminum hydride in 10 mL of toluene was added 1.0 g (5.87 mmol) of ketone **4**. The mixture was stirred under nitrogen at room temperature for 15 min, poured into ether, and washed with acid, water, and brine. The ether solution was dried ($MgSO_4$), filtered, and concentrated. The crude reaction product was chromatographed (silica gel, 2–50% ether in hexane) to give, after evaporative distillation (105 °C (0.1 mm)), 470 mg (46%) of alcohol: IR (film) 3350 cm^{-1}; ^{1}H NMR δ 1.6 (s, CH_3), 1.0–2.4 (m, 4 H), 2.5–3.0 (m, 2 methine protons and OH), 3.6 (d, J = 7 Hz, CHOH), and 5.8 (bs, olefinic protons). Irradiating the methine region (δ 2.8) caused the doublet to collapse to a singlet. The addition of $Eu(fod)_3$ caused the two methine protons to separate into a doublet for the allylic proton and a lower field multiplet. Irradiation of the proton on the carbon bearing the OH did not affect the doublet but did cause the multiplet to appear as a poor doublet. Irradiation of the multiplet caused both the methine and the –CHO– doublets to collapse into singlets.

7-*endo*-Methyl-7-*exo*-(hydroxymethyl)bicyclo[4.1.0]hept-2-ene (11). To 4.0 g of ester **5** (24 mmol) in 150 mL of tetrahydrofuran was added an excess of lithium aluminum hydride. After 2 h, excess hydride was destroyed by the addition of ethanol. The mixture was poured into ether and washed with saturated ammonium chloride solution until the aluminum salts were removed, and then the ether solution was washed with bicarbonate and brine. The aqueous solutions were washed with ether (2×). The combined ether solutions were dried ($MgSO_4$), filtered, and concentrated. Evaporative distillation (110 °C (0.2 mm)) yielded 3.2 g (97%) of alcohol **11**: IR (film) 3300 cm^{-1}; ^{1}H NMR δ 1.0 (s, CH_3), 0.9–1.3 (m, 2 methine protons), 1.4–2.2 (m, 4 H), 3.0 (s, OH), 3.3 (s, CH_2OH), and 5.7 (bs, olefinic protons); ^{13}C NMR δ 126.8 (C-3), 124.8 (C-2), 72.6 (C-9), 30.9 (C-7), 22.3 (C-4), 19.3 and 18.6 (C-1 and C-6), 16.5 (C-5), and 10.9 (C-8).

7-*endo*-Methyl-7-*exo*-(chloromethyl)bicyclo[4.1.0]hept-2-ene (12).[10] A solution of 8.1 g (50 mmol) of hexamethylphosphorus triamide in 50 mL of ether was added over a 30-min period to 3.1 g (22.5 mmol) of alcohol **11** in 100 mL of ether and 10 mL of carbon tetrachloride at 0 °C. The solution was stirred overnight and then washed with water (4×) and brine. The ether solution was dried ($MgSO_4$), filtered, and concentrated. This material was used immediately in the next reaction: IR (film) no OH; ^{1}H NMR δ 3.4 (s, CH_2Cl).

7-*endo*-Methyl-7-*exo*-(cyanomethyl)bicyclo[4.1.0]hept-2-ene (13). Crude chloride **12** from the previous reaction was added to a solution of 5 g of sodium cyanide in 100 mL of dimethyl sulfoxide. This solution was stirred for 10 h, poured into ether, and washed with water (3×) and brine. The aqueous extracts were washed with ether (3×), and the combined ether extracts were dried ($MgSO_4$), filtered, and concentrated. The crude material was chromatographed (silica gel, ether/hexane) and evaporatively distilled (100 °C (0.15 mm)) to yield 1.0 g (30% from **11**) of nitrile **13**: IR (film) 2230 cm^{-1}; ^{1}H NMR δ 1.1 (s, CH_3), 1.0–1.3 (m, 2 methine protons), 1.4–2.3 (m, 4 H), 2.3 (s, CH_2CN), and 5.8 (bs, olefinic protons); ^{13}C NMR δ 127.6 (C-3), 123.8 (C-2), 118.4 (C-10), 29.8 (C-9), 24.5 (C-7), 21.8 (C-4), 21.1 and 20.4 (C-1 and C-6), 16.1 (C-5), and 13.1 (C-8); MS *m/e* (rel intensity) 147 (M^+, 4), 146 (8), 132 (17), 107 (67), 106 (26), 105 (33), 91 (70), 79 (100), 78 (22), 77 (45), 53 (26), 51 (33), 41 (39), 39 (67). Anal.[13] Calcd for $C_{10}H_{12}N$ ($M^+ - 1$, peak at 147 too weak for measurement): 146.096799. Found: 146.09670 (MS); 3.2 ppm error.

7-*endo*-Methyl-7-*exo*-(formylmethyl)[4.1.0]hept-2-ene (14).[11] Diisobutylaluminum hydride (12 mL of a 20% solution in hexane) was added to 1.0 g (6.8 mmol) of nitrile **13** in 50 mL of hexane at −78 °C. This mixture was stirred for 0.5 h, poured into ether, and washed with dilute sulfuric acid until the aluminum salts were removed. The ether was washed with bicarbonate and brine, dried ($MgSO_4$), filtered, and concentrated. The resultant oil was evaporatively distilled (110 °C (0.2 mm)) to yield 750 mg (74%) of aldehyde **14**: IR (film) 2700 and 1720 cm^{-1}; ^{1}H NMR δ 1.0 (s, CH_3), 0.9–1.3 (m, 2 methine protons), 1.3–2.2 (m, 4 H), 2.2 (d, J = 4 Hz, CH_2CHO), 5.9 (bs, olefinic protons), and 9.7 (t, J = 4 Hz, CHO); ^{13}C NMR δ 202.6 (C-10), 127.1 (C-3), 124.4

(C-2), 55.9 (C-9), 23.8 (C-7), 22.0 (C-4), 21.0 and 20.3 (C-1 and C-6), 16.4 (C-5), and 13.4 (C-8).

7-*endo*-Methyl-7-*exo*-(2-hydroxy-4-methyl-3-pentenyl)bicyclo[4.1.0]hept-2-ene (15). An ether solution of isobutenyllithium (ca. 20 mmol, prepared from isobutenyl bromide and lithium wire) was added to 750 mg (5.0 mmol) of aldehyde **14** in 10 ml of ether at 0 °C. This mixture was stirred for 6 h and then poured into ether. The ether solution was washed with saturated ammonium chloride solution, bicarbonate, and brine. The ether was dried ($MgSO_4$), filtered, and concentrated. The resulting oil was chromatographed on a short silica gel column (ether/hexane) to yield 920 mg (89%) of alcohol **15**: IR (film) 3350 cm^{-1}; ^1H NMR δ 1.6 (bs, 2 olefinic methyls), 4.5 (m, CHOH), 5.1 (broad doublet, J = 9 Hz, C-1 vinyl proton), and 5.8 (bs, ring olefinic protons); ^{13}C NMR δ 133.8 (C-12), 128.6 (C-3), 126.3 (C-11), 125.2 (C-2), 67.5 (C-10), 50.1 (C-9), 25.9 (C-7 and C-13), 22.2 (C-4), 21.6 and 20.8 (C-1 and C-6), 18.2 (C-14), 16.5 (C-5), and 12.9 (C-8).

7-*endo*-Methyl-7-*exo*-(2-acetoxy-4-methyl-3-pentenyl)bicyclo[4.1.0]hept-2-ene (16). A solution of 540 mg (2.62 mmol) of alcohol **15**, 2 mL of pyridine, and 10 mL of acetic anhydride was refluxed for 3 h. This solution was poured into ether and washed several times with water, bicarbonate, and brine. The aqueous extracts were washed with ether and the combined ether extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was evaporatively distilled (120 °C (0.1 mm)) to yield 550 mg (85%) of acetate **16**: IR (film) 1725 cm^{-1}, no OH; ^1H NMR δ 2.0 (s, O_2CCH_3).

Demethylsesquicarene (3).[12] Acetate **16** (540 mg, 2.18 mmol) was added to 25 mL of ethylamine (distilled from a small piece of sodium) and 60 mg (8.6 mg-atoms) of lithium. This solution was stirred until the lithium had completely reacted and then ammonium chloride was added. The solution was poured into ether and washed with water (3×), acid (2×), bicarbonate, and brine. The ether solution was dried ($MgSO_4$), filtered, and concentrated. The residual oil was evaporatively distilled to yield 400 mg (97%) of product: IR (film) 3040, 1640, 1450, and 1375 cm^{-1}; ^1H NMR δ 0.9 (s, CH_3), 0.7–2.2 (m), 1.60 and 1.65 (s, two olefinic methyls), 5.1 (t, J = 7 Hz, 1 H), and 5.7 ppm (bs, olefinic protons on ring); ^{13}C NMR δ 130.9 (C-12), 127.1 (C-3), 125.8 (C-11), 124.8 (C-2), 43.1 (C-9), 25.7, 22.3, 22.1 21.3, 21.0, 17.6, 16.9, 16.6, and 12.6; MS m/e (rel intensity) 190 (M^+, 7), 121 (19), 107 (55), 105 (50), 93 (33), 91 (38), 82 (21), 81 (21), 80 (19), 79 (67), 77 (26), 69 (60), 67 (29), 55 (43), 53 (24), 41 (100), 39 (33). Anal.[13] Calcd for $C_{14}H_{22}$: 190.172150. Found: 190.171598 (MS); 2.9 ppm error.

Acknowledgements. We thank the Robert A. Welch Foundation for generous financial support of this research. The JEOL PFT-100 NMR spectrometer was purchased with grant support from the National Science Foundation (GP-32912).

Registry No.—**3**, 63764-90-9; **4**, 63813-94-5; **5**, 63813-95-6; **10**, 63764-91-0; **11**, 63764-92-1; **12**, 63764-93-2; **13**, 63764-94-3; **14**, 63764-95-4; **15**, 63764-96-5; **16**, 63764-97-6; 8-chloro-8-*exo*-methyl-*cis*-bicyclo[4.2.0]oct-2-ene-7-one, 63813-96-7; isobutenyllithium, 29917-94-0.

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Pyridopyrimidines. 8. A Novel Ring Opening during the Acylation of 6-Amino-1,3-dimethyluracil

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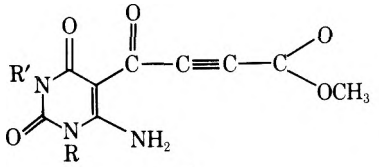
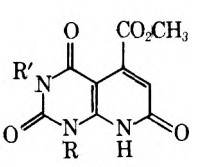
The use of dimethyl acetylenedicarboxylate (DMAD) in the synthesis of pyrido[2,3-*d*]pyrimidines has been the subject of several recent papers.[1-4] During the course of these investigations, it was found that the reaction of 1-alkyl-6-aminouracil derivatives with DMAD under aprotic conditions gave rise to 5-(3-carbomethoxy-2-propynoyl)uracils (**1**).[4] When the same reaction was carried out in a protic solvent (water, methanol), on the other hand, the pyridopyrimidine (**2**) was formed.[1-3]



1

a, R = R′ = CH_3
b, R = CH_3; R′ = H



2

In an attempt to gain additional insight into the mechanism of the formation of ketones having the general structure **1**, the reaction of 1,3-dimethyl-6-aminouracil (**3**) with DMAD was followed by ^1H NMR spectroscopy using $(CD_3)_2SO$ as solvent. Spectra were obtained at various time intervals and revealed the disappearance of **3** and the ultimate formation of **1a**. However, a number of additional peaks appeared in the spectrum such that, about 1 h after the initiation of the reaction, the spectrum was a composite of all the peaks (and only the peaks) seen in Figure 1a–c. After 6 h the spectrum (Figure 1c) corresponded to that of the propynoyl adduct **1a**.

The most striking feature of the composite spectrum was the disappearance of one *N*-methyl resonance at δ 3.27 and its replacement by a doublet at δ 2.60. Addition of a small amount of D_2O to the solution caused an immediate collapse of the δ 2.60 doublet to a singlet with the concomitant disap-

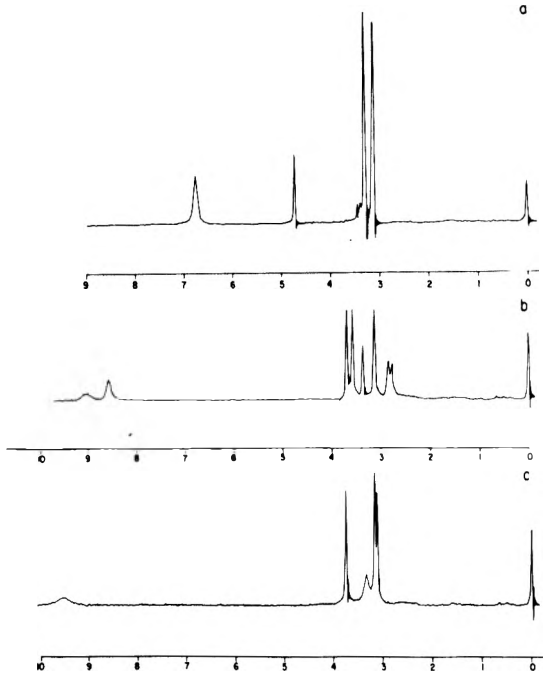


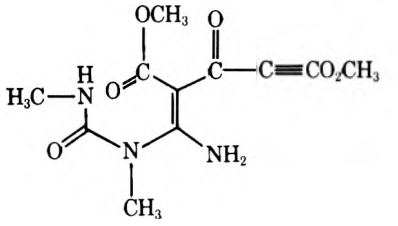
Figure 1. ^1H NMR spectra in $(CD_3)_2SO$ with DSS as internal reference (multiplet at δ 2.5 due to solvent was eliminated for the sake of clarity): (a) 6-amino-1,3-dimethyluracil; (b) reaction mixture; (c) 5-(3-carbomethoxypropynoyl)-1,3-dimethyl-6-aminouracil.

pearance of a broad doublet at δ 9.03 attributable to a single N–H proton.

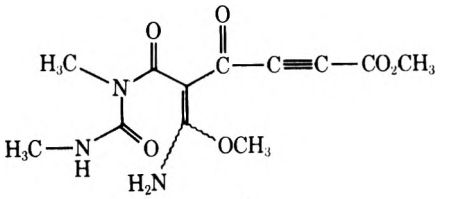
The reaction was repeated on a larger scale in $(CH_3)_2SO$. Addition of methanol to the reaction mixture after 1 h led to the precipitation of a pale yellow solid which was recovered in 57% yield. The ^1H NMR spectrum of this solid (Figure 1b) showed very clearly the presence of the δ 2.60 doublet. In addition there were seen two low-field signals (δ 9.03 and 8.55) which disappeared rapidly upon addition of D_2O and which corresponded to one and two protons, respectively. These data are consistent only with an $NHCH_3$ moiety which must have resulted from opening the pyrimidine ring. The ring-opened intermediate was unstable and was converted to the intensely orange propynoyl derivative **1a** simply by gentle warming or allowing the solution to stand at room temperature in either protic or aprotic solvents. Even at −10 °C the pure solid intermediate was converted to **1a** within a few months.

The intermediate gave an elemental analysis consistent with a simple adduct of **3** and DMAD, but electron impact or chemical ionization mass spectrometry gave only the molecular ion (*m/e* 265) of the cyclized final product **1a**. Although this result was not surprising in view of the marked instability of the intermediate, it was clearly desirable to demonstrate that the true molecular ion did contain the additional elements of methanol (*m/e* 297). A freshly prepared sample of the intermediate was subjected to field desorption mass spectrometry which did lead to the demonstration of a prominent molecular ion at *m/e* 297.

To account for these observations, two ring-opened intermediates could be proposed. Cleavage of the N3–C4 bond, a reaction well-documented in the 5,6-dihydrouracil series,[5,6] would lead to ester **4**. Cleavage of the N1–C6 bond, on the other hand, would lead to the ketene acetal-type structure **5**. In order to determine which mode of ring opening was operative, the same reaction was followed by ^1H NMR using 6-amino-1-methyluracil (**1b**). Again the *N*-methyl signal (in this case the only such signal) moved to higher field as a doublet. This observation is consistent *only* with ring opening at the N1–C6 bond.



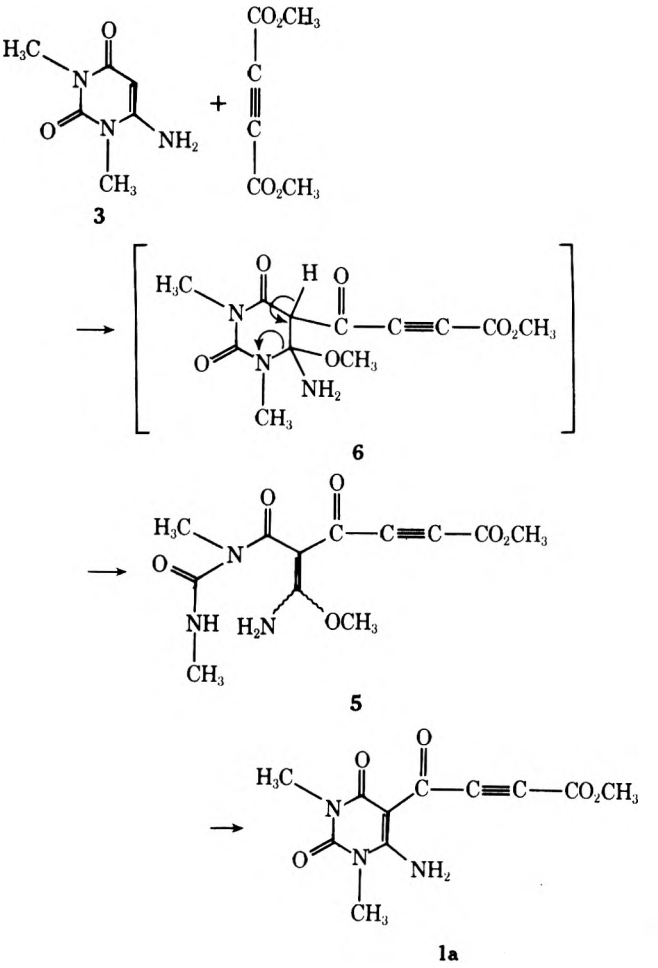
4



5

Based upon the above data, a logical mechanism for the formation of intermediate **5** is presented (Scheme I). The first step is presumed to involve addition of DMAD across the 5,6 double bond giving intermediate **6**. The subsequent elimination reaction should proceed with rupture of the bond leading to the greatest stabilization of negative charge (the least basic anion). The only anion subject to resonance stabilization is that resulting from cleavage of the 1,6 bond; such a cleavage leads to intermediate **5**. Upon recyclization, again the least basic anion is eliminated (in this case methoxide) to give **1a** as the final product. The cyclization is very similar to that recently reported by Shealy and O'Dell[7] whereby uracil derivatives were readily prepared by the cyclization of 3-methoxyacryloylureas.

Scheme I



Experimental Section

The ^1H NMR spectra were recorded on a JEOL C60H spectrometer with 2,2-dimethyl-2-silapentanesulfonic acid, sodium salt as internal reference. Mass spectra were obtained using an LKB-GC/MS Model 9000S (electron impact), a Varian 112S MS (chemical ionization), and a Varian MAT 731MS (field desorption). 1,3-Dimethyl-6-aminouracil was purchased from Het-Chem Co., Harrisonville, Mo.

***N,N'*-Dimethyl-*N*-[3-amino-3-methoxy-2-(3-carbomethoxypropynoyl)acryloyl]urea (5).** To a suspension of 1,3-dimethyl-6-aminouracil (1.55 g, 10 mmol) in $(CH_3)_2SO$ (20 mL) was added dimethyl acetylenedicarboxylate (1.35 mL, 11 mmol). The suspension was stirred at 25 °C for 1 h. Methanol (30 mL) was added. After 8 h at −5 °C, the pale yellow solid was filtered and washed with Et_2O to give 1.68 g (57%) of **5**: MS, *m/e* 265 (EI, CI), 297 (field desorption); ^1H NMR [$(CD_3)_2SO$] δ 9.03 (br d, 1 H, NH), 8.55 (br s, 2 H, NH_2), 3.68 (s, 3 H, OCH_3), 3.57 (s, 3 H, OCH_3), 3.12 (s, 3 H, NCH_3), 2.60 (d, 3 H, NCH_3, J_{H,CH_3} = 4 Hz). The signal appearing at δ ~3.4 arose from H_2O in the solvent.

Anal. Calcd for $C_{12}H_{15}N_3O_6 \cdot 0.5H_2O$: C, 47.05; H, 5.27; N, 13.71. Found: C, 47.35; H, 5.26; N, 13.54.

Acknowledgment. This study was supported by Research Grant 12823 from the National Cancer Institute, NIH. One of us (G.L.A.) wishes to express his appreciation to the American Foundation for Pharmaceutical Education for the Albert H. Diebold Memorial Fellowship, 1974–76. We are grateful to Drs. James A. McCloskey and David Smith for obtaining the mass spectral data reported herein.

Registry No.—**1a**, 32970-29-9; **3**, 6642-31-5; **5**, 63744-45-6; dimethyl acetylenedicarboxylate, 762-42-5.

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Identification of Alkaloids in Crude Extracts by Mass-Analyzed Ion Kinetic Energy Spectrometry

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Complex mixtures can be analyzed by a new method[2] based upon ion kinetic energy measurements. We show here that this procedure, which does not require chromatography and involves minimal sample pretreatment, is applicable to the identification of alkaloids in crude plant extracts.

The procedure involves the following steps. (i) The mixture is ionized by electron impact (EI) or by chemical ionization (CI). (ii) An ion of interest, usually the molecular ion or the protonated alkaloid, is selected by mass analysis. (iii) The mass-analyzed ion is excited by collision which causes it to fragment. (iv) The fragments are identified by kinetic energy analysis. Mass-analyzed ion kinetic energy (MIKE) spectra were obtained in this way for selected ions from crude extracts of the cacti *Dolichothele longimamma* (DC.) Br. and R., *Dolichothele uberiformis* (Zucc.) Br. and R., *Lophophora williamsii* (Lem.) Coult., and *Opuntia spinosior* (Eng.) Toumey. Alkaloid structures were deduced either directly from these spectra in the cases of new alkaloids or by comparison with MIKE spectra of authentic alkaloids.

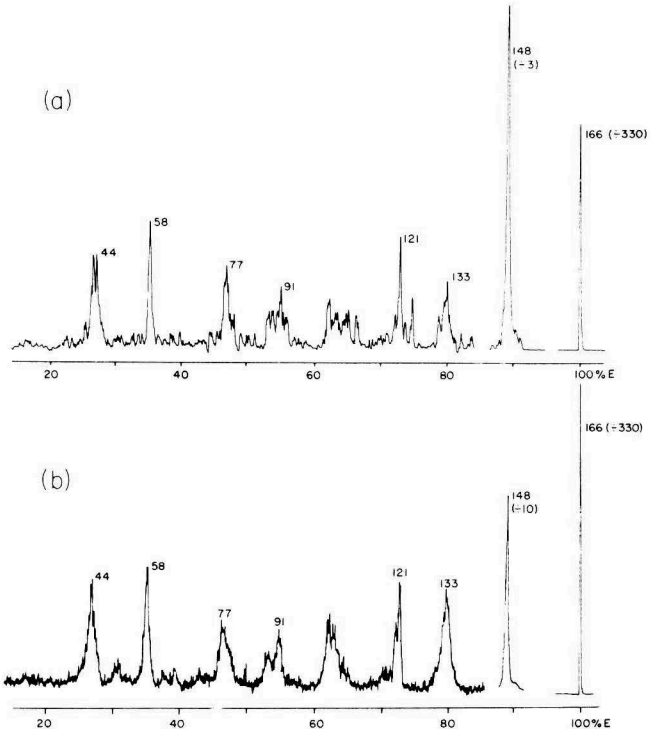


Figure 1. MIKE spectra of *m/e* 166 obtained from (a) a crude *D. longimamma* extract and (b) ubine hydrochloride. The major fragment ions are indicated on the spectra and their origins explained in Scheme I.

Experimental Section

The MIKE spectrometer has been described elsewhere.[3] Samples were introduced from a direct insertion probe at a source temperature (100–200 °C) appropriate for evaporation of the component of interest. Chemical ionization reagent gases were methane or isobutane as indicated. The ion accelerating voltage was 7 kV, the electron emission current was 0.1–0.2 mA (CI and EI), and the indicated pressure of collision gas (always introduced for these studies) was 5×10^{-5} Torr.

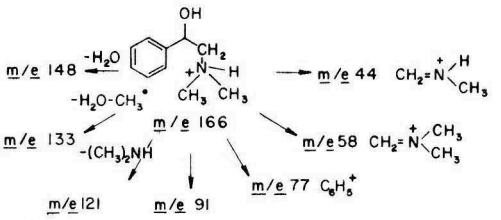
The alkaloid extract used in the EI study was the phenolic fraction obtained from *D. uberiformis* as described elsewhere.[4] The other extracts were obtained from 1 g of freeze-dried cactus from which lipids were removed by overnight Soxhlet extraction with cyclohexane. Extraction with chloroform–methanol–ammonium hydroxide (2:2:1) and evaporation yielded an alkaloid-containing mixture which was analyzed without further work-up. Only a small portion of the extract was used in the analysis.

Results and Discussion

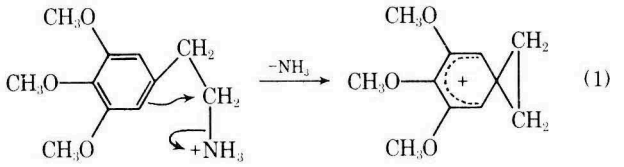
The power of the ion kinetic energy method can be illustrated by the identification of ubine (**1**) in *D. longimamma*. Studies by traditional chromatographic and spectroscopic methods[5] revealed a number of new as well as previously known alkaloids in this plant not including ubine. The CI (isobutane) mass spectrum of the plant extract shows an ion which corresponds in mass to protonated ubine (*m/e* 166). The MIKE spectrum of this ion (Figure 1a) was interpreted as requiring the ubine structure for the alkaloid. Scheme I summarizes the fragmentation pattern upon which this assignment was based. The MIKE spectrum of authentic protonated ubine (Figure 1b) confirmed the assignment. It is noteworthy that these results were obtained in a few hours using a very crude plant extract. Other constituents of *D. longimamma* studied in this way will be discussed elsewhere.

Our procedure can be used in a survey of plant materials for

Scheme I. Major Collision-Induced Fragmentations of Protonated Ubine



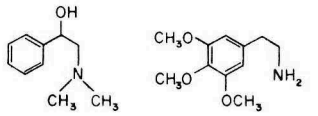
alkaloids of particular interest as well as in the characterization of new alkaloids. The occurrence of mescaline (**2**) in cactus extracts provides a case in point. The MIKE spectrum of protonated mescaline is characterized by an intense peak due to elimination of a fragment of 17 mass units. It is suggested that reaction 1 occurs as shown. The double analysis inherent



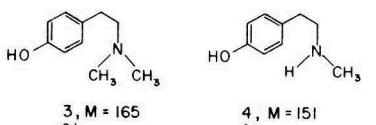
(1)

in the MIKES method, viz. analysis for the mass of the precursor ion as well as that of the fragments, makes the method highly specific. Mescaline could, therefore, be identified in *O. spinosior* simply on the basis of its molecular weight (211) and its fragmentation by loss of NH_3 from the protonated species. The MIKE spectrum of a peyote extract was studied to confirm this assignment. Further confirmation of the presence of mescaline in *O. spinosior* was obtained by comparing the MIKE spectra of the *fragment* ion due to NH_3 loss with that for the same ion in authentic mescaline hydrochloride and in peyote extracts.

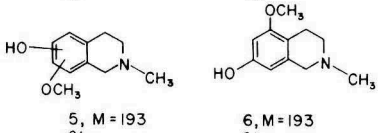
The foregoing studies were made by chemical ionization. Electron impact ionization is also useful in this type of study although the resulting mass spectra can show extensive fragmentation which is a disadvantage in recognizing molecular ions. On the other hand, MIKE spectra obtained on molecular ions compare well with electron impact mass spectra of the pure compounds and this facilitates structural assignments. Hordenine (**3**) and *N*-methyltyramine (**4**) were identified in the *D. uberiformis* extract on the basis of the MIKE spectra shown in Table I. For comparison the electron impact mass spectra of the pure compounds are also shown.



1, M = 165 2, M = 211



3, M = 165 4, M = 151



5, M = 193 6, M = 193

Electron impact also showed the presence of a new alkaloid, molecular weight 193 in *D. uberiformis*. The MIKE spectrum of this alkaloid showed fragments formed by loss of 1, 15, 17, and 43 mass units. This was interpreted[6] as corresponding to the structure **5** in which the positions of the aryl substituents were not established. In independent work[4] the new alkaloid uberine (**6**) was isolated from this plant and its structure was established by conventional methods.

Table I. Fragment Ions in Mass and MIKE Spectra

Hordenine (3)		*N*-Methyltyramine (4)	
Mass spectrum	MIKES	Mass spectrum	MIKES
121 (0.05)	(0.05)	149 (0.02)	
120 (0.04)	(0.01)	121 (0.03)	(0.01)
107 (0.09)	(0.05)	120 (0.05)	(0.01)
91 (0.08)	(0.01)	108 (0.06)	(0.13)
77 (0.15)	(0.02)	107 (0.11)	(0.07)
58 (1.00)	(1.00)	91 (0.03)	
		78 (0.02)	(0.01)
		77 (0.08)	(0.02)
		58 (0.42)	(0.01)
		44 (1.00)	(1.00)

In conclusion, the ion kinetic energy method of mixture analysis has been shown to be applicable to the identification and structural elucidation of alkaloids in crude plant extracts. The method represents an alternative to GC/MS and has comparable sensitivity and specificity. It may be particularly appropriate in studies of alkaloids and other involatile compounds for which gas chromatography is difficult.

Acknowledgment. This work was supported by the National Science Foundation and the National Institute of General Medical Sciences (GM 21,211). T.L.K. acknowledges partial support from the Ball State Special Leave Program.

Registry No.—**1,** 34469-09-5; **2,** 54-04-6; **3,** 539-15-1; **4,** 370-98-9; **5,** 63715-57-1; **6,** 63596-58-7.

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Synthetic Studies on the Side Chains of Cephalotaxus Esters

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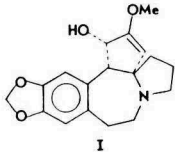
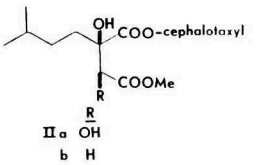
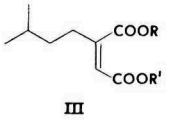
The naturally occurring antileukemic esters of cephalotaxine (I), e.g., isoharringtonine (IIa) and deoxyharringtonine (IIb), have proven to be formidable synthetic objectives due to steric problems in attaching the side chain to cephalotaxine;[1] in fact, the only reported success involved esterification with an α-keto acid (good yield) followed by addition to the keto group (very low yield) to give IIb.[2] It was also possible to esterify cephalotaxine (I) with two other acids with sp^2 hybridized α carbons: *p*-bromobenzoic acid[3] (80% yield) and half-ester IVa[4] (57% yield). We have independently been working on approaches to half-esters IIIa and Va in the hope that they might be sufficiently sterically unhindered to combine with cephalotaxine (I) to form esters which could be further transformed into IIa and IIb and wish to report more efficient routes to compounds in the III, IV, and V series than



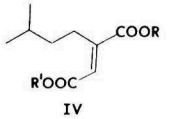
I



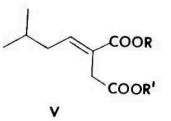
IIa R = OH
b R = H



III

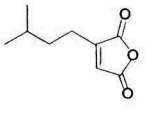


IV

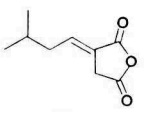


V

	R	R'
a	H	Me
b	Me	Me
c	H	H
d	Me	H



VI



VII

those used earlier.[4,5] These new routes permit entry into each series in one step rather than several and in better yield.

Diisoamylcopper lithium added in the expected 1,4 manner[6-8] to dimethyl acetylenedicarboxylate, producing a mixture of IIIb and IVb. As expected,[6-8] the syn addition product IIIb predominates at −78 °C (89% in ether, 92% in THF), and on warming to 5 °C before quenching, the major product (60%) becomes IVb. Although diesters IIIb and IVb were readily separated by chromatography, the crude reaction mixture was suitable for the preparation of IIIa due to convergence at a later step.

Saponification of these esters was accompanied by shift of the double bond position to give Vc in excellent yield; any of the esters IIIb, IVb, and Vb with sodium methoxide gave an equilibrium mixture consisting almost exclusively of Vb. On acidic hydrolysis, however, IIIb and IVb gave the corresponding diacids IIIc and IVc smoothly without double bond shift. While IVc was readily purified by crystallization, IIIc was a viscous oil.

IIIc and Vc quantitatively produced the corresponding anhydrides, VI and VII, respectively, when refluxed in acetic anhydride. IVc, however, required heating with P_2O_5 at 200 °C to give VI.[5] With methanol at room temperature, anhydride VII reacted predominantly at the less hindered carbonyl,[10] giving desired half-ester IIIa (79%), along with lesser amounts of IIId (13%) and Va (8%).

A second good route to half-ester Va started with the Stobbe condensation of dimethyl succinate with 3-methylbutanal to the half-ester Vd (82%), which was hydrolyzed to diacid Vc (79%) and then converted to Va as above. The double bond could be partially shifted to the position between the carbonyl groups by equilibrating anhydride VII with anhydride VI using tri-*n*-butylamine at 125 °C; the equilibrium mixture contained only 35% of VI, however.

Our initial efforts to esterify cephalotaxine with half-esters IIIa and Va have been unsuccessful; apparently IIIa is sufficiently more sterically hindered than its stereoisomer IVa[4] to make esterification difficult.[11]

Experimental Section

Nuclear magnetic resonance (NMR) spectra of all compounds were measured on a Varian T-60 spectrometer. Melting points were obtained with a Thomas Hoover capillary melting point apparatus and were corrected. Ethyl ether was distilled from Na before use, THF from $LiAlH_4$, and methanol and *tert*-butyl alcohol from Mg. All apparatus was flame dried.

Methyl (*Z*)- and (*E*)-3-Carboxy-6-methyl-2-heptenoates (IIIb and IVb). To 13.2 g (1.90 g-atom) of lithium wire, flattened and cut into ~2-cm pieces, in 275 mL of ether under argon was added about 35 drops of a solution of 60.9 g (0.403 mol) of isoamyl bromide in 50 mL of ether. The reaction mixture was then cooled with a dry ice–acetone bath, the remainder of the isoamyl bromide was added over 45 min while maintaining a temperature between −35 and −40 °C, and then the mixture was allowed to warm to −10 °C while stirring for an additional 90 min. The reaction mixture was filtered under argon pressure through glass wool and the product was transferred into a precalibrated bottle, yielding 270 mL of 1.36 N isoamyllithium (0.367 mol), a 91% yield as determined by double titration.[12]

To a slurry of 9.52 g (0.050 mol) of cuprous iodide and 40 mL of ether under argon was added 104 mL of 0.97 N isoamyllithium (0.100 mol) over 15 min at −78 °C. Then 7.10 g (0.050 mol) of dimethyl acetylenedicarboxylate in 40 mL of ether was added to the cold stirring mixture over 15 min. After stirring for 3 h at −78 °C the reaction was quenched while still cold with methanol and neutralized with 3 N HCl. The organics were extracted with ether (centrifuging necessary), the ether layers were combined, dried over magnesium sulfate, and filtered, the ether was evaporated, and low-boiling organics were removed under reduced pressure. The crude product (10.5 g) by NMR contained 80% IIIb (NMR (CCl_4) 0.92 (6 H, d), 1.0–1.9 (3 H, m), 2.33 (2 H, t), 3.68 (3 H, s, MeOCOCR=), 3.75 (3 H, s, MeOCOCH=), 5.72 (1 H, t, J = 1.5 Hz)) and 10% IVb (NMR (CCl_4) 0.85 (6 H, d), 1.0–1.8 (3 H, m), 2.67 (2 H, ~t), 3.60 (3 H, s), 3.64 (3 H, s), 6.50 (1 H, s)). Reported[5] vinyl hydrogen shifts for IIIb and IVb prepared differently are δ 5.85 and 6.80, respectively. These isomers could be separated with 80% recovery by GC (0.25 in. × 7 ft Carbowax 20M on Chromosorb P at 200 °C) or by column chromatography (Silica, 4:3 cyclohexane–ethyl acetate); IVb moved faster in both cases.

(*Z*)- and (*E*)-3-Carboxy-6-methyl-2-heptenoic Acids (IIIc and IVc). To a 50-mL flask containing 30 mL of 3 N HCl was added 2.0 g of crude product from the dialkyl cuprate reaction (80% IIIb, 10% IVb). After refluxing for 8 h, the reaction mixture was cooled to 25 °C and filtered, yielding 0.121 g of diacid IVc, mp 204–205 °C, from $HCCl_3/CCl_4$ (lit.[5] mp 203–204 °C): NMR (Me_2CO-d_6) 0.93 (6 H, d), 1.0–1.9 (3 H, m), 2.78 (2 H, ~t), 6.71 (1 H, s), 10.6 (2 H, s). Following thorough ether extraction of the filtrate, the product was extracted with saturated aqueous sodium bicarbonate (unhydrolyzed ester remaining in the ether layer can be recovered and recycled). Acidification of the bicarbonate extracts with concentrated HCl was followed by extraction with ether. The ether layers were combined, dried over magnesium sulfate, and filtered, and the ether was evaporated, yielding 1.29 g of viscous oil that contained: 83% diacid IIIc, NMR (CCl_4) 0.92 (6 H, d), 1.0–1.9 (3 H, m), 2.40 (2 H, t), 5.80 (1 H, t, J = 1.2 Hz), 10.75 (2 H, s); 4% diacid IVc (vinyl H peak at δ 6.76); and 13% anhydride VI (vinyl H peak at δ 6.53 t, J = 1.7 Hz).

(*Z*)-3-Carboxy-6-methyl-2-heptenoic Anhydride (VI). Diacid IIIc was refluxed overnight with excess acetic anhydride. Distillation of excess acetic anhydride and acetic acid gave an essentially quantitative yield of anhydride VI: NMR (CCl_4) 0.95 (6 H, d), 1.2–1.9 (3 H, m), 2.50 (2 H, td, J = 7 Hz, 1.7 Hz), 6.53 (1 H, t, J = 1.7 Hz). Alternatively, diacid IVc was refluxed with a large excess of P_2O_5 in benzene for 2 h in a micro-Hickmann apparatus.[5] Evaporation of the benzene under a stream of argon followed by heating to 200 °C at 0.75 mm yielded virtually pure anhydride VI as a distillate.

Methyl (*Z*)-3-Carboxy-6-methyl-2-heptenoate (IIIa). When anhydride VI in CCl_4 was mixed with a sixfold excess of anhydrous methanol in an NMR tube complete reaction was indicated in 24 h to yield: 79% IIIa, NMR (CCl_4) 0.91 (6 H, d), 1.0–1.9 (3 H, m), 2.35 (2 H, t), 3.74 (3 H, s), 5.76 (1 H, t, J = 1.4 Hz), 11.60 (1 H, s); 13% IIId, NMR like IIIa except MeO at δ 3.67 and vinyl H at δ 5.79; and 8% Va (MeO at δ 3.65, CH_2 at δ 3.29, vinyl H at δ 7.07 t, J = 7.5 Hz). Similar results were obtained when anhydride VI was refluxed with a large excess of methanol for 3 h (77% IIIa, 19% IIId, and 4% Va).

3-Carbomethoxy-6-methyl-3-heptenoic Acid (Vd). To a refluxing solution of 4.30 g (0.110 g-atom) of potassium in 60 mL of anhydrous *tert*-butyl alcohol under argon was added over 15 min a mixture of 8.6 g (0.100 mol) of 3-methylbutanal and 19.5 g (0.133 mol) of dimethyl succinate. The reaction mixture was refluxed for an additional 1.5 h, then most of the solvent was removed under reduced pressure, the residue was made slightly acidic with 3 N HCl, the remaining solvent was removed, and the organics were ether extracted. The product was extracted into saturated aqueous sodium bicarbonate, the bicarbonate extracts were combined and made strongly acid with concentrated HCl, and the resulting mixture was extracted

with ether. Evaporation left 16.3 g (82%) of residual yellow oil which was very largely Vd: NMR (neat) 0.95 (6 H, d), ~1.8 (1 H, m), 2.07 (2 H, t), 3.38 (2 H, s), 3.68 (3 H, s), 6.97 (1 H, t, J = 7.5 Hz), 10.15 (1 H, s). This product was used without further purification.

3-Carboxy-6-methyl-3-heptenoic Acid (Vc). When 2.00 g of half-ester Vd from the previous reaction was refluxed overnight in 20 mL of 3 N HCl, white crystals formed. Recrystallization from chloroform yielded 1.47 g (79%) of diacid Vc: mp 164–165 °C; NMR (Me_2CO-d_6) 0.95 (6 H, d), ~1.8 (1 H, m), 2.17 (2 H, t), 3.36 (2 H, s), 7.00 (1 H, t, J = 7.5 Hz), 10.60 (2 H, s).

3-Carboxy-6-methyl-3-heptenoic Anhydride (VII). Diacid Vc was refluxed overnight with excess acetic anhydride. Distillation under reduced pressure to remove excess acetic anhydride and acetic acid gave an essentially quantitative yield of anhydride VII: NMR (neat) 0.97 (6 H, d), ~1.8 (1 H, m), 2.20 (2 H, ~t), 3.53 (2 H, ~s), 6.92 (tt, J = 7.5 and 2.6 Hz).

Methyl 3-Carboxy-6-methyl-3-heptenoate (Va). When a neat sample of anhydride VII was mixed with a twofold excess of anhydrous methanol in an NMR tube complete reaction was indicated in 24 h to yield half-ester Va which was by NMR 94% pure. Preparative TLC (silica: 55:45:2 ether–hexane–acetic acid) gave pure Va, NMR ($DCCl_3$) virtually identical to that reported.[4]

Equilibrium between Anhydrides VI and VII. Neat 0.5-g samples of VI and VII in separate NMR tubes with 1 drop of tri-*n*-butylamine were heated in increments of 25 °C from 25 to 150 °C for 10 min with ^{1}H NMR spectra being taken after each heating. By integration of the vinyl hydrogen signals at δ 6.5 (VI) and 6.8 (VII), the relative amounts of the two anhydrides were estimated. At 125 °C equilibrium was reached with 65% VII–35% VI in both tubes; at 150 °C, the equilibrium mixture contained 70% VII.

Methyl 3-Carbomethoxy-6-methyl-3-heptenoate (Vb). A. From Half-Ester Vd. After refluxing 2.00 g of Vd with 20 mL of methanol and 1 mL of acetyl chloride overnight, the neutral fraction from an extractive workup was distilled to give 1.77 g (83%) of diester Vb, bp 143 °C (22 mm): NMR (neat) 0.92 (6 H, d), ~1.8 (1 H, m), 2.12 (2 H, t), 3.33 (2 H, s), 3.57 (3 H, s), 3.65 (3 H, s), 6.93 (1 H, t, J = 7.5 Hz).

B. By Isomerization of IIIb and IVb. Refluxing 0.5 g of a mixture of 87% IIIb and 13% IVb with 10 mL of 1 M sodium methoxide in methanol overnight followed by an extractive workup and removal of solvent by distillation gave a quantitative yield of residual oil which had a ^{1}H NMR spectrum virtually identical with that of Vb prepared as described above.

Acknowledgment. We thank the National Cancer Institute (CA-10944) for financial support.

Registry No.—IIIa, 63731-47-5; IIIb, 51804-78-5; IIIc, 16110-97-7; IIId, 63731-48-6; IVb, 51804-76-3; IVc, 51804-75-2; Va, 63731-49-7; Vb, 63731-50-0; Vc, 63731-51-1; Vd, 63731-52-2; VI, 51804-77-4; VII, 63731-53-3; isoamyl bromide, 107-82-4; isoamyl lithium, 7488-31-5; dimethyl acetylenedicarboxylate, 762-42-5; 3-methylbutanal, 590-86-3; dimethyl succinate, 106-65-0.

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(10) Cf. R. B. Bates, E. J. Eisenbraun, and S. M. McElvain, *J. Am. Chem. Soc.*, **80,** 3413 (1958), and the references in ref 6 for previous reactions of succinic anhydrides with methanol at the less hindered carbonyl.
(11) We repeated the osmium tetroxide *syn*-hydroxylations of diesters IIIb and IVb,[5] obtaining the same products in higher yield (92% with IIIb and 72% with IVb after recrystallization, compared to 40 and 65%[5]) with pyridine as solvent.
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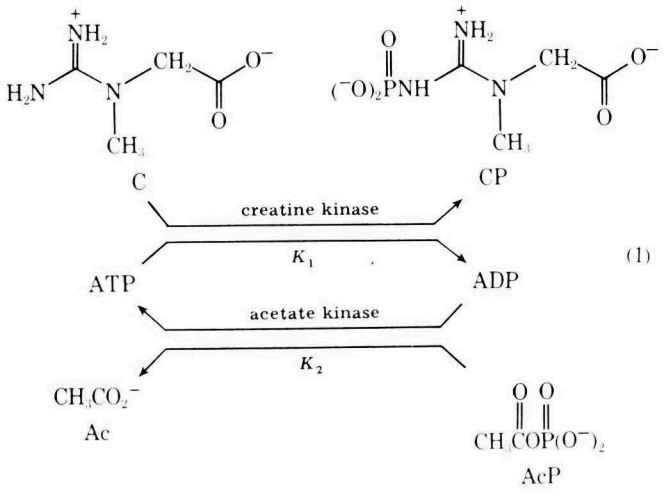
Large-Scale ATP-Requiring Enzymatic Phosphorylation of Creatine Can be Driven by Enzymatic ATP Regeneration[1]

Summary: Phosphorylation of creatine to creatine phosphate has been accomplished on a synthetically useful scale (0.16 mol) using creatine kinase (E.C.2.7.3.2), a catalytic quantity of ATP, and an ATP regeneration system based on acetate kinase (E.C.2.7.2.1) and acetyl phosphate.

Sir: We have previously used the hexokinase-catalyzed conversion of glucose to glucose 6-phosphate to illustrate the practicality of ATP regeneration in enzyme-catalyzed organic synthesis.[2] The equilibrium constant for phosphate transfer from ATP to glucose is large ($K \simeq 1.5 \times 10^2$ at pH 6.0),[3] and this reaction goes to completion. ATP is, however, only a moderately strong biological phosphorylating agent,[4,5] and many ATP-requiring enzymatic transformations of potential interest in organic synthesis have unfavorable equilibrium constants. Acetyl phosphate, the ultimate phosphorylating reagent in our ATP regeneration scheme, has a significantly greater thermodynamic potential for phosphorylation than ATP, and an important advantage of an ATP regeneration scheme based on acetyl phosphate is its ability to drive to useful conversion a reaction whose equilibrium constant is unfavorable based on the phosphate-donor potential of ATP alone.[4,6] Here we provide an example of a reaction of this type by the phosphorylation of creatine (C) to creatine phosphate (CP) on a practical scale (eq 1). The maximum value reported



(1)

for the equilibrium constant for phosphorylation of C to CP by ATP is $K_1 = 2.5 \times 10^{-1}$ (pH 9);[7] that for phosphorylation of ADP to ATP by AcP at this pH is $K_2 \simeq 1.5 \times 10^2$.[8] The equilibrium constant (eq 2) for the coupled equilibrium reactions (eq 1) was maximized empirically under conditions appropriate for large-scale synthesis by varying the pH, ionic strength, and composition of the solvent: $K = 140$ (pH 9, 10% v/v aqueous ethylene glycol solution).[9]

$$K = \frac{(CP)(Ac)}{(C)(AcP)} = \frac{(CP)(ADP)}{(C)(ATP)}\frac{(ATP)(Ac)}{(ADP)(AcP)} = K_1K_2 \quad (2)$$

Synthesis of CP was carried out in a 5-L round-bottomed flask equipped with a pH electrode, a magnetic stirring bar, and 6 g of glass beads to facilitate stirring the heterogeneous reaction mixture. The flask was charged with 3000 mL of 10% aqueous ethylene glycol solution (pH 9, no buffer)[9] containing creatine hydrate (100 g, 667 mmol, only partially soluble), ATP (5.0 mmol), $MgSO_4 \cdot 7H_2O$ (20 mmol), and dithiothreitol (5.0 mmol).[10] Polyacrylamide gel particles containing immobilized acetate kinase (AcK, E.C.2.7.2.1, 980 U, 4 mL of gel) and creatine kinase (CK, E.C.2.7.3.2, 312 U, 160 mL of gel) were suspended in the mixture.[11] Diammonium acetyl phosphate in 10% aqueous ethylene glycol solution (1 M, pH 9.0) was added continuously over 36 h at 25 mL h^{-1} to the stirred solution.[12] The solution was maintained between pH 8.8 and 9.2 by the addition of 5.0 N NaOH solution (10% aqueous ethylene glycol) using an automatic pH controller. The reaction was conducted at ambient temperature, and the reaction mixture and reagent solutions were deoxygenated before use and maintained under argon. After 36 h of operation (675 mmol of AcP added), enzymatic assay[13] indicated that the reaction was close to equilibrium. The concentration of CP was 56 mM. This quantity (234 mmol in 4200 mL) corresponds to a 63% yield based on dissolved C (56 g) and a 35% yield based on AcP.

The polyacrylamide gel particles and a white precipitate composed primarily of magnesium phosphate were allowed to settle, and the solution was decanted and centrifuged. Inorganic phosphate (666 mmol, estimated by the difference between the AcP and phosphate-containing impurities added and the CP produced) was partly precipitated by the addition of a stoichiometric amount of $MgSO_4 \cdot 7H_2O$ (666 mmol) at pH 9.2–9.3 and removed by centrifugation. The supernatant was adjusted to pH 7.6 with 5.0 N HCl solution and was treated with $BaBr_2$ (370 mL of 1.8 M solution) to precipitate the remaining inorganic phosphate. The mixture was allowed to stand for 20 min, the precipitate was separated by centrifugation, and the supernatant was treated with 234 mmol of $BaBr_2$ (130 mL of 1.8 M solution) and four volumes of absolute ethanol precooled to 0 °C. The mixture was stirred for 20 min and allowed to stand for 5 h at 4 °C. The supernatant was discarded and the white precipitate was washed twice with 800-mL portions of absolute ethanol (0 °C) and with 1000 mL of anhydrous ether (0 °C). The precipitate (74.4 g) was dried over Drierite for 12 h under vacuum: it contained 79% BaCP (159 mmol) by enzymatic assay.[13] This quantity corresponds to a 24% yield based on AcP. The activities of creatine kinase and acetate kinase were recovered in the gel in 79 and 71% yield, respectively.

The conversion of C to CP using ATP provides a severe test for enzymatic synthesis: it is endothermic; neither the product (CP) nor AcP has high hydrolytic stability;[14] the enzymatic reaction is inhibited by CP at low concentrations;[10] the specific activity of CK is only moderate. Nonetheless, these results establish that by careful adjustment of reaction conditions it is possible to use the high phosphate donor potential of AcP to drive the coupled enzymatic reactions (eq 1) to synthetically useful conversions. This coupled pair of reactions defines the least thermodynamically favorable scheme that can be used in practical synthesis with the AcP-based ATP regeneration sequence: if the net equilibrium constant for the CP synthesis and ATP regeneration reactions were smaller by a factor of 10, problems with recovery of low concentrations of products from large volumes of phosphate-containing solution would begin to be troublesome.

References and Notes

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(8) R. S. Langer, C. R. Gardner, B. K. Hamilton, and C. K. Colton, *AIChE J.*, **23,** 1 (1977) and references cited therein.
(9) No correction was made for the influence of ethylene glycol on the measured pH: cf, P. Maurel, G. Hui Bon Hoa, and P. Douzou, *J. Biol. Chem.*, **250,** 1376 (1975).
(10) The limiting solubility of C·H_2O in water is ~13 g L^{-1} = 110 mM: R. M. C. Dawson et al., Ed., "Data for Biochemical Research", Oxford University Press, London 1969, p 16. The presence of an excess of suspended creatine in the mixture assured that the solution was saturated, and had no apparent ill effects on the reaction. The Michaelis constants for CK are (mM) = 0.4 (MgATP), 0.14 (MgADP), 110 (C), and 3.3 (CP).[7]
(11) Enzymes, obtained from Sigma and used without purification, had specific activities (μmol min^{-1} mg^{-1}): AcK 300 U (following treatment with DTT); CK 2.5 U (defined for C → CP, pH 9.0, 25 °C). Immobilization yields were 48% for CK, and 55% for AcK. Enzyme immobilization was carried out as described by A. Pollak, R. L. Baughn, O. Adalsteinsson, and G. M. Whitesides, *J. Am. Chem. Soc.*, in press.
(12) G. M. Whitesides, M. Siegel, and P. Garrett, *J. Org. Chem.*, **40,** 2516 (1975). The AcP used was 70–80% pure, with NH_4Ac, $(NH_4)_3PO_4$, and CH_3CONH_2 as the principal impurities. The solution was maintained at 0 °C before addition to minimize hydrolysis.
(13) H. U. Bergmeyer, Ed., "Methods of Enzymatic Analysis", 2nd ed, Academic Press, New York, N.Y., 1974, p 1777.
(14) Qualitative examination indicated hydrolysis rates of ~4% h^{-1} for AcP and 0.17% h^{-1} for CP under the conditions used for the enzymatic synthesis.

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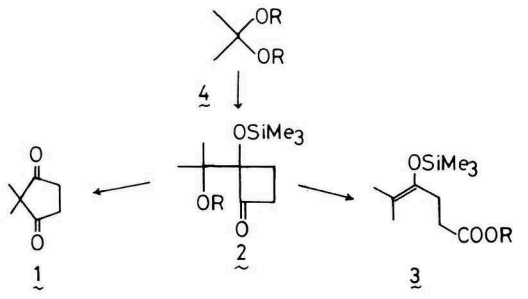
A Novel Ring-Opening Reaction. An Improved Method for Reductive Succinoylation

Summary: In the presence of stannic chloride, 1,2-bis(trimethylsiloxy)-1-cyclobutene and a ketal undergo two successive reactions, aldol and a new ring cleavage reaction, to give an enol silyl ether of γ-keto ester: the overall reaction represents a new, single-pot reductive succinoylation method.

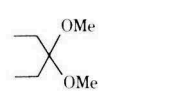
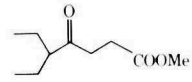
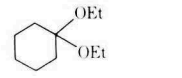
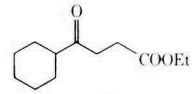
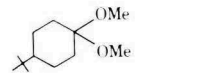
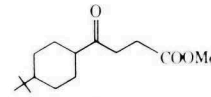
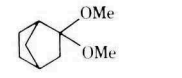
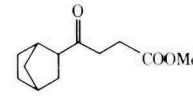
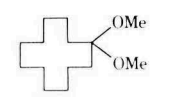
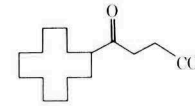
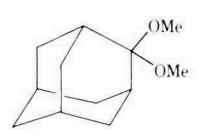
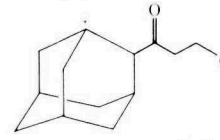
Sir: We recently reported a synthetic method for the construction of five-membered ring **1** onto carbonyl groupings: the reaction consists of treating pinacol **2** with protic acid to



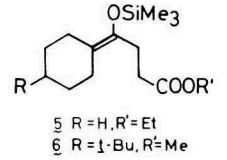
induce ring enlargement.[1] We have now found that certain Lewis acids bring about a novel and quantitative cleavage of the cyclobutanone ring of **2** to form **3.** The primary purpose of this communication is to show the synthetic utility of this reaction, which constitutes a new approach to reductive succinoylation of a ketone function.[1]

1,2-Bis(trimethylsiloxy)-1-cyclobutene (**4**) undergoes aldol-type addition with ketals under the influence of BF_3·Et_2O to afford **2** in excellent yields,[1] yet in the presence of some Lewis acids ($AlCl_3$, $TiCl_4$, $SnCl_4$, $SbCl_5$) **2** is reactive enough to transform into **3.** Subsequently, $SnCl_4$ proved especially effectual, realizing both the initial aldol reaction of **4** and the ring cleavage of **2** in a single step. For instance, 50 mol % of $SnCl_4$ effected the reaction with cyclohexanone diethyl acetal, affording pure **5** in 86% yield after distillation.

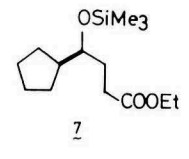
Table I. Reductive Succinoylation Method[a]

Ketal	Product	% yield[b]
		87
		93
	8	
		92
		90[c]
		91
		68[d]

[a] Reactions (1.5–30 mmol) were carried out with a reactant ratio: ketal/4/$SnCl_4$ = 1:1:0.3–1. Reaction conditions are essentially the same as those of the typical example. [b] Yield of the pure isolated product. [c] 1.24 equiv of **4** was used. [d] An appreciable amount of adamantanone was recovered.



5 R = H, R' = Et
6 R = t-Bu, R' = Me



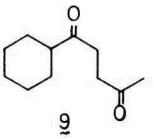
7

It is essential for the isolation of pure enol silyl ether to treat the reaction mixture with triethylamine followed by hexane (for dilution) before aqueous workup. Preparation of **6** and **7** was similarly accomplished in 84 and 80% yield, respectively.[2] The experimental procedure for **5** is illustrative. To a solution of $SnCl_4$ (0.3 mL, ~3 mmol) in 3 mL of methylene chloride at −78 °C was added during 10 s a mixture of cyclohexanone diethyl acetal (864 mg, 5.02 mmol) and **4** (1.163 g, 5.06 mmol) in 2 mL of methylene chloride. After 5 min, the pale yellow solution was warmed to −40 °C and stirred for an additional 10 min. Triethylamine (2.5 mL) and then 20 mL of hexane were added. The organic layer was separated from tarry material and washed successively with 1 N HCl, saturated NaCl, saturated $NaHCO_3$, and finally with saturated NaCl. The crude product (1.256 g) was distilled to give 1.215 g of silyl ether **5** (86%).[3]

Bifunctional compound **3** is a useful synthetic intermediate. First, the enol silyl ether moiety can react with various electrophiles. Hydrolysis is achieved simply by quenching the reaction mixture with water. Distillation usually gives an *analytically pure* product. Thus, the present reaction pro-

vides a simple, high-yield procedure for reductive succinoylation of the ketone functionality, which has been performed in lower yield through multiple steps.[1] In addition, the reaction conditions are definitely milder than those required in the former procedure. Results are summarized in Table I.[4]

The potential of γ-keto ester for further transformation is notable: 1,4-diketone **9** was prepared in 67% overall yield



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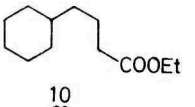
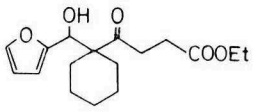


10

(thiacetalization, OH^-, MeLi, and $CuCl_2/CuO$), and ester **10** was obtained by hydrogenolysis of the ketone function (thioacetalization and W-2 Raney nickel) in 74% yield starting from keto ester **8**.

Carbon electrophiles also react with **3**. Of two possible approaches, one involves specific activation of enol silyl ether to form an enolate species without affecting the neighboring ester group. Quaternary ammonium fluoride allowed such reaction to occur.[5] Treatment of silyl ether **5** and furfural (1 equiv) with tetrabutylammonium fluoride[6] (30 mol %) at low temperature gave pure aldol **11** in 69% yield after chromato-



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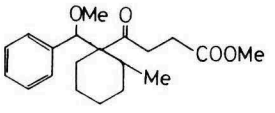
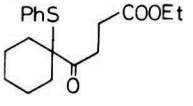


12

graphic purification. We were unable to detect any regioisomer or lactone which might be formed by intramolecular O-acylation reaction of the enolate species.

Another methodology is to trap the enol silyl ether by a Lewis acid activated carbonyl carbon.[7] On such occasions, further reaction of **3** may be best carried out in situ. Thus, the coupling of three components, 2-methylcyclohexanone, succinate moiety, and benzaldehyde acetal was quickly achieved without isolating any intermediates. The isolated yield of **12** was 70%. Two procedures descrbed here represent new entries to the conversion of C–O bonds of the carbonyl group to two C–C bonds, namely, geminal alkylation.[8]

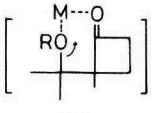
Regiospecific introduction of a heteroatom to **3** is also possible.[9] Addition of phenylsulfenyl chloride[10] to **5** prepared in situ gave **13** in 78% yield (from acetal).



13

Comparison of **2** and **3** reveals that the ketone group of the ring cleavage product is "masked" in **2**, and thereby selective functionalization with respect to the ester moiety of **3** at the stage of **2** is envisioned. Actually, such a possibility has already been demonstrated.[1] In light of these studies, the present method proved versatile for preparing substituted γ-keto esters, as well as synthetic transformations centered on the parent ketone group.

On the basis of a crossover experiment,[11] we suggest here that a complex **14**, instead of hemiacetal **15** or diketone **1**, di-



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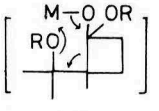
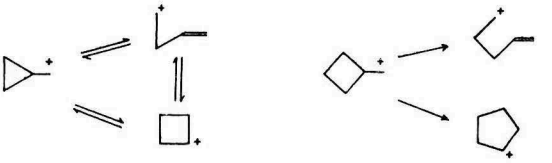


15

rectly breaks down to silyl ether **3**. The completely different effect of proton[1] and Lewis acid on cyclobutanone **2** is remarkable, and probably indicates that cyclobutanone **2** behaves as a bidentate ligand of the Lewis acid as in **14**.

Cyclopropylcarbinyl cation is known to undergo both a ring enlargement and a ring cleavage reaction.[12] Nonetheless, only a ring enlargement reaction has been recorded in the reactions



of cyclobutylcarbinyl cation.[12] It is interesting to note that the present reaction represents, at least in a formal sense, a ring-opening reaction of cyclobutylcarbinyl cation. We are presently investigating the generality of the ring-cleavage reaction.

References and Notes

(1) E. Nakamura and I. Kuwajima, *J. Am. Chem. Soc.*, **99**, 961 (1977).
(2) Yields are based on spectroscopically pure products. Enol silyl ethers were characterized by IR, NMR, and mass spectra, and hydrolyzed to the corresponding keto esters, which showed correct elemental compositions. Other products in the text were characterized by IR and NMR as well as microanalysis or high-resolution mass spectroscopy.
(3) Bp 110 °C (bath temp) (0.04 mm); IR (neat) 1745 (s), 1677 (m); NMR (CCl_4) 0.12 (s), 1.26 (t, J = 7 Hz), 1.3–2.6 (m), 2.36 (s), 4.10 ppm (q, J = 7 Hz). This compound is sensitive to moisture and should be stored in a sealed ampule.
(4) Reaction rates differ greatly among substrates. The adduct of **4** and acetone dimethyl acetal rearranges slowly even at 0 °C (1 equiv of $SnCl_4$), whereas cyclohexanone acetal forms the expected rearranged product rapidly at −40 °C.
(5) I. Kuwajima and E. Nakamura, *J. Am. Chem. Soc.*, **97**, 3257 (1975); R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura, and M. Shimizu, *ibid.*, **99**, 1265 (1977).
(6) Commerical TBAF hydrate was dried at ~20 °C (0.5 mm).[5] We thank Fluka AG for the gift of this reagent.
(7) T. Mukaiyama and M. Hayashi, *Chem. Lett.*, 15 (1974); T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, **96**, 7503 (1974).
(8) See ref 5 of ref 1.
(9) Review: J. K. Rasmussen, *Synthesis*, 91 (1977).
(10) S. Murai, Y. Kuroki, K. Hasegawa, and S. Tsutsumi, *J. Chem. Soc., Chem. Commun.*, 946 (1972).
(11) A mixture of cyclohexanone diethyl acetal and 4-*tert*-butylcyclohexanone dimethyl acetal was treated with 2 equiv of **4** and a catalytic amount of $SnCl_4$, and the analysis of the reaction mixture revealed that little crossover occurred in the reaction. The conclusion was made on the basis of the comparison of the mass spectrum of the reaction mixture with those of the authentic samples and their mixture. The fact that trimethylchlorosilane which might trap free alkoxide anion did not prevent the rearrangement also supports intramolecular alkoxyl migration.
(12) H. G. Richey, Jr., *Carbonium Ions*, **3**, 1201–1294 (1972).

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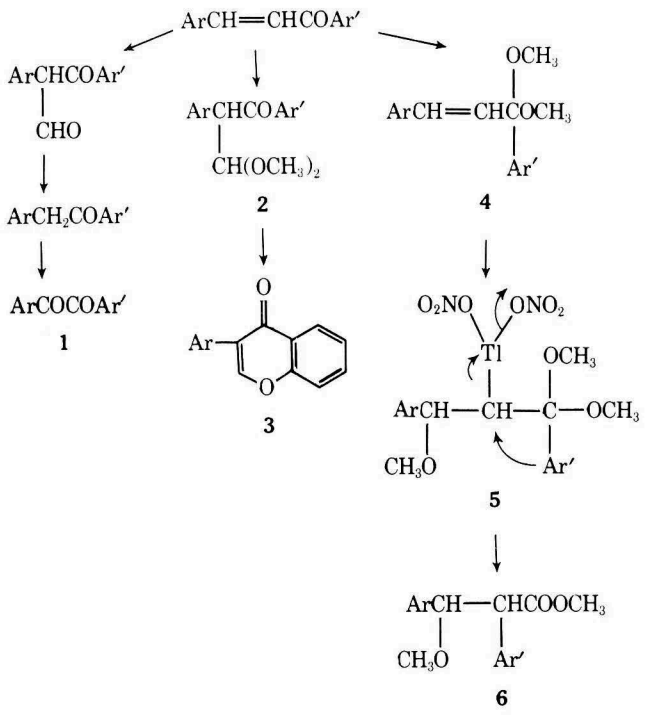
Thallium in Organic Synthesis. 49. Oxidative Rearrangement of Chalcone Dimethyl Ketals to Methyl 2,3-Diaryl-3-methoxypropanoates with Thallium(III) Trinitrate in Trimethyl Orthoformate[1]

Summary: Treatment of chalcones (ArCH=CHCOAr′) with thallium(III) trinitrate (TTN) in acidic methanol gives 3,3-dimethoxy-1,2-diarylpropan-1-ones (**2**) by rearrangement of the Ar group. However, prior conversion of chalcones to their dimethyl ketals (which can be carried out in situ in trimethyl orthoformate as solvent), followed by reaction with TTN, yields methyl 2,3-diaryl-3-methoxypropanoates (**6**) by rearrangement of the Ar′ group.

Sir: During the past decade, thallium(III) trinitrate (TTN)

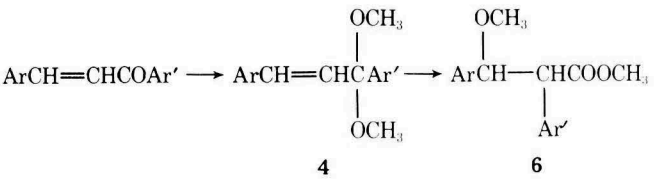
Scheme I



has been shown to be a versatile reagent in organic synthesis and has been used to effect many useful and unique transformations.[2] As an example, the readily accessible and phytochemically significant chalcones are converted to benzils (**1**)[3] by oxidation in acidic aqueous glyme, while oxidation in acidic methanol gives 3,3-dimethoxy-1,2-diarylpropan-1-ones (**2**),[3] key intermediates (Ar′ = 2-ROC_6H_4) in the synthesis of isoflavones (**3**).[4] In the formation of both **1** and **2** from chalcones, it is the Ar ring which migrates during the oxidative rearrangement.

We have recently observed that the reaction of chalcone with TTN *in trimethyl orthoformate* (TMOF) gives a 50:50 mixture of 3,3-dimethoxy-1,2-diphenylpropan-1-one (**2**, Ar = Ar′ = C_6H_5) and methyl 2,3-diphenyl-3-methoxypropanoate (**6**, Ar = Ar′ = C_6H_5) (Scheme I). The keto acetal **2** is formed by normal Ar ring migration, but the ester **6** clearly must have resulted from migration of the Ar′ ring. This unique Ar′ ring migration can be rationalized as follows. Since the reaction of chalcone with TTN is slow due to deactivation of the carbon–carbon double bond by the carbonyl group, and since both aldehydes and ketones are rapidly converted to acetals and ketals with TMOF in the presence of TTN (acting as a Lewis acid),[5] ketalization of chalcone presumably competes with normal oxidative rearrangement to **2**. This would have two consequences: (i) removal of the deactivating carbonyl would make the double bond more reactive to electrophilic attack by TTN, and (ii) the *gem*-methoxy groups in the intermediate **5** should greatly favor migration of the Ar′ group rather than the Ar group. It would thus be expected that methyl 2,3-diphenyl-3-methoxypropanoate (**6**, Ar = Ar′ = C_6H_5) should be the exclusive product of TTN-mediated oxidative rearrangement of the preformed chalcone dimethyl ketal (**4**, Ar = Ar′ = C_6H_5), and this indeed proved to be the case (see above). This reaction pathway cannot be followed, however, if the reaction of chalcone with TTN is carried out under conditions which exclude rapid ketal formation; this is consistent with our previous observation that oxidative rearrangement of chalcone with TTN in acidic aqueous methanol led exclusively to the keto acetal **2** (Ar = Ar′ = C_6H_5).[3]

Table I. Methyl 2,3-Diaryl-3-methoxypropanoates from Chalcones



4 **6**

Ar	Ar′	Mp, °C
C_6H_5	C_6H_5	93.5–95.5
C_6H_5	4-$CH_3C_6H_4$	97.0–98.5
C_6H_5	4-$CH_3OC_6H_4$	80.5–82.0
4-ClC_6H_4	4-$CH_3OC_6H_4$	91.5–93.0
4-$O_2NC_6H_4$	C_6H_5	91.0–93.0
4-$O_2NC_6H_4$	4-$CH_3OC_6H_4$	97.0–99.0

Thus, the in situ preparation of chalcone dimethyl ketals followed by reaction with TTN in TMOF constitutes a convenient synthesis of methyl 2,3-diaryl-3-methoxypropanoates (see Table I), provided, however, that the migratory aptitude (ma) of the Ar′ group is moderate to good.[6] When maAr ≫ maAr′, complex mixtures of products are obtained from the preformed ketals, and their reactions with TTN have no synthetic significance. Full details of a study of the effects of substrate modification, relative migratory aptitudes of the Ar and Ar′ groups, and solvents on these oxidative rearrangements will be reported in the full paper.

The general procedure for the preparation of methyl 2,3-diaryl-3-methoxypropanoates is as follows. The chalcone ketals are prepared in situ by stirring the chalcone (0.01 mol) with 2–6 g of Dowex 50W-X4 cation-exchange resin in 35 mL of TMOF at room temperature. After ketal formation is complete (15–24 h, monitored by TLC using $HCCl_3$ and silica gel), the mixture is filtered into a solution of 5.0 g (0.011 mol) of TTN·$3H_2O$ in 20 mL of TMOF. When the oxidative rearrangement is complete (6–24 h), a small amount of solid sodium bisulfite is added to ensure complete reduction of Tl(III), 200–300 mL of diethyl ether is added, and the reaction mixture is chilled. The precipitated thallium(I) nitrate is removed by filtration and the ether layer is washed with saturated sodium chloride (2 × 50 mL), followed by saturated sodium bicarbonate (2 × 50 mL) and saturated sodium chloride (1 × 50 mL), and dried over $MgSO_4$. Removal of the ether gives the esters in almost quantitative yield (90–98% purity by NMR). All products are best recrystallized from methanol. The esters all exhibit carbonyl bands (IR) at 1730–1740 cm^{-1} and methinyl protons (NMR) at approximately δ 3.75 and 4.70 (J = 9.5–11.0 Hz).[7]

References and Notes

(1) For the previous paper in this series, see E. C. Taylor, J. G. Andrade and A. McKillop, *J. Chem. Soc., Chem. Commun.*, 538 (1977). We gratefully acknowledge financial support for this work from the National Science Foundation (Grant No. CHE7616506).

(2) For a recent review, see A. McKillop and E. C. Taylor, *Endeavor*, **35**, 88 (1976).

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(4) (a) L. Farkas and A. Wolfner, *Acta Chim. Acad. Sci. Hung.*, **88**, 173 (1976); (b) A. Levai and L. Balogh, *Pharmazie*, **30**, 747 (1975); (c) L. Farkas, S. Antus, and M. Nogradi, *Acta Chim. Acad. Sci. Hung.*, **82**, 225 (1974).

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(6) Even with the last three compounds in Table I, where maAr′ ≫ maAr, prior ketal formation was essential for synthetically useful transformations to the esters **6**. In TTN/TMOF (i.e., without prior ketal formation), isolation of pure **6** proved to be extremely difficult because of the simultaneous formation under these reaction conditions of degradation products of the initial chalcone.

(7) Satisfactory analytical and spectroscopic data were obtained for all new compounds.

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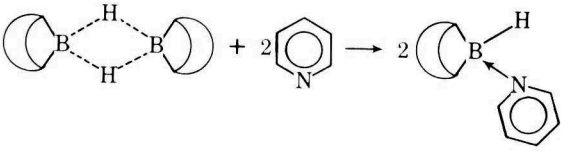
A New Reagent, 9-Borabicyclo[3.3.1]nonane–Pyridine, for the Selective Reduction of Aldehyde Groups in the Presence of Keto and Other Functional Groups

Summary: The exceptionally mild, highly selective, new reducing agent, 9-borabicyclo[3.3.1]nonane–pyridine (9-BBN·py), cleanly reduces the aldehyde group in the presence of keto and many other functional groups, making possible the clean, selective reduction of aldehyde groups in complex molecules.

Sir: The selective reduction of one carbonyl group in the presence of other such groups is a frequent synthetic problem. It has been solved in various ways.[1] A difficult, yet commonly encountered, problem in organic synthesis is the clean reduction of aldehyde in the presence of keto groups. Although aldehydes are reduced faster than ketones, the absolute rates are often too fast to take advantage of the favorable difference in the relative reduction rates. Consequently, in recent years, various reagents have been developed for such selective reductions. These include tetrabutylammonium cyanoborohydride,[2] sodium triacetoxyborohydride,[3] lithium tri-*tert*-butoxyaluminohydride,[4] 9-borabicyclo[3.3.1]nonane (9-BBN),[5] and Li-*n*-Bu_2-9-BBN "ate" complex.[6] More recently, diisopropylcarbinol on dehydrated alumina has been reported to be superior to all of these earlier reagents in its ability to distinguish effectively between an aldehyde and unhindered cyclohexanone.[7] However, this method requires large amounts of alumina with a tedious workup procedure resulting from the presence of both diisopropylcarbinol and diisopropyl ketone in the reaction mixture.

In this communication, we report application of the newly synthesized reagent, 9-borabicyclo[3.3.1]nonane–pyridine (9-BBN·py, **1**),[8] for the selective reduction of aldehydes in the presence of ketones. The reagent **1** is conveniently prepared by a simple reaction between the readily available 9-BBN dimer[9] and pyridine in pentane solution (eq 1).[8] The product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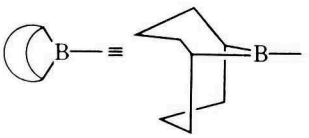


thus obtained is a stable crystalline solid, indefinitely stable under nitrogen.[10]

The selectivity in reduction and the functional group tolerance exhibited by **1** is quite remarkable, far better than that exhibited by the parent 9-BBN itself.[5] Thus a wide variety of aldehydes are reduced almost completely in 2 h at 25 °C in THF or Et_2O solutions (eq 2), whereas, under similar experimental conditions, even unhindered ketones are not reduced significantly (Table I). Competition experiments carried out by adding 10 mmol of **1** to a mixture of 10 mmol of aldehyde and 10 mmol of ketone in Et_2O reveal that **1** is highly selective toward aldehydes (Table II).[11] Also, various representative functional groups, such as ester, lactone, *N,N*-dialkylamide,

Table I. Reduction of Aldehydes and Ketones by 9-BBN·py in THF Solutions[a] at 25 °C

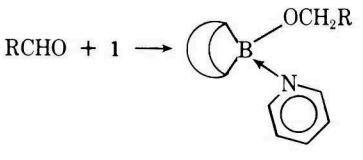
Compd	Time, h	% reduced[b]
Benzaldehyde	1.0	95
	1.5	100
Cinnamaldehyde	1.0	86
	1.5	98
Cyclohexylcarboxaldehyde	1.0	91
	3.0	100
Octanal	1.0	91
	2.0	99
Hexanal	1.0	94
	2.0	100
Propanal	1.0	85
	1.5	97
Cyclohexanone	1.0	0
	1.5	3
2-Methylcyclohexanone	2.0	0
2-Hexanone	1.0	5
	12.0	43
Dicyclopropyl ketone	1.5	8
3-Pentanone	1.0	5
	7.0	10
Acetophenone	1.0	3
	9.0	5
Phenylacetone	1.0	6
	8.0	46

[a] The reaction mixture was 0.25 M in the substrate and 0.25 M in 9-BBN·py. [b] Progress of the reaction was followed by the measurement of residual hydride in the aliquot; for details of the procedure, see H. C. Brown, "Organic Syntheses via Boranes", Wiley, New York, N.Y., 1975, Chapter 9.

Table II. Relative Reactivities of Aldehydes with Respect to Ketones toward 9-BBN·py in Et_2O at 25 °C. Competition Experiments

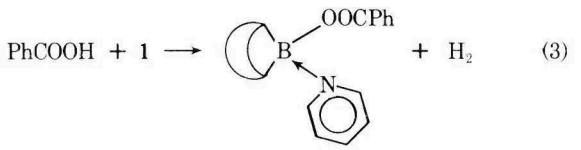
Compd used	Product	Mol %[a]
Cyclohexanone	Cyclohexanone	98.5
+	Cyclohexanol	1.5
Benzaldehyde	Benzaldehyde	6.0
	Benzyl alcohol	93.0
Acetophenone	Acetophenone	96.0
+	1-Phenylethanol	2.0
Benzaldehyde	Benzaldehyde	4.0
	Benzyl alcohol	94.0
3-Pentanone	3-Pentanone	96.0
+	3-Pentanol	2.5
Octanal	Octanal	4.5
	1-Octanol	94.5

[a] Determined by GLC (ref 11) from the response ratios determined for authentic samples.


(2)

2

nitrile, alkyl halide, benzylic halide, epoxide, alkene, alkyne, and nitroalkane, are not affected by **1**. Carboxylic acids, alcohols, and water react relatively rapidly, liberating hydrogen (eq 3).[8] However, no further reaction of the initially formed

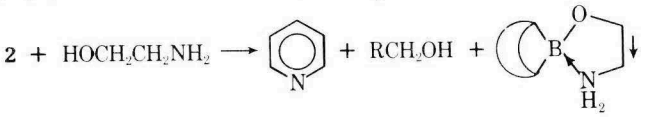


(3)

3

B-acyloxy-9-BBN·py (**3**) occurs with excess **1**. On the other hand, acid chlorides and anhydrides are reduced rapidly. Consequently, with the exception of these groups, the reagent permits the selective reduction of aldehyde groups in the presence of nearly all other functional groups. Such a remarkable inertness toward most of the functional groups, combined with a high selectivity for the reduction of aldehydes, has not been realized with any of the reagents previously described.[2-7]

The isolation of the primary alcohol product from the *B*-alkoxy-9-BBN·py (**2**) intermediate is quite simple, requiring only addition of β-aminoethanol. This displaces the alcohol with precipitation of the ethanolamine complex (**4**) of 9-BBN (eq 4). The latter can be removed by filtration in air.



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(4)

The following experiment is representative for the determination of relative reactivities of aldehydes with respect to ketones. To a mixture of benzaldehyde (10 mmol, 1.02 mL), acetophenone (10 mmol, 1.17 mL) and *n*-tetradecane (5 mmol, 1.23 mL; an internal standard for GLC analysis) in 30 mL of Et_2O under nitrogen was added a solution of **1** in Et_2O (10 mmol, 6.7 mL of 1.5 M solution). After stirring for 2 h at 25 °C, the mixture was diluted with 30 mL of pentane, and β-aminoethanol (10 mmol, 0.61 mL) was added to precipitate **4**. The supernatant liquid was analyzed by GLC[11] (Table II).

The reduction of hexanal is representative for the isolation of alcohols. To a well-stirred solution of hexanal (150 mmol, 18.5 mL) in 100 mL of Et_2O under nitrogen was added an ether solution of **1** (165 mmol, 110 mL of 1.5 M solution). After stirring for 2 h at 25 °C, pentane (300 mL) and β-aminoethanol (165 mmol, 9.97 mL) were added. The precipitate of **4** was filtered off and the Et_2O–pentane extract was washed with dilute HCl to remove pyridine and dried over anhydrous Na_2SO_4. The solvent was pumped off and the product distilled: 11.8 g of 1-hexanol (77% yield), bp 80–82 °C (25 mm). Similarly, benzyl alcohol and cyclohexylmethanol were isolated in yields of 74 and 78%, respectively.[12]

In conclusion, the present study reveals that 9-BBN·py complex is a highly selective, unique reducing agent which should find application in situations requiring the selective reduction of aldehydes in the presence of other functional groups. The full scope and limitations of such reductions are being examined.

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(8) H. C. Brown and S. U. Kulkarni, *Inorg. Chem.*, in press.
(9) Available from Aldrich Chemical Co., Milwaukee, Wisc.
(10) Although 9-BBN·py is reasonably stable in air, it was used under nitrogen and exposure to air and moisture minimized.
(11) A 14 ft × 1/8 in. column packed with 5% Carbowax 20M deposited on Varaport-30 was used for separation of the complex mixture.
(12) The yields are not optimized. The isolated alcohols contain trace amounts of aldehydes.
(13) Graduate research assistant on Grant GM 10937-14 from the National Institutes of Health.

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High-Pressure Cycloadditions of Pyrones: Synthesis of Highly Functionalized Six-Membered Rings by Inhibition of Carbon Dioxide Loss

Summary: A series of highly functionalized bicyclic adducts (**3–6**) have been prepared via the high-pressure (20–40 kbar) cycloaddition of 3-hydroxy-2-pyrone (**2**) with various dienophiles at room temperature.

Sir: The application of pressure accelerates the rates of chemical reactions which have a negative volume of activation and retards the rates of those which have a positive volume of activation.[1] Dauben has recently shown that pressures in the 8–20-kbar range are useful in effecting cycloaddition reactions of enamines, dienamines, and furans.[2] The requisite apparatus for executing large-scale high-pressure syntheses is only moderately expensive,[3] making its use practical in preparative chemistry.

Highly negative (−25 to −45 cm^3/mol) volumes of activation have been measured for both 4 + 2 and polar 2 + 2 cycloadditions.[1,4] Under thermodynamically ideal conditions, transition state stabilization of such reactions should be on the order of 1 kcal/mol per kilobar of pressure applied. Also, the thermal extrusion of small, stable molecules such as CO_2 and N_2 from neutral organic compounds should be retarded by pressure both on kinetic ($\Delta V^{\ddagger} > 0$) and thermodynamic ($\Delta V_{rxn} > 0$) grounds. We reasoned that this combination of factors would enable the preparation of highly functionalized six-membered rings from pyrone derivatives, which usually extrude CO_2 under conventional (100–200 °C) Diels–Alder conditions (Scheme I).[5,6] In the event of 100% regioselectivity

Scheme I

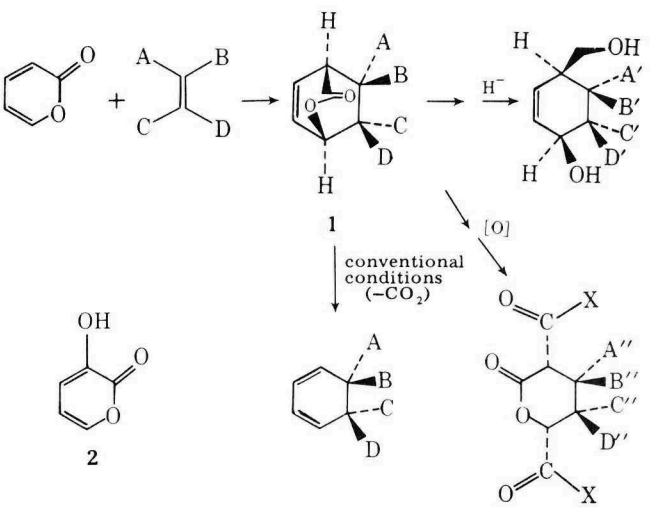
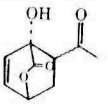
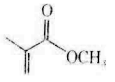
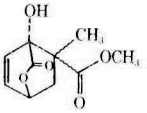
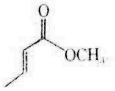
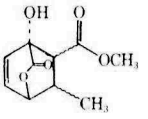
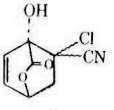
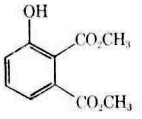


Table I. High-Pressure Cycloadducts of 3-Hydroxy-2-pyrone

Dienophile reacted with 2	Pressure, kbar	Product	Endo/exo ratio[10]	IR ($CHCl_3$), cm^{-1}	NMR ($CDCl_3$), Me_4Si internal standard[a]
	17	 3	>10:1	1752 (s) 1710 (s)	^{1}H: δ 1.85–2.61 (2 H, complex m), 2.28 (3 H, s), 3.17 (1 H, d of d, J = 5.0, 9.5 Hz), 5.34 (1 H, m), 6.15–6.63 (2 H, complex m) ^{13}C: 205.5, 175.0, 134.2, 130.1, 76.0,[b] 74.3, 47.7, 3.20, 30.6 ppm
	32	 4	3:1	1740 (s, br)	^{1}H: δ 1.37 and 1.31 (2 s, 3 H total area, relative area 3:1, assigned to endo and exo isomers), 1.76–2.93 (2 H, complex m) 3.71 (3 H, s), 5.28 (1 H, m), 6.48 (2 H, m) ^{13}C:[c] 174.5, 173.5, 137.5, 129.5, 78.7,[b] 73.7, 52.9, 46.5, 40.4, 21.9 ppm
	40	 5	3:2	1760 (s) 1737 (s)	^{1}H: δ 1.00 and 1.33 (2 d, J = 7 Hz, total area 3 H, relative area 3:2, assigned to endo and exo isomers), 2.07–2.45 (2 H, m), 3.73 (3 H, s) 4.97 (1 H, m), 6.47 (2 H, pseudo d, J = 4 Hz) ^{13}C endo:[b] 174.1, 171.6, 135.1, 130.1, 79.0, 52.6, 50.3, 40.1, 18.3 ppm ^{13}C exo:[b] 173.2, 172.5, 137.8, 129.1, 77.3, 53.8, 50.3, 39.4, 18.9 ppm
	30	 6	2:1	1775 (s)[d]	^{1}H:[e] 5 d (total area 2 H) at δ 2.40 (J = 2 Hz), 2.66 (J = 2), 3.00 (J = 3), 3.21 (J = 4), and 3.48 (J = 4), 5.43 (1 H, m), 6.35–7.00 (2 H, complex splitting) ^{13}C:[c,e] 169.6, 134.6, 131.9, 117.3, 71.9, 67.3,[b] 56.8, 46.1 ppm
	20	 7[12]	—	1723 (s) 1674 (s)	^{1}H: δ 3.92 (3 H, s), 3.88 (3 H, s) 6.90–7.65 (3 H, complex m) 10.47 (1 H, br, from authentic sample) ^{13}C: 169.4, 161.0,[f] 135.3, 134.4, 120.0, 119.3, 110.7, 52.8, 52.6 ppm

[a] The –OH group in adducts **3–6** is deuterated under the reaction conditions. [b] The bridgehead carbon bearing the –OH group is weak in intensity, even in the presence of $Cr(acac)_3$. In **3** and **4**, its chemical shift assignment is tentative due to overlap with $CDCl_3$. In **5**, the resonance is completely obscured, and in **6** it is upfield from $CDCl_3$ but still considered tentative due to its low intensity. [c] For the major (endo) isomer only. [d] The absence of $\nu_{C\equiv N}$ in α-chloronitriles has been previously noted: R. M. Silverstein, G. C. Bassler, and T. C. Morrill, "Spectrometric Identification of Organic Compounds", 3rd ed, Wiley, New York, N.Y., 1974, p, 110. [e] Obtained in $CDCl_3$/acetone. [f] An apparent degeneracy of the two carbonyl groups or a carbonyl group and the –OH carbon exists. In the presence of $Cr(acac)_3$, the 169.4 peak is ca. twice the 161.0 peak. Compare with methyl salicylate and methyl benzoate in L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley, New York, N.Y., 1972.

and endo cycloaddition, a single adduct of structure **1** would be obtained which contains two asymmetric carbons of fixed relative configuration otherwise lost upon CO_2 elimination. Possible reductive and oxidative elaborations of **1** to highly functionalized monocycles are also illustrated in Scheme I.

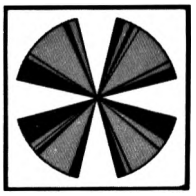
We report herein that the initial step in Scheme I can be realized at *room temperature* by the application of pressures in the 20–40-kbar range. All cycloadditions examined were quantitative, regiospecific, and to varying degrees, stereoselective. 3-Hydroxy-2-pyrone (**2**) was utilized to enable comparison with the recent work of Corey and Kozikowski.[6]

Reactions were conducted in a 0.3 mL Teflon screw-top vial in acetone-d_6 utilizing approximately a 10% excess of dienophile.[7] The filled capsule was placed inside a graphite–talc sleeve and fitted into a cylindrical high-pressure vessel of sintered tungsten carbide. Pressure was generated by forcing a carbide piston into the sample vessel with the aid of a 600-ton hydraulic ram.[8] Pressure was calculated from a master ram Heise gauge. Workup consisted merely of opening the vial and blowing off solvent and any excess dienophile, after which only product remained.[7b]

The cycloadducts obtained and supporting spectral data are summarized in Table I. Reactions were allowed to run overnight at the pressure indicated. Compounds **3–5** partially decomposed upon attempted silica gel chromatography,[9] so the products were characterized as a mixture of endo/exo stereoisomers. The stereoisomer ratios were determined by ^{13}C NMR and ^{1}H NMR.[10] The absence of regioisomers was established by decarboxylation (pyrolysis at 150–200 °C) of each stereoisomeric mixture to a single compound; in the cases of **4–5**, the decarboxylation products had been previously characterized by Corey and Kozikowski.[6] Authentic samples were prepared by their method for comparison. Although the highest molecular weight ions in the mass spectra of **3–6** were $M^+ - 44$ peaks, IR and ^{13}C NMR data clearly indicate the presence of lactone functionality. The hydroxyl hydrogen of **2** was found to exchange with acetone-d_6 under the reaction conditions. Based upon data with other weak proton acids,[1] acetone would be expected to be a much stronger acid under pressure.

The high-pressure reactions of **2** with methyl methacrylate and methyl crotonate occur at temperatures 180 °C lower than those employed by Corey and Kozikowski. Adducts **4** and **5** are instantly destroyed under their conditions, which precludes observation of the effect of pressure on the endo/exo ratio.[10,11] When 3-hydroxy-2-pyrone was reacted with α-chloroacrylonitrile by conventional thermal means, only *o*-cyanophenol was produced.[6] Utilization of high pressure blocks CO_2 and HCl loss and enables isolation of **6**. The bicyclic adduct of **2** and dimethyl acetylenedicarboxylate rapidly evolves CO_2 when the sample capsule is opened at room temperature, affording the known diester **7**.[12] Since this decarboxylation involves breaking bonds at two doubly allylic positions and formation of an aromatic ring, its activation

Polyethers



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The following is a short summary of the most important synthetic uses of some of our boron hydride reagents. For more detailed discussions, please consult the leading references cited.

1) **Borane-tetrahydrofuran** is a well-known hydroboration reagent.[2] This solution is also useful for the selective reduction of organic functional groups.[3]
2) **Borane-methyl sulfide (BMS)** is a highly concentrated

BMS

source of BH_3 which is soluble in a variety of aprotic solvents.[4] This reagent is an active hydroboration reagent[4] which also shows great utility as a selective reducing agent.[5]

3) **9-Borabicyclo[3.3.1]nonane (9-BBN)** is a very valuable

9-BBN

selective hydroboration reagent.[2,6] Recently, **9-BBN** showed great promise as a selective reducing agent.[7]

4) **Catecholborane (CB)** is the best reagent available for the

CB

preparation of synthetically useful *B*-alkyl- and *B*-alkenylboronic acids and esters.[8] Presently, this boron hydride is only packaged neat in a small, 25-g research size. Bulk orders of 500g will be packaged in our Sure/-Seal bottle.

5) **Super-Hydride®** is an extremely powerful (yet selective) reducing agent.[9]

Super-Hydride®

6) The **Selectride** reagents represent an exciting new class of stereoselective reducing agents.[9,10]

L-Selectride® K-Selectride®

The reagents mentioned above constitute only a small sample of the many boron reagents which are available from Aldrich. In a continuing program, Aldrich-Boranes, Inc. is actively developing other new boron reagents. If there is any particular reagent that you would like to be made available, let us know. We welcome your suggestions!

References: (1) *Aldrichimica Acta*, **10**, 11 (1977). (2) H.C. Brown, "Organic Syntheses *via* Boranes," John Wiley and Sons, Inc., New York, N.Y., 1975 (Aldrich Catalog No. Z10,144-3, $19.50). (3) *Chem. Rev.*, **76**, 773 (1976); *Aldrichimica Acta*, **10**, 41 (1977). (4) *J. Org. Chem.*, **39**, 1437 (1974). (5) *Ibid.*, **39**, 3052 (1974); *Aldrichimica Acta*, **8**, 20 (1975). (6) *J. Am. Chem. Soc.*, **96**, 7765 (1974); *ibid.*, **98**, 5297 (1976). (7) *Aldrichimica Acta*, **9**, 31 (1976). (8) *Tetrahedron*, **32**, 981 (1976). (9) *Aldrichimica Acta*, **7**, 55 (1974). (10) *J. Am. Chem. Soc.*, **94**, 7159 (1972); *ibid.*, **95**, 4100 (1973); *J. Org. Chem.*, **41**, 2194 (1976).

17,871-3	**9-BBN**, crystalline	**25g $25.00; 100g $80.00**
19,385-2	**9-BBN**, 0.5*M* in hexane.....	**500ml $20.00**
15,107-6	**9-BBN**, 0.5*M* in THF.....	**500ml $17.00**
17,982-5	**Borane-methyl sulfide**...	**80g $19.50; 500g $71.10**
19,211-2	**Borane-methyl sulfide**, 2*M* in ethyl ether	**500ml $25.00**
19,303-8	**Borane-methyl sulfide**, 1*M* in methylene chloride	**500ml $18.00**
19,212-0	**Borane-methyl sulfide**, 2*M* in THF	**500ml $26.00**
19,482-4	**Borane-methyl sulfide**, 2*M* in toluene	**500ml $24.00**
17,619-2	**Borane-tetrahydrofuran**, 1*M* in THF	**500ml $15.70**
18,891-3	**Catecholborane**	**25g $17.00; 500g $250.00**
18,014-9	**K-Selectride®**, 0.5*M* in THF.....	**500ml $24.00**
17,849-7	**L-Selectride®**, 1*M* in THF	**500ml $25.00**
18,086-6	**Super-Deuteride®**, 1*M* in THF	**100ml $10.40; 500ml $52.00**
17,972-8	**Super-Hydride®**, 1*M* in THF.....	**500ml $21.00**

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